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Health Effects from Radiofrequency Electromagnetic Fields

Report of the independent Advisory Group on Non-ionising Radiation

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Chairman: Professor A J Swerdlow

This report from the independent Advisory Group on Non-ionising Radiation reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.

Executive Summary

In the years since the last AGNIR review on radiofrequency (RF) electromagnetic fields, in 2003, large research programmes in the UK and across Europe have come to fruition. The amount of research published has greatly increased and much of it has been of higher quality than was previously available.

Exposure of the general public to low level RF fields from mobile phones, wireless networking, TV and radio broadcasting, and other communications technologies is now almost universal and continuous. Additional sources of exposure to RF fields are appearing from new technologies such as domestic smart meters and airport security scanners. In addition, some members of the public are exposed to higher levels of exposure from certain medical uses of RF fields, notably MRI and diathermy. The greatest occupational exposures to RF fields are from dielectric heating, but there are also high exposures from several other industrial sources including induction heating, sputtering and welding.

Current exposure guidelines are based on the thermal effects of RF fields. Individual exposures and doses associated with many RF field sources are well documented, enabling predictions to be made of associated temperature rises *in vivo*.

Studies of the effect of RF field exposure on cells *in vitro* now include an increasing number that have re-tested findings from previous studies. No consistently replicable effects have been found from RF field exposure at levels below those that produce detectable heating. In particular, there has been no convincing evidence that RF fields cause genetic damage or increase the likelihood of cells becoming malignant.

Studies of animals have employed a wide range of biological models, exposure levels and signal modulations. Taken together, these studies provide no evidence of health effects of RF field exposures below internationally accepted guideline levels. In particular, well-performed large-scale studies have found no evidence that RF fields affect the initiation and development of cancer, and there has been no consistent evidence of effects on the brain, nervous system or the blood-brain barrier, on auditory function, or on fertility and reproduction.

The evidence suggests that RF field exposure below guideline levels does not cause acute symptoms in humans, and that people, including those who report being sensitive to RF fields, cannot detect the presence of RF fields. Similarly, well-conducted studies do not suggest that exposure to RF fields gives rise to acute cognitive effects. There is, however, some evidence that RF field exposure may affect EEG and other markers of brain function. However, these effects have not been consistent across studies. In addition, the size of these reported effects is often small relative to normal physiological changes, and it is unclear whether they have any implications for health.

Short-term exposures to RF fields at levels well above the limit set in current exposure guidelines can cause thermal injury to tissues. The highest occupational levels of exposure to RF pulses can cause perception of a banging or clicking sound ('microwave hearing').

Although research on the potential long-term effects of RF field exposures below guidelines levels on other non-cancer outcomes in humans has been very limited, the literature provides no substantial evidence of such effects, in particular in relation to cardiovascular morbidity, reproductive function and non-cancer mortality.

Epidemiological studies on cancer risks in humans in relation to occupational RF field exposures and residential exposures from proximity to RF transmitters have had considerable methodological weaknesses, particularly in exposure assessment. They give no evidence of any causal effect but also give no strong evidence against it.

There is now a substantial body of epidemiological research published on cancer risks in relation to mobile phone use. Although some positive findings have been reported in a few studies, overall the evidence does not suggest that use of mobile phones causes brain tumours or any other type of cancer. The data, however, are essentially restricted to periods of less than 15 years from first exposure.

Conclusions

The quantity, and in general quality, of research published on the potential health effects of RF field exposure has increased substantially since AGNIR last reviewed this subject. Population exposure to RF fields has become more widespread and heterogeneous. There are still limitations to the published research that preclude a definitive judgement, but the evidence considered overall has not demonstrated any adverse health effects of RF field exposure below internationally accepted guideline levels. There are possible effects on EEG patterns, but these have not been conclusively established, and it is unclear whether such effects would have any health consequences. There is increasing evidence that RF field exposure below guideline levels does not cause symptoms and cannot be detected by people, even by those who consider themselves sensitive to RF fields. The limited available data on other non-cancer outcomes show no effects of RF field exposure. The accumulating evidence on cancer risks, notably in relation to mobile phone use, is not definitive, but overall is increasingly in the direction of no material effect of exposure. There are few data, however, on risks beyond 15 years from first exposure.

In summary, although a substantial amount of research has been conducted in this area, there is no convincing evidence that RF field exposure below guideline levels causes health effects in adults or children.

1 Introduction

1.1 Advisory Group on Non-ionising Radiation and its Remit

The Advisory Group on Non-ionising Radiation (AGNIR) was set up in 1990, reporting to the Director of the former National Radiological Protection Board (NRPB) – now part of the Health Protection Agency (HPA) – and with the terms of reference:

> 'to review work on the biological effects of non-ionising radiation relevant to human health and to advise on research priorities'

AGNIR was reconstituted in 1999 as an independent advisory group and now reports to the board of the HPA. In addition to the work of the AGNIR, subgroups are convened from time to time in order to address specific issues.

AGNIR has issued 14 major reports in the *Documents of the NRPB/Health Protection Agency: Radiation, Chemical and Environmental Hazards* series and a number of statements that are listed in an appendix to this report. The AGNIR publications have reviewed experimental and epidemiological studies, together with exposure data, relevant to assessing possible health effects from exposures to electromagnetic fields (EMFs), ultraviolet radiation (UVR), static magnetic fields, ultrasound and infrasound. They have been a valuable input to HPA, and previously NRPB, advice and have been used in the development of exposure guidelines as well as being widely circulated and used by government and the devolved administrations. AGNIR last published a review of the health effects of radiofrequency (RF) electromagnetic fields in 2003.

This AGNIR review, like its predecessors, reflects the consensus of the AGNIR members.

1.2 RF Field Exposures in the UK: Sources and Public Concern

People are exposed to RF fields from many sources, including radio and TV transmitters, telecommunications links and satellite communications, as well as mobile phones and their supporting transmitters (base stations), and a myriad of other wireless applications such as Wi-Fi. There are also occupational exposures in the telecommunications and manufacturing industries. The use of mobile phones has increased considerably in recent years and has come to be seen as an essential means of communication in commerce and society. There are now over 80 million mobile phones in use in the UK supported by nearly 53,000 base stations. The number of phones, which is more than the number of people in the UK, and the widespread domestic, workplace and public access to the internet through wireless applications, reflects the utility and pervasiveness of these technologies in modern life.

There have, however, been concerns expressed for a number of years about the possible health effects associated with exposure to RF fields. These were particularly common when many tall masts for mobile

phone base stations were being erected across the country at the turn of the century. Public concerns remain today, but have not apparently hindered the uptake of new wireless technologies. Expressions of concern continue (Rowley, 2004; European Commission, 2007, 2010; Dolan and Rowley, 2009) and are often focused on new applications. In particular, concerns about the use of Wi-Fi in schools have grown in recent years, while the technology has become extensively deployed. The HPA has conducted a detailed investigation of exposures from Wi-Fi, the results of which are summarised in Appendix A. It is clear from enquiries to the HPA and media coverage that there is continuing public interest in these issues.

1.3 History of Scientific Review and Advice about the Health Effects of RF fields

The UK Independent Expert Group on Mobile Phones (IEGMP, 2000) drew attention to concerns on this topic in its report and called for more research. Around the same time a number of other reviews were issued by national bodies concerned with the possible health effects of exposures to RF fields from mobile phones and base stations. These included a review of research needs by a European Commission Expert Group (1996), a review by an Expert Panel of the Royal Society of Canada (1999), the Zmirou Report for Health France (2001), reviews of both base stations and mobile phones for the Health Council of the Netherlands (2000, 2002), an interim report by the British Medical Association on mobile phones and health (2001) and a French Senate Report (OPECTS, 2003). The results of these and additional expert group reports have been reviewed by Sienkiewicz and Kowalczuk (2004). Similar calls for research were raised in other countries around the same time, and also within the European Union (EU) and the World Health Organization (WHO). The result has been a substantial programme of research supported by governments, industry and the EU.

In recognising that research would proceed apace, the IEGMP recommended that a further review of the science should be carried out within three years of its own report and the AGNIR prepared such a review in 2003. At that time, many studies were in progress and, in particular, epidemiological research on mobile phone users was at an early stage. Hence, it was agreed in 2003 that the AGNIR should produce a further review of studies relevant to concerns about health for publication in a few years' time.

After the 2003 AGNIR review, the NRPB produced updated advice entitled 'Mobile Phones and Health 2004' (NRPB, 2005) and also published a review of the evidence about the health effects of electromagnetic field exposure (in the range 0–300 GHz), as well as revised guidelines for public and occupational exposures (NRPB, 2004a,b).

The first phase of the UK Mobile Telecommunications and Health Research (MTHR) Programme has finished and reported (MTHR, 2007), and the majority of funded studies have been published in the peer-reviewed scientific literature. The initial phases of work funded in other countries and by the EU are also largely complete. Some results from a large international pooling study of brain tumour and other cancer risks in relation to mobile phone use, which brings together the data from a number of national studies, have been published (Interphone Study Group, 2010).

1.4 Need for a New Review of RF Field Health Effects

Since the last AGNIR review of RF field exposure there has been a marked increase in the use of wireless devices across the world. The worldwide interest in the topic and investment in scientific programmes in the early 2000s has resulted in a rapid expansion in the number of peer-reviewed scientific papers relevant to this review.

Despite a wealth of new scientific information there remain substantial problems with the interpretation of some individual studies and the outputs from broader research programmes. Some studies (both epidemiological and experimental) appear to have problems with selection of adequate controls, others are complicated by, for example, multiple testing or positive findings confined to subgroups. Careful scientific review is needed to draw sound conclusions from this mass of evidence and the recent publication of major studies makes this an appropriate time for AGNIR to undertake a new review. Work on this review began in 2009 and it contains published evidence up to the end of 2010 with a few 2011 papers included where they add particularly to the body of evidence in Chapters 2, 4, 5, 6 and 8.

1.5 Scope of the Review

For the purposes of this review, RF fields are defined as that part of the electromagnetic spectrum between 100 kHz and 300 GHz. These frequencies are used for a great variety of applications, including radar and navigation, induction and dielectric heating, asset tracking and identification, professional radio communications systems and medical applications, as well as the now ubiquitous mobile phones and their associated base stations. Since the previous AGNIR review, a number of new technologies using RF fields have emerged or become much more widespread, notably Wi-Fi, and these systems are considered in Chapter 2.

This review addresses the scientific research related to the potential health effects from exposures to RF fields, concentrating on new evidence since 2003. In Chapter 6 on symptoms in humans there was very little information in the 2003 review, so the whole of the literature is reviewed and referenced there. The conclusions drawn, however, take account of the entire literature, irrespective of the year of publication. It covers sources of RF field exposure as well as experimental and epidemiological studies relevant to concerns about human health. The RF fields to which people may be exposed from a variety of devices cover a wide range with very variable signal characteristics and these are considered. The report is limited, however, to the direct effects of RF fields and does not consider the indirect effects associated with the use of mobile phones or other wireless devices, eg distraction and accident risk from the use of a mobile phone while driving. The report does not include an in-depth review of the already well-established heating effects of RF field exposure.

In this review the term ‘biological effect’ is used to describe a detectable effect on a living system. It does not imply that this is necessarily an adverse health effect. Many things – for example, food, water and exercise – have detectable ‘biological effects’.

This review considers many hundreds of scientific studies. The convention that has been used to summarise succinctly results of individual studies is to refer to a ‘positive’ study as one where a statistically

significant effect was found and a 'negative' study as one where no statistically significant effect was found. A 'positive' study finding does not necessarily imply a causal association. Several additional criteria need to be met to demonstrate causality.

Readers wishing to consider the detailed view of AGNIR on individual studies from before 2003 should consult the previous report on RF fields (AGNIR, 2003), which is not repeated here.

The scientific papers reviewed here have been carefully examined to determine what weight should be given to individual findings. This includes consideration of scientific quality as well as expert judgement about each study and how it fits within the canon of work. Consistency with the existing body of evidence is an important criterion, but AGNIR also recognises that the quest for alternative explanations for data is an important part of the scientific process.

Summing the number of positive and negative studies is not an adequate way to review a scientific field, not least because of publication bias which favours publication of new positive findings. Also, pure replication studies of positive findings may be less likely to be published, even though they may strengthen the body of evidence.

1.6 Structure of the Review

There are far more published cellular and animal studies than experiments with human participants or epidemiological studies. However, human experiments and epidemiological studies are of the greatest direct relevance to public health. Epidemiological studies are often complex to interpret due to the effects of chance, bias and confounding. Therefore individual human and epidemiological studies have, in general, been considered in greater detail in this review. Each chapter is separately referenced with its own conclusions which are brought together in Chapter 9.

The executive summary summarises the report and its conclusions and recommendations.

Chapter 2 considers the exposures, mechanisms of action of RF fields, the way that exposure and dose to the body can be estimated (dosimetry), and how the public are exposed to them (sources).

Chapter 3 considers the mechanisms of interaction of RF fields with living tissue and the cellular studies that have been done to investigate them.

Chapter 4 considers experimental studies of RF field effects on various tissues in animal models. Much work has concentrated on investigating whether exposure to RF fields may increase the risk of cancer, but work on other endpoints and behaviour is also reviewed.

Chapter 5 considers acute cognitive and neurophysiological effects of mobile phone signals including experimental human provocation studies and observational studies.

Chapter 6 considers whether exposure to RF fields can cause symptoms and also considers the issue of whether some people are sensitive to RF fields.

Chapter 7 considers non-cancer observational studies (epidemiology) and experimental human studies on the effects of RF fields on a range of outcomes, including sexual function, fertility, birth outcome, child development and cardiovascular function.

Chapter 8 considers observational studies of cancer risks in relation to RF field exposures, including studies of residence near RF transmitters and mobile phone use in relation to a wide range of cancer endpoints with a preponderance related to head and neck tumours. Occupational and domestic studies are considered.

The principal conclusions and recommendations for further research are given in Chapters 9 and 10, respectively.

The report has three appendices describing the results of an HPA project to assess exposures from Wi-Fi in schools, a summary of the International Commission on Non-Ionizing Radiation Protection exposure guidelines and a list of previous AGNIR publications.

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2 Exposures, Interaction Mechanisms, Dosimetry and Sources

Exposure of the general public to low level man-made radiofrequency (RF) electromagnetic radiation is now essentially universal. Furthermore, some sectors of the working population may be exposed to higher levels than the general public, arising from equipment used in their particular workplace, and patients may be exposed as part of medical procedures. This chapter reviews the characteristics of these exposures from a wide range of sources, each in terms of its frequency bandwidth, exposure levels and modulation characteristics. These sources are used for communications, medical diagnosis, treatment and surgery, and a wide range of industrial applications. Experimental and computational dosimetry is reviewed, including the current emphasis on the development of age-specific models. With the current, very rapid proliferation of devices and techniques, the most important developments are included and, where possible, future trends are identified. Other detailed authoritative reviews, including one focusing on emerging RF technologies, may be found elsewhere (ICNIRP, 2008, 2009).

2.1 Characteristics of RF Fields

The term RF (radiofrequency) refers to the parts of the electromagnetic spectrum that can be readily used for radio communications purposes and which lie below the infrared region: specifically, for this document, frequencies in the range of 100 kHz to 300 GHz. Frequency bands within this range have been named more formally by the International Telecommunications Union (ITU). Figure 2.1 shows these bands, together with the ranges of frequencies commonly used for various applications considered later in this chapter, including those for telecommunications, in medicine, and for industry. Human exposure to RF fields may arise from their deliberate use – for example, as part of the global telecommunications networks – or adventitiously, as part of industrial and other processes utilising RF energy. The term radio wave is used in this chapter to denote a radiofrequency electromagnetic field that is transmitted from a source for communications purposes, while the term microwave can be used to refer to RF fields with frequencies between 300 MHz and 300 GHz.

2.1.1 Quantities and units

Electromagnetic waves are characterised by an electric field strength E expressed in units of volts per metre (V m^{-1}) and magnetic field strength H expressed in units of amperes per metre (A m^{-1}) that typically oscillate sinusoidally between positive and negative values at a frequency f. The distance along a wave between two adjacent positive (or negative) peaks is called the wavelength, λ, and is inversely proportional to the frequency. The strength of the electric or magnetic field can be indicated by its peak

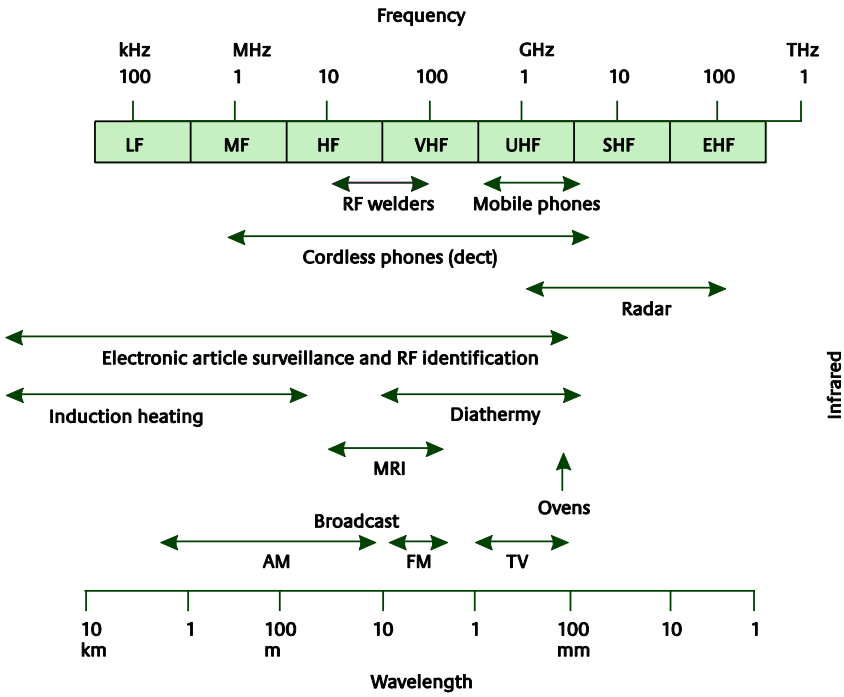

FIGURE 2.1 RF spectrum and sources

The International Telecommunications Union (ITU) band abbreviations are given as LF, low frequency; MF, medium frequency; HF, high frequency; VHF, very high frequency; UHF, ultra high frequency; SHF, super high frequency; and EHF, extremely high frequency

value (either positive or negative), although it is more usually denoted by the rms, or root mean square, value (the square root of the average of the square of the field). For a sinusoidally varying field, this is equal to the peak value divided by √2. At a sufficient distance from the source where the wave can be described as a plane wave, the electric and magnetic field directions are at right angles to each other and also to the direction in which the energy is propagating.

The quantity of electromagnetic energy per unit area at right angles to the direction of flow and per second is called the power density (intensity), S, and is expressed in units of watts per metre squared (W m^{-2}). In other words, if a power of one watt passes through one square metre, the power density is 1 W m^{-2}. Beyond about one wavelength from a transmitter (see Section 2.1.6), the positive (or negative) peaks in the electric and magnetic fields occur at the same points in space. In other words they are in phase, and the power density equals the electric field strength multiplied by the magnetic field strength:

$$S = E\,H$$

Power density decreases with increasing distance from the source because the waves spread out as they travel. In free space, power density in the far field follows the inverse-square law (S is proportional to $1/d^2$, where d is the distance from the source).

2.1.2 Waveforms

In considering how to categorise human exposure, it is important to account consistently for the signal characteristics of particular communication systems when summing them together in the context of a chosen exposure metric. This involves considering whether the waveform is continuous or intermittent and whether the way information is carried affects important aspects of the signal (Foster and Repacholi, 2004).

2.1.2.1 Modulation

The signals generated by various sources across the spectrum may be very different in character. While the underlying waveform from a source is usually sinusoidal, the signal may then, for example, be amplitude modulated (AM) or frequency modulated (FM) for radio communication. The aim of modulation is to carry a message signal, such as a speech signal, on another signal that can be physically transmitted. The RF signal that carries the information is called the carrier wave. Modern digital radio communications systems can use more than one type of modulation in the same signal. Many industrial sources produce waveforms with high harmonic content resulting in complex waveforms. Complex waveforms are not confined to signals generated by communications systems.

Older analogue radio systems tend to produce signals that are essentially continuous. For example, radio signals in the VHF broadcast band involve audio information that is encoded on to slight changes in the frequency of the signal, while signals in the long and medium wave bands use amplitude modulation. Some modern digital systems involve radio transmitters that take it in turn to transmit on a given frequency channel, which means that the signals from any given transmitter are pulse modulated (see Section 2.1.2.2 below).

2.1.2.2 Pulsing (pulse modulation)

RF signals are often transmitted in a series of short bursts or pulses – for example, in radar applications. Radar pulses last for a time that is very short compared with the time between pulses. The pulse duration could be one microsecond (one-millionth of a second), while the time interval between pulses could be one millisecond (one-thousandth of a second). The detected signal arises from reflections from objects where the distance of the object is determined by the time between a transmitted pulse and its reflection. The long interval between pulses is needed to ensure that an echo from the most distant object arrives before the next transmitted pulse is sent. Thus, with a pulse modulated signal the time-averaged power is lower than the peak power (power during transmission) by a quantity known as the duty factor, which is the ratio of the time-averaged power to the peak power.

Signals from Global System for Mobile Communication (GSM) mobile phones and Terrestrial Trunked Radio (TETRA) handsets are also pulsed. In these cases pulsing is introduced to achieve time division multiple access (TDMA), which allows each frequency channel to be used by several other users who take it in turn to transmit. For GSM phones and base stations, a 0.58 ms pulse is transmitted every 4.6 ms, resulting in pulse modulation at a frequency of 217 Hz; pulsing also occurs at 8.34 Hz and at certain other frequencies because of changes in the pattern of bursts produced. For TETRA handsets and mobile terminals, the main pulse frequency is 17.6 Hz. The signals from TETRA base stations are continuous and not pulsed.

Third-generation mobile phones employ a different modulation technique called code division multiple access (CDMA), which allows several users to use the same frequency channel simultaneously by 'labelling' each of their transmissions with a specific coding scheme. Communications are carried out between handsets and base stations using frequency division duplex (FDD) mode, although a time division duplex (TDD) mode is also provided for by the standard. FDD mode uses separate frequency channels for transmissions from the handset and the base station. Each transmission is continuous and so there is no pulsing, although the Adaptive Power Control (APC) updates that occur at a rate of 1500 Hz will cause this component to 'colour' the otherwise broad spectrum of the power modulation. With TDD mode, transmissions are produced in bursts at the rate of 100 Hz and so pulsing would occur at this frequency, in addition to the frequency of the APC.

Another technology that uses pulse modulated signals is Digital Enhanced Cordless Telecommunication (DECT), and is commonly used for cordless phones in homes. A DECT base station on standby (when not making a call) transmits for 0.8% of the time on average. The power during transmission (peak power) is 250 mW and so the average power level is 2 mW (see Section 2.4.3.4).

2.1.3 Signal fading and multipath propagation

Fading is a fundamental characteristic of radio signals in the environment, particularly at relatively high frequencies. Radio signals are reflected from buildings and other structures, leading to multiple paths for a signal to follow from the transmitter to the receiver. The signal contributions arriving by these different paths travel different distances and so arrive at slightly different times. Also, the path lengths differ by amounts that are larger than the wavelength (typically around 10 cm), meaning that the signal contributions can sum to reinforce or diminish at a given position. The consequence of multipath propagation is to create large variations in field strength over distances of the order of the wavelength, and also over short time intervals (fractions of a second). Fading implies that the exposure of a person is generally a dynamic quantity, even if the person is not moving, and the statistical characteristics of the fading in space and time have to be taken into account in how exposure is assessed.

2.1.4 Source-dependent considerations

The properties of an electromagnetic field change with distance from the source. They are simplest at distances more than a few wavelengths from the source. In general, the field can be divided into two components: radiative and reactive. The radiative component is that part of the field which propagates energy away from the source, while the reactive component can be thought of as relating to energy stored in the region around the source. The reactive component dominates close to the source in the *reactive near-field* region, while the radiative part dominates a long way from it in the *far-field* region. Whilst reactive field components do not contribute to the radiation of energy, the energy they store can be absorbed and indeed they provide a major contribution to the exposure of people in the near-field region. The measurement of the reactive components of the field can be particularly difficult since the introduction of a probe can substantially alter the field.

2.1.4.1 Far-field and near-field characteristics

Roughly speaking, distances within about one-sixth of a wavelength ($\lambda/2\pi$) from the source define the reactive near-field region, while distances greater than $2D^2/\lambda$ (where D is the largest dimension of the antenna) define the far-field region. Since D is usually comparable in size to λ (or larger), $2D^2/\lambda$ is roughly comparable to λ (or greater). Distances between $\lambda/2\pi$ and $2D^2/\lambda$ form a transition region in which radiative field components dominate, but the angular distribution of radiation about the source changes with distance. This is known as the radiating near-field region. Since wavelength is inversely proportional to frequency, it varies considerably, from 10 km to a few millimetres over the range of radiofrequencies considered here (100 kHz – 300 GHz). Antennas with a high degree of gain, eg dish antennas, have large radiating near-field regions around them. For frequencies above 300 MHz (or 1 m wavelength) human exposure more usually occurs in the far-field region. A near-field exposure occurs when approaching very close to the source – in particular, for example, with mobile phones and body-mounted devices. This is not the case at lower frequencies.

As already noted, the power density of an electromagnetic wave, S, is equal to the product of the electric and magnetic fields, $S = E\,H$. Since $E = 377H$ beyond the reactive near-field region (assuming the quantities are all expressed in SI units), this becomes:

$$S = E^2/377 = 377H^2 \quad (\mathrm{W\,m^{-2}})$$

Hence $E = 19\sqrt{S}$ $(\mathrm{V\,m^{-1}})$ and $H = 0.052\sqrt{S}$ $(\mathrm{A\,m^{-1}})$

Table 2.1 gives the far-field values of electric field strength and magnetic field strength for power densities from 0.1 to 100 W m^{-2}.

The field structure in the reactive near-field region is more complex than that in the far-field region. Generally, the electric and magnetic fields are not at right angles to each other and they do not reach their largest values at the same points in space, ie they are out of phase. Hence, the simple relation between S, E and H given in Table 2.1 is not obeyed and calculations of energy absorption in tissue in this region are more complicated than in the far-field region.

TABLE 2.1 Examples of far-field (plane-wave) relationships

Power density (W m^{-2})	Electric field strength (V m^{-1})	Magnetic field strength (A m^{-1})
0.1	6.1	0.016
1.0	20	0.052
10	61	0.16
50	140	0.36
100	200	0.51

2.1.5 Exposure to RF fields

People are exposed both at home and at work to electric and magnetic fields arising from a wide range of sources that use RF electrical energy. It should be noted that even at the highest frequency of the range, 300 GHz, the energy quantum, $h\,f$, where h is Planck's constant and f is frequency, is still around three orders of magnitude too small to cause ionisation in matter. This region of the spectrum, together with optical frequencies, is therefore referred to as non-ionising.

In contrast to ionising and ultraviolet radiations, where natural sources contribute the greater proportion of the exposure to the population, man-made sources tend to dominate exposure to time-varying electromagnetic fields over the spectrum shown in Figure 2.1. Over parts of the frequency spectrum, such as those used for electrical power and broadcasting, man-made fields are many thousands of times greater than natural fields arising from either the sun or the Earth (see Section 2.4.1). In recent decades the use of electrical energy has increased substantially for telecommunications purposes and it is clear that exposure of the population in general has increased.

Everyone is exposed continually to low level RF fields from transmitters used for broadcast television and radio, and for mobile communications. Many individuals will also be exposed to low level fields from microwave communications links, radar, and from domestic products, such as microwave ovens, televisions and display screen equipment. Higher exposures can arise for short periods when people are very close to sources such as mobile phone handsets, portable radio antennas and RF security equipment. Some of the sources of electromagnetic fields and the estimated levels to which people are exposed, both at work and elsewhere, are shown in Table 2.2, and details are given in Section 2.4.

Depending on the frequency, output power and the distance from the RF source, direct or indirect coupling into the human body can occur. The result of this coupling can be the induction of fields and, consequently, currents inside the body, or a rise in local or whole-body temperature. A more detailed explanation of the interaction between RF fields and the human body is given in Section 2.2.

For exposure assessment purposes, both physical quantities of the electromagnetic fields (E, H and S) and dosimetric quantities (induced current density or rise in temperature, see Section 2.2.1) are considered. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) provides basic restriction and reference level values based on both physical and dosimetric quantities (see Appendix B). ICNIRP recommends that these restrictions should not be exceeded if the population's health is to be protected from non-ionising radiation.

2.1.6 Measurement of electromagnetic fields

As mentioned earlier, RF sources give rise to electric and magnetic fields and these fields in turn can induce currents or raise temperature inside the human body. It is therefore important to assess the strength of the fields in order to protect the body from harmful effects. The physical quantities (E and H, and to some extent the induced current) can be directly measured outside the body, while the dosimetric quantities (induced current density or rise in temperature) are mainly assessed by indirect means inside the body. Here the methods used to measure electric and magnetic fields outside the human body are explained. Dosimetric quantities are critically assessed in Section 2.3.

There is no single method to evaluate the electric and magnetic field components of an RF source. This is because the type and characteristics of different sources vary greatly. In addition, the magnitude and direction of *E* and *H* vary throughout space and over time. Other factors affecting the measurements of electric and magnetic field strengths are: the frequency and power of the source; the modulation of the signal; the propagation and fading of the signal; the radiation pattern and direction of propagation; the polarisation of the field; and the physical environment. Measurement approaches also differ when the exposure is considered in the near-field or far-field regions.

For all the factors mentioned above, it is important to follow a standard protocol for assessing the electromagnetic field strengths, in particular when the purpose of the assessment is to demonstrate compliance with exposure guidelines. To achieve harmonisation, technical standards are provided by international standardisation bodies such as the International Electrotechnical Commission (IEC), the European Committee for Electrotechnical Standardisation (CENELEC) and the Institute of Electrical and Electronic Engineers (IEEE).

2.1.6.1 Instrumentation

For assessment of RF field exposure, field measurement equipment can be segregated into two types: broadband and narrowband. Broadband instrumentation usually does not provide frequency information and will indicate field strength independently of frequency. Narrowband instrumentation enables assessment of both frequency and field strength information over a selected frequency bandwidth. Spectrum analysers are often used for this purpose and allow the field strength to be measured in a 'window' of a certain bandwidth which is swept across a chosen frequency range. Broadband instrumentation is the most widely used for RF hazard assessment due to its ease of use and portability. Narrowband instrumentation is used where frequency resolution and high sensitivity are required.

Narrowband assessment is undertaken where measurements have to be made on a large number of frequencies with different limits and relatively small signal strengths. Dipoles, loops and horns, which are commonly used for field measurements, are polarisation sensitive and, to assess the total field strength, the antenna used is rotated in three orthogonal directions or orientated for maximum signal strength. Antennas that are large compared to the wavelength are unsuitable for evaluating rapidly changing amplitudes over small regions of space.

Instruments covering a broad band of frequencies for field strength measurements consist of the field sensing probe and signal display equipment. Physically small dipoles are used in electric field probes and physically small loops in magnetic field probes. The detection of RF voltage usually takes place in the probe sensing element and the rectified voltage is processed and displayed by the instrument. Usually probes are designed to indicate either one field component or the sum of all field components. Probes with a single sensor element respond to one field component only and require orientation to obtain the maximum value. Multiple sensor arrangements in suitable configurations can be used to sum the spatial field components and enable measurements independent of polarisation and direction of incidence.

Body currents induced by exposure to RF fields can be evaluated by measuring the current flowing to ground, using either parallel-plate or current transformer approaches. Both techniques allow measurements up to approximately 100 MHz and in some cases personal current meters using transformers have been designed to extend beyond 200 MHz.

TABLE 2.2 Sources of RF fields across the spectrum, with typical field strengths and power densities at accessible locations

Frequency band	Description	Source	Frequency	Typical exposure*	Comments
300 kHz	Medium frequency (MF)	AM radio	415 kHz – 1.6 MHz	450 V m^{-1}	Occupational exposure at 50 m from AM broadcast mast
		Induction heating	300 kHz – 1 MHz	0.2–12 A m^{-1}	Occupational exposure
3 MHz	High frequency (HF)	Short-wave broadcast	3.95 – 26.1 MHz	340 V m^{-1}	Occupational exposure beneath wire feeders of 750 kW transmitter
		EAS	8 MHz	0.2 A m^{-1}	Public exposure close to a tag deactivating system
		PVC welding	27.12 MHz	Body: 100 V m^{-1}, 5 A m^{-1} Hands: 1500 V m^{-1}, 7 A m^{-1}	Operator position close to welding platform of a 10 kW dielectric heater
		Wood gluing	27.12 MHz	170 V m^{-1}	Operator body exposure at 50 cm from a 2 kW wood gluing machine
		CB radio	27 MHz (<10 W)	1 kV m^{-1}, 0.2 A m^{-1}	Public exposure close to antenna of radio
30 MHz	Very high frequency (VHF)	FM radio	88–108 MHz	4 V m^{-1}	Public exposure at 1500 m from a 300 kW FM mast
300 MHz	Ultra high frequency (UHF)	TV, analogue	470–854 MHz	3 V m^{-1}	Public exposure (maximum at ground level) from a high power 1 MW effective radiated power TV transmitter mast
		GSM handsets	900 MHz 1800 MHz	400 V m^{-1}, 0.8 A m^{-1} 200 V m^{-1}, 0.8 A m^{-1}	At 2.2 cm from a 2 W phone At 2.2 cm from a 1 W phone
		GSM base station	900 and 1800 MHz	1 mW m^{-2} (0.6 V m^{-1}, 1.6 mA m^{-1})	Public exposure at 50 m from a mast operating at a maximum of 50 W per channel

Frequency band	Description	Source	Frequency	Typical exposure*	Comments
300 MHz (continued)		Very Small Aperture Terminal (VSAT) Satellite Earth Station	1.5/1.6 GHz	8 W m^{-2}	Main beam direction
		Microwave cooking	2.45 GHz	0.5 W m^{-2}	Public exposure at 50 cm from an oven leaking at BSI emission limit (BSI, 1997)
3 GHz	Super high frequency (SHF)	Radar air traffic control (ATC)	1–10 GHz 2.8 GHz	0.5–10 W m^{-2} 0.16 W m^{-2}	Exposure at 100 m from ATC radars operating over a range of frequencies
		VSAT	4–6 GHz	<10 W m^{-2}	Maximum in the main beam
		Satellite news gathering	11–14 GHz	<10 W m^{-2}	Maximum in the main beam
		Traffic radar	9–35 GHz	<2.5 W m^{-2} <1 W m^{-2}	Public exposure at distances of 3 m and 10 m from 100 mW speed check radar
30 GHz – 300 GHz	Extremely high frequency (EHF)	Transmission digital and analogue video signals	38 GHz/55 GHz	<10^{-4} W m^{-2}	Public exposure at 100 m outside main beam of microwave dish

* These are typical exposures at high frequencies and in the far field of sources where the electric and magnetic field strengths are orthogonal to each other and to the direction of propagation and there is a simple relationship between *E* and *H* that means the wave can be described in terms of its power density. Measurement of either *E* or *H* is sufficient to determine the power density. At lower frequencies and in the near field no such simple relationship exists. Sources that operate at relatively high current and low voltage, eg induction heaters, tend to be defined by measurement of the magnetic field. At frequencies above 30 MHz fields tend to be determined using electric field strength measurements. In situations where people couple closely to the transmitter, such as in the use of mobile phones, the external field strengths are not an appropriate indicator of exposure and comparison with exposure guidelines requires an assessment of the relevant internal dosimetric quantity.

Recent advances have been made in the capability of body-worn instruments for measuring the strengths of environmental RF signals. These personal exposure meters (PEMs) can now be regarded as sufficiently robust and reliable for use in studies of exposure trends related to people's health. Detection thresholds on the most sensitive instruments are around 1% of the ICNIRP occupational reference level (ICNIRP, 1998). However, care is required in interpreting the readings from the PEMs and these have to be treated appropriately when developing exposure metrics in studies (Mann, 2010). Also, the field strength at the body surface is heavily perturbed and different from the field strength that would be found at the same location in the absence of the body. Care is therefore required in the interpretation of the readings from body-worn instruments and a rigorous calibration should take account of the field perturbation by the body. The current generation of PEMs responds to the peak power of pulse modulated (TDMA) signals and this should be taken into account so that the contribution of DECT, GSM uplink and Wi-Fi to time-averaged exposure is not overestimated.

2.2 Interaction Mechanisms between RF Fields and the Body

2.2.1 Direct and indirect effects

As for all electromagnetic radiation, high frequency electromagnetic fields carry energy. When the body is exposed to radio waves, some of the energy is absorbed from the waves, a direct effect which leads to heating of the body tissues (World Health Organization, 1993). Contact with a radio antenna or metallic conductor placed in an RF field can lead in some circumstances to electric shock or burn, indirect effects that result from current flow in the body tissues (Chatterjee et al, 1986). Shock is related to electrostimulation of tissues and burn occurs due to intense and rapid localised heating.

At frequencies below 100 kHz, the physical quantity identifiable with most biological effects is the electric field strength in tissue, which is related to the current density. However, at the higher (RF) frequencies considered here, the rate at which the body is heated is a more appropriate measure to assess the exposure. The absorption of energy from radio waves causes molecules to vibrate, which in turn leads to heating of body tissues. This heating is governed by a quantity known as the specific energy absorption rate (SAR), with units of watts per kilogram (W kg^{-1}). The SAR is derived from the square of the (instantaneous) electric field strength, *E,* in tissue:

$$\mathrm{SAR} = \frac{1}{2}\frac{\sigma}{\rho}E^2$$

where σ and ρ are the conductivity (in siemens per metre, S m^{-1}) and the density (kg m^{-3}), respectively, of the tissue of interest. For a sinusoidally varying electric field, the factor of ½ may be omitted and the rms (root mean square) value of the field substituted in this equation.

The SAR provides a measure of the power absorbed from the radiation per kilogram of body tissue. It is a measure of the energy absorption inside the body and is often used as a proxy for the amount of heating or temperature rise in the body. The SAR provides the link between exposure to an external RF field, whose strength is quantified in terms of power density, and temperature rise inside the body. The SAR cannot be measured easily in a living human and is usually estimated from simulations using experimental or computer-based models of the human body (see Section 2.3).

Contact with either a transmitting radio antenna or a metallic conductor that is radiating in an RF field can lead to electric shock or burn. Electrical burns can be much deeper than burns that result from contact with hot objects and they can occur at points where current exits the body as well as where it enters. High RF voltages can build up on RF antennas and, unless they are well grounded, a surge of energy can occur at the point of contact, causing a shock and/or burn as energy flows through the body to ground. A similar effect can occur through contact with any ungrounded metal objects such as ladders or handrails that are absorbing and re-radiating energy in an RF field. The main factors that determine the potential for burn or shock are the power density and frequency of the radio waves, the grounding conditions, whether the structure has resonant dimensions and how much of the body is in contact with the conductor. Whilst constituting a hazard for those working near antennas, in medicine such contact burns are usefully applied for electrosurgery (see Section 2.4.5.2).

2.2.2 Factors affecting human exposure

2.2.2.1 Power density

Power density is one of the most important factors that influence the amount of energy absorbed in the body. It depends primarily on the output power of the radio transmitting device and the configuration of the transmitting antenna. As the distance from an antenna increases, the radio waves spread out and the power density ultimately decreases according to the inverse square law. The power density close to antennas varies in a complicated way with distance and is generally less than would be predicted from inverse square law considerations.

2.2.2.2 Distance from source

The potential for people to be exposed depends not only on the strength of the electromagnetic fields generated but also on their distance from the source and, in the case of directional antennas such as those used in radar and satellite communications systems, proximity to the main beam. High power broadcast and highly directional radar systems do not necessarily present a source of material exposure except to specialist maintenance workers or engineers. Millions of people, however, approach to within a few centimetres of low power RF transmitters such as those used in mobile phones and in security and access control systems where fields can give rise to non-uniform, partial-body exposure. The field strengths typically decrease rapidly with distance from a particular source according to the inverse square law.

2.2.2.3 Tissue type

When radio waves are incident on a material, three main processes occur, namely reflection, absorption and transmission. The extent to which each of the processes occurs depends on the type of material and its thickness in relation to the frequency of the waves. When radio waves are incident on metal surfaces, reflection is the dominant process; some absorption will occur and there will be near-zero transmission. In the case of biological materials, there will be some reflection and the relative proportions of absorption and transmission will depend on the thickness of the material. Radio waves at telecommunications frequencies generally penetrate into the body tissues for a few centimetres and tend to be absorbed. In being absorbed, they give up their energy to the body tissues and this adds to the energy being produced by the body's metabolism.

The SAR is different in different parts of the body because different tissues in the body have different electrical properties – for example, some tissues are better electrical conductors than others. On exposure to radio waves, energy is not deposited uniformly throughout the body, even if the incident radiation has uniform power density. When radio waves are incident on a homogeneous slab of material, the proportion of energy transmitted decreases exponentially with the thickness of the slab. Consequently more energy will be absorbed in the material towards the front surface facing the incoming waves than towards the rear.

2.2.2.4 Frequency

Radio waves become less penetrating into body tissues as the frequency increases. The electric field component of a wave penetrating into a material reduces to 37% of its initial value after a distance known as the skin depth (see Figure 2.2). The skin depth of tissues depends on their electrical permittivity and conductivity. The general expression for skin depth for poor conductors (non-metals) at high frequencies is as follows (Griffiths, 1989):

$$\delta = \frac{1}{\omega}\left\{\left(\frac{\mu\varepsilon}{2}\right)\left[\left(1+\left(\frac{\sigma}{\omega\varepsilon}\right)^2\right)^{1/2}-1\right]\right\}^{-1/2}$$

where ω is the angular frequency and ε, σ and μ are the permittivity, conductivity (S m^{-1}) and magnetic permeability of the materials, respectively. In biological materials, μ in tissues has essentially the same value as that of free space, $4\pi \times 10^{-7}$ H m^{-1}.

The skin depths of tissues with low water content such as fat and bone are greater than those with higher water content such as muscle and skin. Table 2.3 provides typical skin depths for low and high water content tissues at selected frequencies.

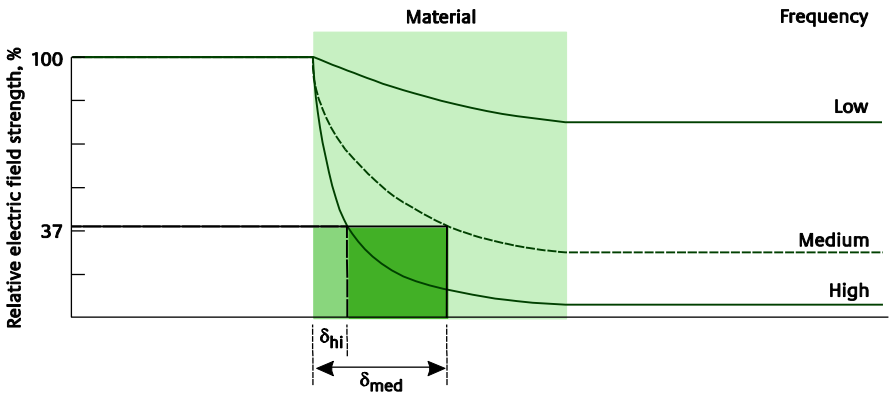

FIGURE 2.2 Absorption of energy in biological material showing how the skin depth decreases with increasing frequency. Reflection of the incident radiation is assumed negligible here. The skin depth at high frequency, δ_{hi}, is less than that for medium frequency, δ_{med}

TABLE 2.3 Conductivity, σ, and skin depth, δ, of low and high water content tissues at selected radiofrequencies*

	Tissues with low water content				Tissues with high water content			
	Fat		Bone		Muscle		Skin	
Frequency	σ(S m^{-1})	δ(mm)	σ(S m^{-1})	δ(mm)	σ(S m^{-1})	δ(mm)	σ(S m^{-1})	δ(mm)
150 MHz	0.04	366.1	0.07	301.0	0.7	67.2	0.5	85.0
450 MHz	0.04	301.9	0.10	202.2	0.8	51.3	0.7	52.9
835 MHz	0.05	252.0	0.14	139.5	0.9	43.5	0.8	41.5
1.8 GHz	0.08	157.1	0.28	66.7	1.3	29.2	1.2	28.3
2.45 GHz	0.10	117.1	0.39	45.8	1.7	22.3	1.5	22.6
3 GHz	0.13	93.6	0.51	35.2	2.1	18.0	1.7	18.9
5 GHz	0.24	49.4	0.96	17.7	4.0	9.3	3.1	10.5
10 GHz	0.58	19.6	2.13	7.3	10.6	3.3	8.01	3.8

* Skin depth data are calculated based on permittivity and conductivity of tissues taken from Gabriel et al (1996c). The formula used for calculation of skin depth is taken from Griffiths (1989).

At 100 MHz, the frequency used for FM radio, bone and fat are poor conductors so they absorb energy weakly and the RF signal penetrates deeply into these tissues. High water content tissues such as muscle and skin, however, are good conductors and these will absorb more strongly (see Table 2.3). At higher frequencies, the skin depth decreases, therefore absorption in the body becomes increasingly confined to surface tissues. At mobile phone frequencies, of the order of 1 GHz or so, the skin depth in the brain is a few centimetres. Consequently most of the energy from the incident radiation is absorbed in one side of the head within a few centimetres of the handset. At 10 GHz the skin depth in most tissues is a few millimetres so almost all the energy will be absorbed in the skin and other surface tissues and there will be very little penetration into the deeper tissues of the body.

Body resonance

The human body is particularly effective at absorbing radio waves under conditions of resonance, which occurs when the wavelength of radiation is comparable with the dimensions of the body (Dimbylow, 1997). At frequencies above about 1 MHz, the orientation of the body with respect to the incident field becomes increasingly important. The body then behaves as an antenna, absorbing energy in a resonant manner that depends upon the length of the body in relation to the wavelength. The frequency of resonance depends on a number of factors such as the height of the individual, their posture, how easily currents can flow from the feet to the ground, the conductivity of the earth beneath their feet, and the polarisation or orientation of the electric field with respect to the body. For standing adults, the peak of

this resonant absorption occurs in the frequency range 70–80 MHz if they are electrically isolated from the ground and at about half this frequency if they are electrically grounded. Smaller adults and children show the resonance characteristic at higher frequencies (Figure 2.3). In addition to whole-body resonance, it is possible for partial-body resonances to occur, eg in the limbs.

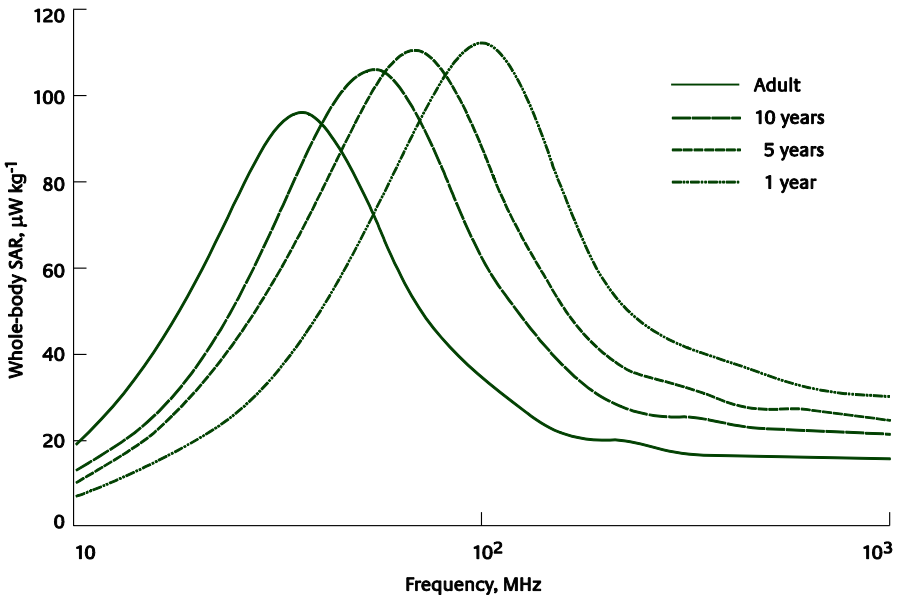

FIGURE 2.3 Whole-body SAR produced in humans of different ages arising from exposure to a uniform electric field strength of 1 V m^{-1}, assuming good contact with the ground

2.2.2.5 Volume and duration of exposure

In general terms, exposure standards that aim to protect against the harmful effects of heating will tend to average the field levels over the entire body. This is based on the assumption that the body has an effective means of controlling core temperature, and that local temperature equilibration occurs through heat conduction and convection (including blood flow). If only part of the body, such as an arm or leg, were to be exposed to an RF source, it would absorb much less energy from a given field strength than if the entire body were to be exposed. Exposure guidelines, as those given in Appendix B, tend to permit higher exposures in small volumes of tissue in the head, body and limbs than are allowed when exposure is averaged over the whole mass of the body. Some organs, such as the eyes, are particularly vulnerable to heating.

The duration of exposure is another important factor in determining the amount of heating of the body. In general, the human body can only survive very-short-term exposure to extremes of heat or cold, and most standards that aim to protect against the adverse effects of heating tend to average the exposure over a certain time interval, typically of the order of several minutes or so, to allow for the thermal equilibrium time for variable and continuous exposures (NRPB, 2004a,b).

2.2.3 Mechanisms for interaction with cells and living tissue

The manner by which exposure to RF fields may give rise to a response in living material has led to the consideration of a wide range of mechanisms that may underlie such a response. In a careful quantitative review of potential mechanisms, Sheppard et al (2008) have demonstrated that the dominant mechanism is dielectric relaxation and ohmic loss, giving rise to an associated increase in temperature, and that most other possible mechanisms, many based upon direct coupling to specific modes in molecules, cells or tissues, are implausible as means for independent energy deposition. Most potential candidates may be excluded because, to be biologically effective, they would be accompanied by temperature rises that would overwhelm any other biological response. Resonant molecular or sub-molecular vibrational modes are precluded because they are too heavily damped, whilst other possible mechanisms involve energy that is far weaker than thermal background. Conditions where an RF field interacts directly with charges or dipoles require field strengths that are greatly in excess of those that would cause dielectric heating.

Dielectric heating has been described in an extensive literature. Any molecule with a permanent dipole moment, when acted on by an alternating electric field, is forced to oscillate. This oscillation is hindered by the molecular environment and intermolecular forces, resulting in dielectric loss and the transfer of energy into heat. Dielectric dispersion, the dependence of the dielectric constant on frequency, arising from the change in phase between the oscillation and the applied field, gives rise to frequency-dependent energy deposition and hence temperature rise.

The energy deposition depends upon the local dielectric properties of the cells or tissue, and upon the local field properties. In principle, therefore, it would appear possible to create very high spatial gradients for heat generation within tissue, either because of localised microfield structure or because of local enhancements of dielectric property. Nevertheless, even if such unlikely conditions were to occur, thermal diffusion in tissue prevents the creation of high spatial gradients on the cellular scale, and any tendency to create localised hotspots cannot occur.

Of specific interest in the context of the safety of mobile phones and other communications devices is the potential that non-linear demodulation of a lower, modulating or pulsing, frequency may create a low frequency electromagnetic field that may directly affect tissue. However, irrespective of demodulation efficiency, the maximum demodulated power is infinitesimally small, at most 77 dB below the carrier, and more probably 90–100 dB below. For example, the demodulated power at 16 Hz from an incident field of 100 V m^{-1} at 900 MHz would be only about 1 pW. Any demodulated signal of biological significance would be accompanied by a carrier frequency of thermally destructive power. However, it is accepted that second-harmonic generation is a necessary and sufficient condition for demodulation. Kowalczuk et al (2010) used a doubly resonant cavity to expose a wide range of cell or tissue samples to a low level continuous wave field at the resonant frequency of the loaded cavity (around 890 MHz) and sought evidence of the generation of the second harmonic (also reported by Davis and Balzano, 2010). Both cancer and non-cancer cell lines were used, as were cells and tissues previously reported to exhibit responses to weak RF fields. No evidence of non-linear energy conversion by any of the samples was found. Overall, these results do not support the possibility that living cells possess the non-linear properties necessary to

demodulate RF energy. Consideration may also be given to naturally occurring endogenous fields associated with wound-healing, development and other time-varying processes of living structures. This has led to the conclusion that there are no biological structures capable of supporting induction at radiofrequencies, and that RF fields cannot couple to the biological systems that respond to endogenous DC or extremely low frequency (ELF) fields by mechanisms involving electric potential at the cell membrane, and that, even in the ELF band, the demodulated signal would be irretrievably lost in membrane noise.

Spin-correlated interactions between radical pairs, and their dependence on magnetic field strength, have been suggested as a mechanism for direction-finding in birds. Behavioural effects in birds exposed to magnetic fields at frequencies below 100 MHz have been attributed to changes in photochemical reactions from this mechanism, and these observations have been supported by associated theoretical work. Broadly, it has been concluded that magnetic field effects on the radical pair mechanism are not a general feature of biochemistry above 10 MHz, and especially not above 100 MHz.

Under conditions of high peak power, a pulsed microwave-stimulated auditory response occurs (Lin and Wang, 2007). Transient localised heating, and associated tissue expansion, generates an acoustic wave that stimulates the ear directly. Peak power densities of a few kilowatts per metre squared are required to exceed the threshold acoustic pressure for hearing in humans (20 mPa).

In conclusion, the evaluation of a wide range of possible mechanisms suggests that dielectric heating, with its associated temperature rise in tissue, is the dominant, and perhaps the only, mechanism needing serious consideration over the RF spectral range. This being so, the following brief exploration of the thermal behaviour of cells, and particularly their response to mild, sub-lethal, heat stress, is included.

2.2.4 Cellular responses to mild heat stress

There is a considerable literature on the toxic effects on cells of severe heat shock, most notably cell cycle arrest, apoptosis and cell death resulting from protein denaturation. Such conditions, associated with increases in cell temperature above 6°C, are of minimal concern here since low level RF field exposure is being considered here, for which any increase in cellular or tissue temperature is more probably of the order of 1°C. It has been commonly accepted that, when reporting biological effects of RF fields, such conditions may be labelled as 'athermal' or 'non-thermal', so setting a hypothesis for cell response that is entirely electromagnetic.

Human body temperature is exquisitely finely controlled, for which a normal population range of core temperature is accepted for working purposes as being 37±0.5°C. The control tolerance for an individual may be much smaller than this, however, with an average individual diurnal variation as small as +0.1°C and −0.4°C (Mackowiac et al, 1992), thermoregulation apparently allowing greater tissue cooling than heating. Changed conditions, such as those arising during exercise, or during the body's normal response to infection, cause increases of a few degrees, but a sustained total body temperature increase of about 4°C or more leads to death.

It is therefore not surprising that cells respond to changes in the temperature of their environment. A locally induced increase in temperature, even of less than 1°C, alters the cell dynamics. Park et al (2005) have reviewed cellular thermal responses to mild heat shock – a summary is presented in Table 2.4.

TABLE 2.4 Some known cellular responses to mild heat stress

Response	Comments
Altered membrane fluidity	May be a thermosensor
Denaturation of polypeptides	Only when newly formed
HSF1 activation	Rac1 dependent
HSP synthesis	Rac1 dependent
Cell proliferation	Depending on cell type
Differentiation	Depending on cell type
Acquisition of thermotolerance	–
Signalling pathways activated	Including Ras/Rac1, PI3K-AKT, ERK1/2, SAPK/JNK, p38MAPK

A change in temperature alters the fluidity of the plasma membrane, changing the physico-chemical environment of membrane proteins, giving a direct means for thermosensing. Membrane-bound proteins such as the Ras superfamily initiate a variety of intracellular biochemical pathways that operate as the environmental conditions, including thermal conditions, change. Mild heat shock appears to affect only newly formed polypeptides. In cells, prefolded nascent polypeptides are more sensitive to heat stress than fully folded proteins. Ion channels such as sodium/potassium and calcium ion flux in mammals are also highly sensitive to alterations in ambient temperature, offering another means of thermosensing by the cell.

The cellular response to changes in temperature depends on cell type. However, under all conditions, the cellular biodynamics are finely tuned to the thermal environment, and changes in local temperature may be expected to alter the activity of cells in a variety of unknown and complex ways.

2.3 RF Dosimetry

The exposure to the body from an RF field is determined by the strength of the electric and magnetic fields inside the body, which are different from those outside. It is not usually possible, however, to measure these internal fields directly. Dosimetry is the term used to describe the process of determining internal quantities (dosimetric quantities) relating to exposure in tissues, such as the electric field strength, induced current density and energy absorption rate, from external fields (physical quantities). The role of dosimetry is to evaluate the induced electric fields in the body, often in terms of the derived dosimetric quantity SAR (see Section 2.2.1), and to correlate them with the biological effect of concern. There are different dosimetric methods available; both experimental and numerical dosimetry techniques can be used to calculate internal fields for a fixed body and source geometry.

2.3.1 Dosimetric assessment of SAR

There are several techniques to assess the SAR inside the body exposed to RF fields. Both experimental and numerical techniques have been well developed and documented. Depending on the exposure scenario and the position of the RF field source with respect to the body, whole-body SAR or localised SAR values can be obtained and compared with restrictions in exposure guidelines (Appendix B).

The SAR is usually averaged either over the whole body or over a small sample volume or mass of tissue. The averaging mass serves two purposes: firstly, it provides a definition of SAR that is robust and not overly sensitive to slight changes in exposure set-up; secondly, it takes into account the spatial dispersion of the deposited energy which is provided by heat transfer mechanisms (NRPB, 2004b). The SAR depends mainly on the geometry of the part of the body exposed and on the exact location and geometry of the source.

For frequencies up to a few gigahertz, as used in wireless communications, the SAR is normally averaged over either 1 or 10 g. The key point is that the averaging mass should be that which maximises the correlation with local temperature elevation (Hirata et al, 2008). The dominant factors influencing the correlation between mass-averaged SAR and temperature elevation are the thermal diffusion length in the biological tissue, which largely depends on the blood perfusion rate, and the penetration depth of the radio waves (Hirata and Fujiwara, 2009). One of the rationales for the 10 g averaging mass is based on the temperature elevation in the brain and eye lens, which has been computed with anatomically based head models. The choice of averaging mass is clearly most important for highly localised exposure. At the other extreme, a uniform SAR distribution gives the same average whatever mass is used. The greatest differences between 1 and 10 g values are expected for situations of near-field exposure to an antenna such as a mobile phone (NRPB, 2004b). Also, these averaging masses may not be appropriate for estimating the power deposited close to medical implants where high SAR gradients can occur (Mattei et al, 2009).

2.3.1.1 Experimental evaluation of SAR

There are no accurate methods to measure the internal induced electric field strength inside a human body non-invasively. Therefore a phantom is used to replicate the human head or body instead. The experimental set-up also consists of other components such as source emulators, electric field sensors, scanning system, remote control and data recording.

The phantom should have electrical properties similar to those of the exposed tissues. Various fluid and solid materials have been developed to match the electrical properties of different human tissues at a wide range of frequencies. Small electric field probes are used to measure the electric fields inside the physical phantom, while minimising the changes in the fields produced by the presence of the probe. These procedures have been standardised for compliance testing of different devices to RF safety guidelines that require high reproducibility (IEEE, 2003; IEC, 2005).

Physical models (phantoms)

A phantom designed to replicate the human body should exhibit similar interaction mechanisms with RF fields as would the real human body. So the phantom must have similar electrical properties to those of the human body. Several liquids, gel and solid types of phantoms have been developed to be suitable

for RF dosimetry (IEEE, 2003; IEC, 2005). Liquid/gel phantoms are easier to develop and more suitable to scan when an electric field probe is inserted in them.

Different organic and inorganic chemicals are used when developing a recipe that is optimised for a given tissue at a given frequency. Electrical properties are frequency dependent and vary for different types of tissue. For the sake of harmonisation, specific recipes matching the target electrical properties of tissue at each frequency are recommended by standardisation bodies for compliance tests (IEC, 2005). Attempts have also been made to develop broadband recipes that simulate the electrical properties of tissues over a wide range of frequencies (Gabriel, 2007).

Due to practical difficulties in developing heterogeneous phantoms, the standard head/body phantoms recommended for compliance tests are developed based on homogeneous tissue (IEEE, 2003; IEC, 2005).

Experimental exposure systems

Experimental arrangements are used to assess the effects of exposure to RF fields of live animals/humans (*in vivo* conditions) as well as excised tissues (*in vitro* conditions) and cell cultures. Purpose-made exposure systems provide a highly defined electromagnetic field exposure to the sample under study, avoiding interference from other sources of exposure. These systems are usually controlled environments in terms of temperature and from physical, chemical and biological agent contaminants. Suitable experimental arrangements for the laboratory assessment of RF field exposure have been widely reported (Guy et al,1999; Kuster and Schönborn, 2000; Schuderer and Kuster, 2003; Zhao, 2005; Zhao and Wei, 2005).

Some exposure systems are designed specifically for studies involving cell cultures and excised tissues. Examples of these systems are transverse electromagnetic (TEM) cells, RF anechoic chambers, radial transmission line (RTL), waveguides and wire patch cells (Laval et al, 2000; Pickard et al, 2000; Schönborn et al, 2000; Ardoino et al, 2004; Schuderer et al, 2004a,b; Calabrese et al, 2006; Ji et al, 2006; De Prisco et al, 2008).

Whole- and partial-body exposure systems are also available for live animal studies to assess the effect of exposure from near-field and far-field sources. These systems are based on similar principles to the *in vitro* systems; in addition, they need to consider the requirements of live animals and variation caused by their movement. Radial waveguides, TEM cells and anechoic and reverberation chambers are examples of whole-body exposure systems (Chou and Guy, 1982; Chou et al, 1985; Balzano et al, 2000; Wang et al, 2002; Wilson, 2002; Ardoino et al, 2005; Tejero et al, 2005; Faraone et al, 2006; Kainz, 2006; Schelkshorn et al, 2007; Jung et al, 2008). Partial-body exposure systems such as carousel and loop antennas consist of local devices targeting an animal's brain/head area (Chou et al, 1999; Swicord et al, 1999; Leveque et al, 2004; Schönborn et al, 2004; Lopresto et al, 2007; Wake et al, 2007).

Although the majority of the experimental dosimetry studies are carried out on animals, human exposure systems provide a useful tool to assess the exposure of volunteers to RF fields. For partial-body exposure scenarios, commercially available telecommunications devices are usually modified so that they can be worn for the duration of the exposure without interruption, being isolated from other sources of exposure and also providing a blinded exposure environment (Loughran, 2005, 2008; Regel et al, 2006; Haarala et al, 2007; Krause et al, 2007; Boutry et al, 2008). Specially developed antenna systems have also been

produced that simulate the exposure from commercially available telecommunications devices. These can be worn for long exposure durations during a whole day or overnight (Bahr et al, 2006). Some studies also involve whole-body exposure conditions where a volunteer is placed in an anechoic chamber at a certain distance from a base station antenna for the duration of exposure (Regel et al, 2006).

2.3.1.2 Numerical evaluation of SAR

The numerical techniques use anatomically realistic computer models of typical people or animals, together with values of the electrical properties for the different simulated tissues in the models. The distribution of the induced electric field and the resulting SAR values in the body can be estimated from Maxwell's equations using different mathematical methods such as finite difference time domain (FDTD) calculations (Taflov and Hagness, 2005).

Numerical models

The computational methods of exposure evaluation rely upon the use of voxel models of the animal/human body that are developed from medical images from magnetic resonance imaging (MRI) and X-ray computed tomography (CT). Each voxel has a defined volume of a few cubic millimetres; up to several million voxels can be defined for a typical model of a human head or body. The model is completed by assigning appropriate dielectric properties and density values for different body tissues. The availability of more advanced computers has made it possible to develop numerical models with very fine voxel resolutions (1 mm) and up to 50 defined tissue types.

Many different numerical models of head and body phantoms have been developed so far (Gandhi and Furse, 1995; Dawson et al, 1997; Dimbylow, 1997, 2005a,b; Mason et al, 2000; Nagaoka et al, 2004; Lee A et al, 2006; Lee C et al, 2006). The differences between numerical models are mainly due to the average size and weight values used for a typical human body.

Although most of the numerical models aim to replicate a typical human body, some recent models have been developed to simulate various body postures as well as different sizes including those of children, pregnant women and fetuses (Findlay and Dimbylow, 2005; Dimbylow, 2006, 2007; Wang et al, 2006a; Cech et al, 2007; Kainz et al, 2007; Nagaoaka et al, 2007; Christ et al, 2008; Findlay et al, 2009; Lee et al, 2009).

2.3.2 Dielectric properties of tissues

Biological tissues contain free and bound charges, including ions, polar molecules and an internal cellular structure. When an external electric field is applied to tissues, the electric charges are shifted from their original position, causing polarisation and ionic drift. The net result would be the establishment of displacement and conduction currents. Dielectric properties of tissues (permittivity and conductivity) are measures of these effects which determine the interaction of electric fields with the human body. The availability of dielectric data for different tissues is vital for both experimental and computational dosimetry techniques.

Dielectric properties of tissues are frequency dependent. The dielectric spectra of tissues consist of three main dispersions predicted by known interaction mechanisms. At low frequencies alpha dispersion is

associated with ionic diffusion processes at the site of the cellular membrane. At intermediate frequencies (kilohertz region), the polarisation of the cellular membrane, which is a barrier to the flow of ions between the intracellular and extracellular media, is the main cause of beta dispersion. Finally, gamma dispersion at microwave frequencies is mainly due to the polarisation of water molecules inside the tissues. Dielectric properties of tissues vary according to the physiological state of the tissue, the intactness of the cellular membrane and the water content of the tissue. Alpha and beta dispersions would have importance in the present context only if demodulated low frequency signals were to be associated with a mechanism with a biological outcome.

Several techniques exist to assess the dielectric properties of biological tissues. One widely used procedure involves the use of coaxial contact probes and measurement of the reflection coefficient, followed by numerical deduction of the dielectric properties of the sample based on a theoretical model of the impedance of the probe (Gabriel, 2000a).

The early literature on the dielectric properties of body tissues has been reviewed by Gabriel C et al (1996) who also produced their own data (Gabriel S et al, 1996a) and developed parametric models to reproduce the relative permittivity and conductivity as a function of frequency (Gabriel S et al, 1996b). This database has been used extensively in dosimetry studies during the last decade. Recently, as part of the Mobile Telecommunications and Health Research (MTHR) Programme, new dielectric data have been collected from live porcine tissues, which are thought to be a good animal substitute for human tissue. This provides an added dimension to the comparison with the data from the 1996 database that were mostly derived from measurement on excised ovine tissue (Peyman and Gabriel, 2003; Peyman et al, 2007).

Until recently, the literature data consisted mostly of dielectric properties of tissues from mature animals with a few older studies reporting systematic changes in the dielectric properties of ageing brain tissues (Thurai et al, 1984, 1985). More recent studies looked at the variation of dielectric properties of several rodent, porcine and bovine tissues as a function of animal age and found similar trends (Peyman et al, 2001, 2007, 2009; Peyman and Gabriel, 2003; Schmid and Überbacher, 2005). The results of these studies generally showed a significant decline with age in both permittivity and conductivity of tissues with high water content such as long bone, skull, skin, muscle and bone marrow. At microwave frequencies, the observed variations are mainly due to the reduction in water content of tissues as animals age. In the case of brain tissue, increased myelination and decreased water content as a function of age are suggested to be the reason for the drop in permittivity and conductivity values of white matter and spinal cord as animals age, as observed by Schmid and Überbacher (2005) and Peyman et al (2007). The largest variation in the dielectric properties as a function of age is observed in bone marrow tissues due to the transformation of high water content red marrow to high fat content yellow marrow as the animal grows (Peyman et al, 2009).

These studies raise a question on the extent to which the variation of dielectric data as a function of age may affect the result of dosimetry in animal exposure studies and, consequently, the possible implications for the exposure of children. Recently, the dielectric spectra of ageing porcine tissues have been parameterised to allow their use at any frequency or multiple frequencies within the confines of the models of children (Peyman and Gabriel, 2010).

2.3.3 Age dependence in dosimetry studies

Until recently, the majority of dosimetric studies were focused on models of human adults. The significant rise in the use of telecommunications devices amongst the young has led to calls for research into the differences in the exposure of children and adults.

The two main factors differentially affecting the exposure of children and adults are the physical size of the body and the differences in the dielectric properties of tissues as a function of age. The earlier dosimetric studies used adult human models and scaled them down linearly to a child's size with the dielectric properties of adult tissues (Gandhi et al, 1996; Gandhi and Kang, 2002; Wang and Fujiwara, 2003). Later studies developed children's head models from magnetic resonance images to obtain a more realistic assessment of the exposure of children (Schönborn et al, 1998; Anderson, 2003; Christ et al, 2005; Dimbylow and Bolch, 2007; Lee et al, 2009). It was noted above that there is a significant decline in both permittivity and conductivity at microwave frequencies due to the decrease in water content of tissues as the animal grows older (Thurai et al, 1984, 1985; Peyman et al, 2001, 2007; Peyman and Gabriel, 2003; Schmid and Überbacher, 2005). In 2001, Peyman et al reported a database of dielectric properties of rat tissues as a function of age. Later, a more comprehensive database became available of porcine tissues at three main developmental stages of growth, as a more suitable animal substitute for human tissues (Peyman et al, 2005, 2007, 2009). In addition, parametric models have been developed to reproduce relative permittivity and conductivity as a function of frequency for several tissues as a function of age (Peyman and Gabriel, 2010). Most recently, Peyman and colleagues have measured the dielectric properties of pregnancy-related human tissues such as placenta and amniotic fluid as well as of rat fetal tissues (Peyman, 2011; Peyman et al, 2011a).

2.3.3.1 Head exposure

Gandhi et al (1996) were amongst the first to use a linearly-scaled child head model with adult dielectric properties to compare the exposure of adults and children to mobile phones. They found a deeper penetration and significant increase (50%) in the maximum 1 g averaged SAR in the child's head. Schönborn et al (1998) used a scaled adult model and two realistic child head models using MRI data for similar comparisons, but did not report any significant differences between the exposure in adults and children. Attempts to repeat the above studies by other researchers have produced contradictory results, in particular when different normalisations were performed for output power or antenna current. In addition, differences in averaging procedures used for spatial peak SAR caused the need for further studies (Wang and Fujiwara, 2003; Bit-Babik et al, 2005). Some of the subsequent studies reported a higher SAR in the head models of children (Anderson, 2003; Fernández et al, 2005; Wiart et al, 2008), while others found no significant difference in SAR between adult and child models or could not reach a conclusion (Martínez-Búrdalo et al, 2004; Christ and Kuster, 2005; Keshvari and Lang, 2005; Fujimoto et al, 2006; Wang et al, 2006a,b; Lee et al, 2007; Wiart et al, 2007).

In 2006, a large study was carried out involving 14 laboratories to study the differences in SAR for adults and children who were exposed to mobile phones (Beard et al, 2006). A single protocol was followed by all the participants using the Specific Anthropomorphic Mannequin (SAM) head model designed for mobile phone compliance measurements, an anatomically realistic adult head model and a scaled 7 year

old head model. Two operating frequencies of 835 and 1900 MHz and two phone positions, denoted *cheek* and *tilt,* were considered. In addition, the SAR values were normalised to both the antenna input power and the feed point current. The results revealed a reverse effect at 1900 MHz, where the peak 1 g SAR values in the head of the adult model were higher in both phone positions and for both normalisation scenarios. At 835 MHz however, the SAR values were higher in the child model than in the adult model, in particular in the tilt position and when normalising to antenna current. Hadjem et al (2005a,b) found that brain exposure depended on the morphological features and, more recently, Wiart et al (2008) reported higher exposure of the cerebral cortex in children than in adults.

In summary, the overall evidence from studies on the exposure of children's heads does not draw a consistent picture to support the assumption that the SAR level in a child's head is higher than that for an adult. This arises because the results are highly model-specific and power absorption in the head is influenced by many factors. It is also notable that even the higher SAR values reported in some of the studies for children's heads, are below the 2 W kg^{-1} ICNIRP restrictions (see Appendix B).

2.3.3.2 Whole-body SAR

It is established that the whole-body SAR depends on the size of the body, and this was considered when the ICNIRP reference levels were set. Starting from the premise that an SAR of 4 W kg^{-1} for a healthy adult is equivalent to a 1°C temperature rise, there is a 50-fold reduction in deriving the basic restriction on whole-body SAR for the general public (0.08 W kg^{-1}). In principle, this reduction factor should be sufficient to take into account all the variations due to different dosimetric factors, including body size. However, it is now apparent that the basic restriction on exposure for small children under worst-case exposure conditions may be slightly exceeded at the public reference level (NRPB, 2004a,b). This is supported by studies carried out for phantoms modelling children in the age range from 9 months to 11 years, which found that whole-body SAR restrictions are exceeded in two frequency ranges: 45–170 and 1400–4000 MHz (Dimbylow, 1997, 2002; Tinniswood et al, 1998; Mason et al, 2000; Bernardi et al, 2003; Wang et al, 2006a; Dimbylow and Bolch, 2007). Dimbylow (2007) reported the highest ratio of 0.83 between the calculated field level and the reference level at 1.6 GHz using a phantom of a 9 month old baby. Higher SAR levels were also observed in phantoms modelling children aged 3, 5 and 7 years in the frequency region around 2 GHz (Neubauer et al, 2006, 2009; Hirata et al, 2007; Conil et al, 2008). In addition, considerations were given to the fact that heterogeneous exposure might lead to somewhat worse conditions and that horizontally polarised electric fields lead to higher exposure above 2 GHz compared with vertically aligned fields (Hadjem et al, 2007; Vermeeren et al, 2007; Hirata et al, 2009; Kühn et al, 2009a,b).

In summary, almost all of the studies conducted on whole-body SAR (from 1997–2009) reported higher exposure for child models than adults in two frequency regions (around 100 MHz and 1–4 GHz). They also showed that, within these specific frequency ranges, exposure at the reference levels can exceed the basic restrictions by up to 40% under worst-case conditions, which means that for children or small persons (shorter than 1.3 m) the reference levels of the ICNIRP recommendations may not be conservative estimates. A recent review by ICNIRP (2009) acknowledges the outcome of the above studies and concludes that this increase in SAR is negligible compared with the large reduction factor of 50 applied in deriving the basic restriction for the general public.

2.3.3.3 Exposure of the fetus

Dimbylow (2007) reported that the whole-body SAR is lower in pregnant women compared with non-pregnant women and that the difference increases with gestation period. The study found that the maximum whole-body SAR for the fetus occurs at 70 MHz for isolated-from-ground conditions and reported lower SAR levels for the fetus compared with the mother. The results also confirmed that for plane-wave exposure the ICNIRP reference levels are sufficient to guarantee compliance with the basic restriction. Two more recent studies reported similar results and confirmed compliance with the ICNIRP guidelines (Nagaoka et al, 2007; Togashi et al, 2008). Kawai et al (2006) developed a model of the abdomen of a pregnant woman based on MRI scans of Japanese women in the late pregnancy period. They then assessed the SAR of a fetus inside this abdomen when exposed to 150 MHz signals, used for portable radio terminals in Japan, and found the values to be sufficiently less than 2 W kg^{-1}.

A recent study by McIntosh et al (2010) used a detailed anatomical model of a pregnant mouse that included eight mature fetuses, to assess their exposure to 900 MHz plane waves. In general, the SAR levels in the fetuses were determined to be slightly lower than those of the dam (around 14% lower) and the peak temperature increase was significantly lower (45%) than the values in the dam.

The majority of the studies mentioned above have used adult dielectric property values in their models of children. A review by Gabriel (2005) used published rat dielectric data by Peyman et al (2001) and assessed the impact of their variation as a function of age on the exposure of rodents to plane-wave fields. The results showed that the increase in permittivity and conductivity had a balancing effect on the energy deposition in the case of plane-wave irradiation, but this may not necessarily be the case when the exposure is in the near field of a source. Two more studies used porcine dielectric properties as a function of age in their modelling of the heads of children when assessing the exposure of children and adults to walkie-talkie devices and mobile phones; neither found any significant differences in SAR values between children and adults (Christ et al, 2009, 2010; Peyman et al, 2009). Although Christ et al (2010) confirmed that there are no age-dependent changes of the peak spatial SAR when averaged over the entire head, they also reported significantly higher locally induced fields in sub-regions of the child's brain (cortex, hippocampus and hypothalamus) and the eye due to closer proximity of the phone to these tissues. The authors observed even larger increase in induced fields for children's bone marrow as a result of its significantly higher conductivity compared with that of adults.

2.3.4 Measurement limitations

As for any other experimental procedure, the assessment of SAR is associated with some uncertainty. Many factors, including the performance of the electric field probe, the dimensions of the phantom, the dielectric properties of the tissue material, the exposure conditions and the repeatability of several measurements, contribute to the total combined uncertainties. Usually, both random and systematic sources of uncertainty are considered in calculations, and typically up to 30% expanded* uncertainty is reported for SAR measurements of a typical RF field exposure source, such as mobile phones (IEEE, 2003;

* Expanded uncertainty values provide a high level of coverage for the unknown true value of the measurement of interest. For coverage values of two and three, confidence levels of 95% and 99%, respectively, are expected.

IEC, 2005). Even numerical methods of calculating SAR are bound with some degree of uncertainty. The choice of the actual reference model, staircase modelling of smooth surfaces, boundary conditions, the type of voxel model and dielectric properties of tissues can cause variation in the results obtained (Hurt et al, 2000; Mason et al, 2000; Gajšek et al, 2001a,b; Findlay and Dimbylow, 2006; Samaras et al, 2006; Wang et al, 2006b; Laakso et al, 2007).

2.3.5 Dosimetric considerations in epidemiological and experimental studies

2.3.5.1 Epidemiological studies

A number of different approaches have been taken for the assessment of exposure to RF fields in epidemiological studies. The most prevalent and rapidly growing source of RF field exposure in recent years is related to increasing use of wireless technologies such as mobile phones, and most of the recent epidemiological studies on RF field exposure deal predominantly with mobile phone use. There are a number of challenges to assessing the exposure of individuals in these types of studies. Most investigations have been retrospective case–control studies that use questionnaire information or billing records to derive estimates of the time and duration of use as the main exposure surrogate (Morrissey, 2007), although some studies have relied upon distance from a fixed RF source such as a radio mast as a proxy for exposure.

In the questionnaire approach, exposure is estimated on the basis of the study subject providing recalled information on the type of phone used and history and frequency of usage. Other proxy parameters may also be considered such as urban/rural status, indoor/outdoor and moving/stationary modes of use, all factors that may influence the output power. The exposure assessment is complicated by the wide range of phone models, transmission modes, the pattern of use and the way the phone is used such as hands-free, the use of text messages, internet access and games, all of which affect the position of the antenna in relation to the body (Schüz, 2005). The use of questionnaires to reconstruct exposure from perhaps 10–15 years in the past is clearly an important limitation of this approach. Substantial exposure misclassification can result from random and differential recall of phone use between cases and controls (Vrijheid et al, 2006; Cardis et al, 2007). In the billing record approach, exposure estimates are derived from the records on phone usage provided by network operators. Although less prone to recall bias, exposure misclassification may still be an issue – for example, if someone other than the subscription owner uses the phone (Cardis et al, 2007; Schuz and Johansen, 2007). Another possible limitation is missing data.

The distance from a fixed RF source such as a radio mast has been used as a proxy for exposure in a number of epidemiological studies. This approach assumes that, at least in general, the power density will tend to decrease with increasing distance from a radio mast. However, in practice many antennas do not radiate energy uniformly and energy is also scattered by objects in the path of the beam. In relation to mobile phone masts, the RF field strength will depend on many factors such as the number of antennas, the type of antennas including power output and direction of the beam, and the frequency, as well as distance. Investigations have shown that distance is unlikely to be a reliable proxy for exposure from base stations, but it might be adequate for TV and radio transmitters (McKenzie et al, 1998; Cooper et al, 2001; Schüz and Mann, 2000).

The quality of epidemiological studies can be improved by combining quantitative approaches based on measurement and computational modelling. The main investigation may also be supplemented by

exposure validation studies and these have improved understanding of the merits and weaknesses of the various approaches taken. Personal exposure meters capable of logging exposure for a number of frequencies are now becoming available, although even these have limitations in terms of application in large-scale studies (Radon et al, 2006), including achieving sufficient sensitivity to measure typical environmental fields and the development of standardised methods for data collection and analysis (Mann, 2010; Röösli et al, 2010).

2.3.5.2 Experimental studies

Experimental studies often involve field measurements in the near field, which are difficult to perform because of the complex field components and coupling relationships with probes and any surrounding objects. External field measurements are at best only generally related to the SAR in these situations, and there are additional uncertainties if the volunteers or animals are free to move. Ideally experimental work should involve a well-characterised exposure system and incorporate modern experimental and computational methods to determine the SAR, making use of more than one exposure level to allow a dose-response relationship to be investigated.

Several exposure systems have been devised that allow excellent control of metrology and dosimetry, although some studies have simply used a commercial mobile phone to irradiate freely moving animals. This will produce highly variable exposures, especially to the head or testes, which not only depend on the animal's own behaviour and on social interactions between animals, but also depend on traffic on the local cellular network and on the network protocols. The use of such devices in experimental work should be avoided because of the lack of control it affords. Although far from ideal, it might be possible to use mobile phones as sources of exposure if it is possible to set them to produce emissions at a fixed frequency and output power using engineering or hardware controls. In animal experiments, there is often a necessary trade-off between the needs for accurate dosimetry and animal welfare. In most exposure systems there will be greater uncertainty in dosimetry with freely moving animals, but preventing their movement will induce restraint stress which in itself could affect the outcome of the experiment. Hence there is a need for cage controls as well as sham-exposed animals, particularly in long-term studies. Reverberation chambers, however, offer the promise of providing good dosimetry without the need for restraint. (See Section 2.3.1.1 for a discussion on experimental exposure systems.)

2.4 Sources of RF Fields

2.4.1 Natural background

The natural background field strength for electromagnetic fields in the frequency range from 100 kHz to 300 GHz is extremely low in comparison with the man-made fields discussed elsewhere in this report. Towards the lower end of the band of frequencies, below about 30 MHz, background mainly arises from lightning discharges during thunderstorms, characterised by random high peak transients. The intense current pulse (up to 100 kA) generates an electromagnetic pulse of duration about 10–50 μs. These intense pulses can propagate up to a few hundred kilometres, aided by natural atmospheric waveguides. At 30 km, a peak electric field strength in the range 5–20 V m^{-1} has been reported (Willett

et al, 1990), and it may exceed 10 kV m^{-1} at close range. The main spectral band of such pulses lies below 100 kHz.

At frequencies above 30 MHz, both terrestrial and extraterrestrial sources contribute to a low level, very-wide-spectrum black-body* radiation. Extraterrestrial radiation arises from the sun and microwave background radiation from the whole sky, and lies predominantly in the frequency band from 30 MHz to 30 GHz because of the transmission properties of the Earth's atmosphere. The power density of this extraterrestrial component is a few microwatts per metre squared. By comparison, the natural background radiation from the warm surface of the ground is a few milliwatts per metre squared, and so this is the dominant source of natural exposure.

The body itself is a source of broadband radiation. This natural emission has been used, for example, for the estimation and imaging of subcutaneous temperature distributions within the body. The black-body radiation from a person in the RF band is approximately 3 mW m^{-2} from the skin surface.

2.4.2 Broadcasting

The frequency bands used for broadcasting terrestrial radio and television services in the UK are shown in Table 2.5. The exposure of the public to RF fields from broadcasting sources is usually very small compared to the exposure of construction and maintenance workers in the towers near the antennas.

TABLE 2.5 Broadcasting bands in the UK

Designation	Frequency range	Usage
MF (medium wave)	526.5–1606.5 kHz	Radio
HF (short wave)	3.9–26.1 MHz	International radio
VHF (Band II)	87.5–108 MHz	FM radio
UHF (Band IV and V)	470–854 MHz	Television, analogue and digital video and audio broadcast (DVB and DAB)

2.4.2.1 MF and HF radio

Medium- and short-wave broadcasting stations operating at frequencies of 0.3–30 MHz require high power antennas in order to reach their target distance. Usually, the field strength is relatively high, up to a distance of a few hundred metres. Therefore there are usually control zones to avoid access by the general public. Typical antennas used in the MF band are vertical monopoles, while large dipole curtain antennas are more commonly used with HF transmitters.

* Black-body radiation is the electromagnetic radiation emitted by an idealised physical body ('black-body') that absorbs and emits all radiation over the complete spectral range. The spectrum of black-body radiation is specified exactly by the temperature of the black body.

Table 2.6 summarises the electric field strengths and induced current densities for transmitters operating in portions of the MF (300 kHz – 3 MHz) and the HF (3 MHz – 30 MHz) bands. In the UK, measurements have been made of the electric and magnetic fields and body currents close to a number of HF broadcast antennas and feeder arrays where fields may be non-uniform and can vary by a factor of two over the body height (Allen et al, 1994).

TABLE 2.6 Examples of electric field strength and induced current around MF and HF broadcasting antennas

Band	Average transmit power (kW)	Electric field (V m^{-1})	Induced current (mA)	Distance from source	Study
MF	50 and 70	60	–	Beneath the antenna feeders	Allen et al, 1994 (UK)
	50 and 70	1500	–	1.5 m from the half-wave vertical antenna mast	Allen et al, 1994 (UK)
	–	<60	<100	Over the body height	Allen et al, 1994 (UK)
	600	40–500	10–100	10–100 m	Jokela et al, 1994 (Finland)
	1–50	3–800	–	1–100 m	Mantiply et al, 1997 (USA)
HF	–	2–200	–	0–300 m	Mantiply et al, 1997 (USA)
	500	35–120	50–400	5–100	Jokela et al, 1994 (Finland)
	4	60–900	–	In the tower	Mantiply et al, 1997 (USA)

2.4.2.2 FM radio and TV

FM radio and TV broadcasting antennas operate at frequencies around 80–800 MHz. Typical antennas can have output powers of 10–50 kW divided between vertically stacked dipole arrays on the sides of each tower. Each dipole can have 50–500 W output power. The FM and TV antennas are designed to radiate a disc-like beam that is pointed slightly below the horizon. Therefore the amount of radiation towards a vertical direction along the tower is less than that along the inaccessible path in the main beam. People subjected to the highest exposures will be antenna riggers and engineering staff working in transmitter halls or under open-wire antenna feed lines. Some reported values in the literature of typical electric field strengths at close distances to FM and TV antennas are presented in Table 2.7. Typical radiated powers for different services are presented in Table 2.8.

Analogue TV and radio broadcasting systems are increasingly being replaced by digital video and audio broadcasting (DVB and DAB). The total power of the DAB and DVB-T transmissions is lower than that for analogue broadcasts; the highest power DVB-T transmitter has an average ERP (effective radiated power)

TABLE 2.7 Examples of electric field strength around FM radio and TV broadcasting antennas

Band	Average transmit power (kW)	Electric field ($V\ m^{-1}$)	Distance from source	Study
VHF	–	300	10–15 cm from the RF cable	Hansson Mild, 1981 (Sweden)
	4	60–900	In tower	Mantiply et al, 1997 (USA)
	40	20–150	20 cm from the tower ladder	Jokela et al, 1999 (Finland)
UHF	30	620	In tower	Hansson Mild, 1981 (Sweden)
	–	526	10–20 cm from antenna	Jokela and Ylönen, 1984 (Finland)

TABLE 2.8 Broadcast transmitters in the UK*

	Effective radiated power (kW)						
	0–0.1	>0.1–1.0	>1–10	>10–100	>100–500	>500	Total number of sites
Analogue TV	406	59	36	14	12	5	532
Digital TV	6	10	11	26	3	0	56
DAB	3	74	130	0	0	0	207
VHF/FM radio	150	79	81	23	17	0	350
MW/LW radio	3	56	21	11	4	0	95

* Data collected from publicly available information on the following websites and are correct at the time of collection (October 2011): www.bbc.co.uk/reception/transmitters and www.aerialsandtv.com/digitalnationwide.html

of 200 kW per multiplex, as opposed to its analogue counterpart with a total of 1000 kW ERP per service. A DAB channel transmitter will also have an ERP up to 10 kW, but often lower. This can be compared with a main VHF FM transmitter ERP of 250 kW per service.

A study carried out by Schubert et al (2007) in Germany compared the field strength at similar locations before and after switchover from analogue to digital broadcasting. The maximum power density of the analogue TV system was 0.9 mW m^{-2}, which increased to 6.5 mW m^{-2} after the switchover to DVB systems. The size of the antenna also plays a role in the amount of radiated power, as for the high power, small size antennas used in DVB systems, the radiated power increases compared with the analogue UHF antennas (Jokela, 2007).

2.4.3 Wireless telecommunication

Wireless communication has become an integrated part of contemporary day-to-day life due to the ease of transfer of information over a distance without the use of physical conductors (wires). It encompasses, amongst others, mobile phones, two-way radios, wireless networks, satellite links and cordless telephones. Other domestic applications such as wireless baby monitors and radio-controlled toys are also increasingly being used.

2.4.3.1 Mobile phones

Mobile phones are probably the most popular wireless device. The first generation (1G) of mobile phones came on to the market in the early 1980s using analogue radio systems operating at 450 MHz or 800/900 MHz. These included the Total Access Communications System (TACS), Nordic Mobile Telephony (NMT), Advanced Mobile Phone System (AMPS), Nippon Telegraph and Telephone (NTT) and the German Net C systems. A narrowband variant of AMPS, known as N-AMPS, was developed to increase the system capacity in North America. TACS networks based on the narrowband variant, N-TACS, were used in Japan. From around 2000, the TACS networks in Europe have tended to be shut down as the majority of their subscribers have moved to second-generation networks.

The second generation of mobile phones (2G) became available following the development of digital mobile communications systems in the early 1990s. The Global System for Mobile Communication (GSM) is the dominant mobile communications system in many countries around the world, operating at 900 and 1800 MHz (850 and 1900 MHz in the USA). The use of the time division multiple access (TDMA) technique enables the transmission to be divided in bursts, resulting in a considerable reduction in the maximum time-averaged output power of the phones over their nominal (peak) transmitter powers. Personal communications systems (PCS) deployed in North America are covered in the GSM standard, but have different uplink/downlink frequency bands and voice coding. The Personal Digital Cellular Telecommunication System (PDC) is widely used as a substitute for the NTT analogue cellular system in Japan with transmission frequencies in the 800 and 1500 MHz bands.

The 2G systems were mainly designed for voice applications. This has led to the development of the next generation of mobile phones (2.5G and 3G). Third-generation (3G) systems, also known as UMTS (Universal Mobile Telecommunications System) in Europe and CDMA-2000 (Code Division Multiple Access) in the USA, operate at 1900–2200 MHz, offering users a variety of applications, including internet browsing, email access and high speed music and video download. Although 3G is the latest mobile communications technology, research is currently underway for even higher data rates to allow applications such as mobile broadband.

The next generations (beyond 3G) will operate at the higher frequency bands of 2 and 6 GHz, although spectrum liberalisation and the reallocation of spectrum from earlier systems to newer ones is also a theme in many countries. The fourth generation of mobile phone systems is called Long Term Evolution (LTE) and is designed to deliver very fast data speeds of up to 100 Mbps (megabits per second) downlink and 50 Mbps uplink (peak rates); this is faster than most home broadband services (GSMA, 2011). The first commercial LTE networks were launched in Oslo, Norway, and Stockholm, Sweden, in December 2009.

In terms of exposure, according to GSMA (2011), the essential characteristics of LTE signals (frequency range and transmission powers) are comparable to those of the existing mobile communications technologies. There are differences in the coding and modulation of the user information for LTE, allowing the support of higher data rates. For instance, LTE uses a transmission process called Orthogonal Frequency Division Multiple Access (OFDM) that enables the data flow to be modulated simultaneously into several narrow frequency bands called subcarriers. The subcarriers can be switched on and off depending on the network requirement for capacity. LTE also makes use of a new type of antenna technology called Multiple Input Multiple Output (MIMO). By using more than one antenna, the signal can reach the recipient through different routes, improving the quality of wireless transmission.

Table 2.9 lists different mobile phone handsets systems together with their frequency of operation and typical maximum output power. GSM mobile phones have maximum (peak) powers of 1 or 2 W according to frequency band; however, the use of TDMA technology, in which one out of eight time-slots is used for radio transmission, results in a maximum time-averaged output power of either 125 or 250 mW*. Where a mobile phone system uses TDMA, each phone transmits at regular intervals. The proportion of time that

TABLE 2.9 Mobile phone systems and handset powers

Handset generation	Main region	System	Handset band (MHz)	Burst duration (μs)	TDMA duty factor	Peak power (W)	Average power (mW)
1	Nordic countries	NMT450 NMT900	453.5–457.5 890–915		1.0 1.0	0.9 0.6	900 600
	Europe Europe Japan	ETACS TACS NTACS	872–888 890–915 860–870		1.0 1.0 1.0	0.6 0.6 0.6	600 600 600
	Germany	NET-C	451.3–455.74		–	–	–
	USA and Canada	AMPS N-AMPS	824–849 824–849		1.0 1.0	0.6 0.6	600 600
	Japan	NTT	915–958		–	–	–
2	USA and Canada	TDMA800* TDMA1900*	824–849 1850–1910	6666 6666	1/3 1/3	0.6 0.6	200 200
	Europe	GSM900 GSM1800	890–915 1710–1785	576.9 576.9	0.12 0.12	2.0 1.0	240 120
	USA and Canada	PCS1900	1850–1910	576.9	0.12	1.0	120
	Japan	PDC800 PDC1500	940–956 1429–1465	3333 or 6666	1/6 or 1/3	0.8	133 or 266
	USA and Canada	CDMA800 CDMA1900	824–849 1850–1910		1.0 1.0	0.2 0.2	200 200
3	World	UMTS	1920–1980		1.0	0.125	125

* Also known as D-AMPS (Digital Advanced Mobile Phone System).

* Every 26th burst is missed out so 120/240 mW in practice.

the phone transmits is defined by the 'duty factor', as listed in Table 2.9. TDMA phones normally transmit one 6.666 ms burst every 20 ms, but they can reduce the rate at which bursts are produced to once every 40 ms in order to increase system capacity at the expense of signal quality (half-rate speech coding). GSM and PCS phones, however, transmit in 576.9 μs time-slots, which occur every 4.615 ms. 3G phones transmit continuously with powers up to 125 mW.

Although mobile phones are designed to have the output powers given in Table 2.9, in reality the output power of a mobile phone may be considerably lower. The strength of the signal transmitted between a mobile phone and base station would vary with separation distance according to the inverse square law, given an obstruction-free path between both antennas. In reality, effects such as shadowing, reflection, blocking of signals by buildings and terrain, and the beam patterns of antennas complicate the propagation characteristics between the mobile phone and the base station and make the signal strength much less predictable. These effects also cause the signal strength to vary rapidly as a user moves over relatively short distances.

Another factor reducing mobile phones output power is the use of the Adaptive Power Control (APC) technique in which mobile phones reduce their output powers so that the signal strength at base stations is constant and just sufficient for good quality reception. The network continually monitors the strength of the received signals and sends instructions to raise or lower radiated powers, as necessary. A recent study by Vrijheid et al (2009) monitored the output power of mobile phones used by more than 500 volunteers in 12 countries using software-modified GSM phones (SMPs) for approximately 1 month. The results showed that for over 60,000 phone calls, the average output power was approximately 50% of the maximum. They also indicated that maximum power was used during a considerable proportion of call-times and the output power decreased with increasing call duration. Although the study showed that APC reduces the output power of GSM phones to 50% on average, the authors concluded that the average power levels are substantially higher than the minimum levels theoretically achievable in GSM networks. Gati et al (2009) recorded and processed data streams exchanged on a live 3G network and found that the real transmitted power is generally a few per cent of the maximum power, meaning that a greater reduction in output power can be achieved for 3G phones than with 2G ones.

Mobile phones have shorter and infrequent transmission when they are in standby mode, although this has not been studied systematically. Moving the phone or managing the traffic of the network in a particular area may cause a handover to a different base station, resulting in a short transmission. The network also occasionally checks that phones with which it has not communicated for a period of time, are still available for incoming calls. Transmissions in standby mode would not normally be relevant to head exposure because the phone would not be held next to the head.

Some mobile phones use discontinuous transmission (DTX) to reduce interference with other mobile phones using the same frequency channel in distant cells – this also increases their battery life. With DTX, mobile phones stop transmitting to the base station when their user is listening passively to someone else talking. Synthesised comfort noise is played to the person who is speaking so that they do not suddenly hear silence and assume the call has been terminated. The use of DTX might be expected to reduce the time-averaged power from a mobile phone by 30% once it is enabled in a network (Wiart et al, 2000). DTX has mostly been used in GSM networks but it is not used with 3G or other CDMA phones because of the need for more rapid and efficient power control in these systems.

In a typical GSM network with adequate capacity, 'full-rate' speech coding usually occurs to allow good call quality. However, occasionally operators find that parts of their networks are becoming congested and it becomes necessary to create capacity by using half-rate speech coding. This allows twice as many phone calls to be handled, but with a degradation of call quality. The consequence in terms of exposure is that the time-averaged power of mobile phones is halved.

When assessing the exposure of people to mobile phone handsets, it is important to consider that the short distance between the mobile phone and the user's head implies a near-field exposure scenario. At distances less than 1 cm from the antenna the localised electric field strengths may be hundreds of volts per metre. However, such localised field strengths produced in the absence of a body and so close to an antenna cannot be used as a ready measure of exposure. In these circumstances, the mutual interaction of the head and phone must be taken fully into account. The approach taken to determine exposure in people has been to use models and assess the internal dosimetric quantity SAR, as a function of the power fed to the antenna (Dimbylow and Mann, 1994). Standardised procedures for assessing SAR have been developed by various bodies including CENELEC (2001) and manufacturers now provide information on measurements made on various models. It is also important to consider the differences between phones that produce a pulse-modulated RF emission (through the use of DTX and reduced speech coding) and those that produce a continuous emission when developing exposure metrics.

Figure 2.4 shows the maximum SAR values measured in a phantom model of the head for a range of mobile phones (Mobile Manufacturers Forum, 2011). The values are maxima found when each of the phones was placed in a set of standard positions and radiated at a number of standard frequencies.

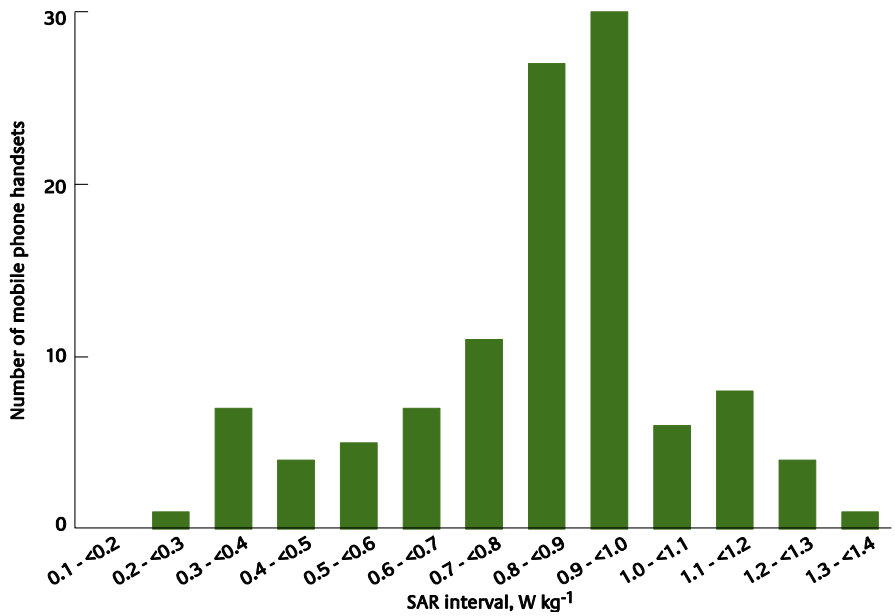

FIGURE 2.4 Distribution of SARs produced by 111 mobile phone handsets, as indicated by their manufacturers in 2003

Whilst the SAR values are based on the maximum output power of the particular phone, the exposure of the user will vary according to location, the position of the phone relative to the head and the size of the head. The geographical location is particularly important since APC can reduce the power emitted by the phone by up to a factor of 1000. Personal exposure will also depend on the average number and duration of calls. Where compliance with guidelines is concerned, it is necessary to average over an appropriate, specified time period, eg any 6-minute period.

Although Figure 2.4 contains SAR values compiled from data up to 2003, it is not expected that the trend has changed since then, as argued by Cardis et al (2011). In their study (Interphone) Cardis et al (2011) compiled a database of maximum SAR values for phones in use before and during the Interphone study which included 1233 values. Their analysis showed a large variation in SAR (two orders of magnitude), with some maximum SAR values measured below 0.01 W kg^{-1} (the current limit of detection), possibly due to measurement errors. Analyses by time period provided little evidence of a trend over time.

A recent study by Joseph et al (2010a) made a comparison between several European countries regarding their typical exposures from mobile phones using the same personal exposure meters. The mean exposure levels were compared between different environments such as homes, public transport or outdoors. The results showed that exposure levels were of the same order of magnitude in all countries, with the highest total personal RF field exposure recorded inside transport vehicles, mainly due to the use of mobile phone handsets. All the recorded exposure values were well below international guideline levels (see Appendix B). Exposure levels were in general lower in private houses or flats than in offices and outdoors.

In relation to mobile phone exposure, the SAR distribution in the head depends on many factors including frequency, irradiation conditions (type of phone and use conditions) and head size. The maximum SAR depends critically on the position of the phone and, in particular, on the distance between the antenna and the brain (AGNIR, 2003; Martínez-Búrdalo et al, 2004). In general, most of the RF energy absorption is superficial and absorption is highest in the outermost layers of the brain (Kuster et al, 2006).

Measurements on experimental phantoms suggest that most energy (97–99% depending on frequency) appears to be absorbed in the brain hemisphere on the side where the phone is used, mainly (50–60%) in the temporal lobe (Cardis et al, 2008). Calculations in scaled human head models using the FDTD method suggest that the peak SAR averaged over 1 or 10 g decreases with decreasing head size, but the percentage of energy absorbed in the whole head increases. Thus compared with adults, higher values of SARs might be expected to occur in children's brains (Figure 2.5) because of the thinner skull and surrounding tissue (Martínez-Búrdalo et al, 2004). (See Section 2.3.3.1 for a more detailed discussion.)

Some mobile phones are being supplied with user information specifying minimum distances at which they should be held from the body when calls are made. These distances apply when phones are clipped to the waist and used elsewhere on the body with hands-free kits, but they do not apply when phones are held to the ear/head. The distances are specified to ensure compliance with both American and European restrictions on people's exposure, limiting the heating of body tissues that can occur when RF energy is absorbed. Such exposure reduces as phones are held further away from the body.

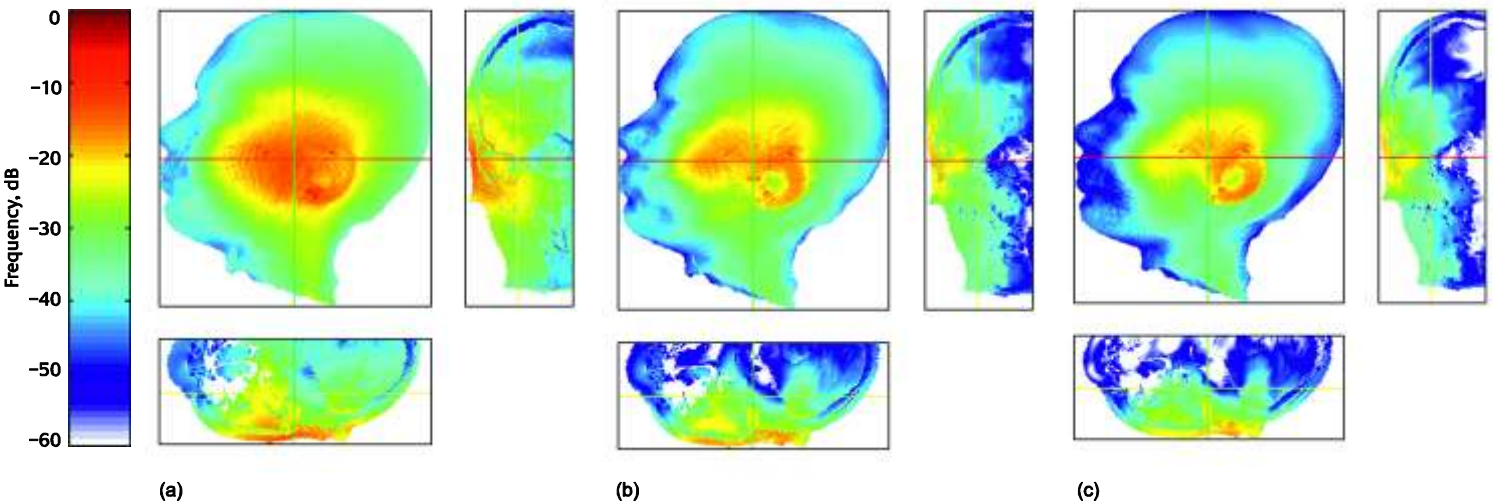

FIGURE 2.5 Local SAR in the head of a 12 year old child exposed to a tri-band mobile phone: (a) 900 MHz, (b) 1800 MHz and (c) 2100 MHz in the cheek position

The scale is 0 to −60 dB for each frequency, and the data have been normalised with respect to the maximum. The profile is a projection of the maximum SAR value to illustrate the SAR hotspot. The other two figures are cuts in the two other (orthogonal) planes

(Courtesy of Joe Wiart and Emmanuelle Conil, Orange France Telecom Group)

2.4.3.2 Mobile phone base stations

In order to give full coverage to users, the mobile phone network is divided into areas called 'cells', each having its own base station to send and receive radio signals. The main coverage for each cell is provided by macrocell base stations with typical output powers of tens of watts and covering distances in the range 1–10 km. Macrocell base station antennas are usually mounted on ground-based masts or rooftops at a height providing a clear view over the surrounding area. Due to the high output power of macrocells, exclusion zones are usually defined around their antennas to prevent public access to regions where exposure guidelines might be exceeded. Additional coverage and capacity are provided by microcells mounted at street level, eg on lamp posts or walls. Microcells have lower output power than macrocells, usually up to a few watts, and can provide coverage up to several hundred metres. Exclusion zones may not be required with microcells or their extent may be so small that the plastic cover over the antenna fully encloses them. For more localised coverage in dense areas such as airport terminals, train stations and shopping centres, indoor picocells with output powers up to around 100 mW are used.

Mann et al (2000) made measurements of power density at 118 locations on 17 sites, where signals were obtained from base stations. Most of the exposures were between 10 μW m^{-2} and 1 mW m^{-2}, the maximum being 8.3 mW m^{-2}. At locations where the power density exceeded 1 mW m^{-2}, the local base stations dominated the measurement and other environmental signals had little additional effect. At 73 locations, all radio signals over the range from 80 MHz to 3 GHz were evaluated; these are summarised in Table 2.10.

TABLE 2.10 Geometric mean power densities around base stations measured at several locations in the UK (Mann et al, 2000)

	Geometric mean and range (5th–95th percentiles) of power density (μW m^{-2})							
Location	**Local base stations**		**Total of all signals**		**Total neglecting local base station**		**Total neglecting all base stations**	
Indoor	17	(0.32–570)	75	(1.9–1000)	16	(0.76–970)	5.0	(0.23–420)
Outdoor	130	(19–930)	240	(49–1700)	37	(0.5–360)	12	(0.5–360)
All locations	33	(0.91–700)	110	(3.5–1100)	21	(0.84–970)	6.6	(0.23–380)

Since 2001, the UK Office of Communication (Ofcom) has carried out measurements as part of a base station audit recommended by the Independent Expert Group on Mobile Phones (IEGMP, 2000). Initially, the audit concentrated on what were described as 'sensitive sites' close to mobile phone base stations, such as schools and hospitals; however, it later covered a broader range of sites. Sites were selected on the basis of requests received via the Ofcom website (http://www.ofcom.org.uk/sitefinder/). Mann (2011) analysed the downloaded data from the Ofcom website for site visits up to the end of 2007. These included 541 sites at which a total of 3321 measurements had been made. The sites comprised 339 schools, 37 hospitals and 165 other locations. Ofcom calculated total exposure quotients from its measured data and the cumulative distribution of these values is shown in Figure 2.6. The quotients are in

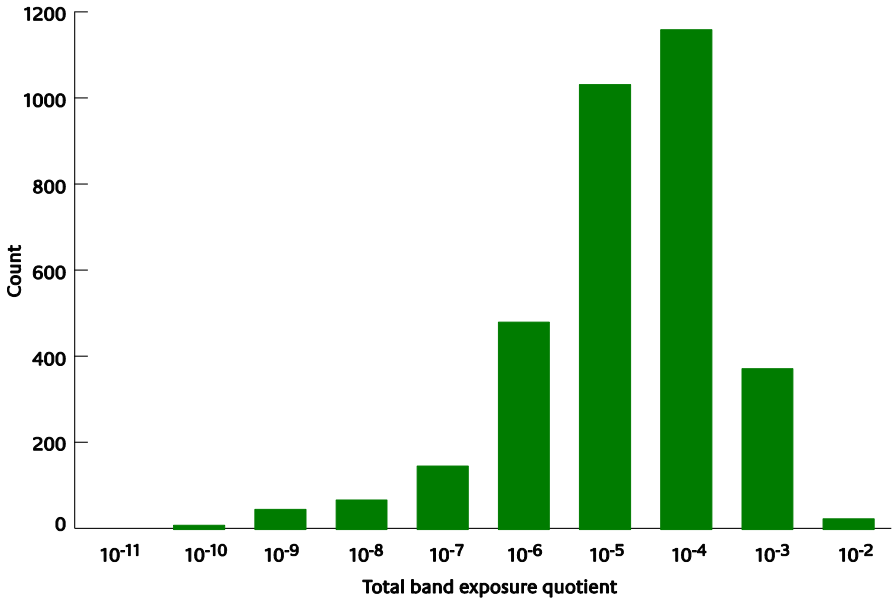

FIGURE 2.6 Total band exposure quotients measured by Ofcom for 541 mobile phone base stations (3321 measurements in total). The *x*-axis values are the maximum values contained in each bar of the chart

TABLE 2.11 Summary of exposure quotients measured during the Ofcom audit up to the end of 2007, and equivalent power densities and electric field strengths assuming a reference level of 4.5 W m^{-2} (Mann, 2011)

	Median value and range (5th–95th percentile)					
Location	**Number of measurements**	**Exposure quotient (× 10^{-6})**		**Power density (μW m^{-2})**		**Electric field strength (mV m^{-1})**	
Indoor	1516	2.8	(0.024–124)	13	(0.11–560)	69	(6.4–460)
Outdoor	1809	17	(0.052–314)	77	(0.23–1400)	170	(9.3–730)
All locations	3321	8.1	(0.03–250)	37	(0.13–1100)	120	(7.1–650)

relation to the ICNIRP general public reference level and they were calculated by dividing the power density of each individual measured signal by the reference level at its frequency and then summing these individual signal quotients to obtain a total quotient of the reference level (Mann et al, 2000). A summary of the exposure quotients measured during the Ofcom audit up to the end of 2007 is shown in Table 2.11.

In another study power density values around 20 randomly selected GSM microcells and picocells were recorded by Cooper et al (2006). The range of antenna heights was 2.5–9 m and the total radiated power ranged from 1–5 W. The results also indicated that the exposure quotients derived from the measured data were generally in the range of 0.002–2% and the greatest exposure at any of the sites was 8.6% of the ICNIRP public reference level.

An Australian study reported exposure levels around 60 mobile phone base stations transmitting CDMA800, GSM900, GSM1800 and 3G (UMTS) signals (Henderson and Bangay, 2006). The authors reported measurements as a function of distance ranging from 50 to 500 m and the highest recorded power density from a single base station was 8.1 10^{-4} W m^{-2}.

More recently, a population based survey was carried out using personal exposure meters to characterise the distribution of residential exposure from mobile phone base station antennas (Viel et al, 2009). Meters with a detection limit of 0.05 V m^{-1} were given to 200 randomly selected people for 24-hour measurements. The results showed that the recorded field strength was mostly below the detection level with a maximum electric field strength of less than 1.5 V m^{-1}. The results also indicated that exposure to GSM and DCS (digital communication systems) signals peaked around 280 and 1000 m from the antennas, respectively. UMTS and TV signals showed no variation with distance from the transmitters.

In Korea, Kim and Park (2010) have made measurements at 50 locations within a range of 32–422 m from CDMA 800 and 1800 MHz base stations. The highest recorded field level was reported to be 1.5 V m^{-1}, which corresponds to 0.15% of the ICNIRP guidelines.

LTE networks are, in principle, very similar to other mobile communications networks. An evolved UMTS terrestrial radio access network (EUTRAN), together with additional new processes, is used to transfer data at very high speeds between the terminal device and base station. A recent pilot study by the German Institute for Mobile Radio and Satellite Technology (IMST) assessed the general public exposure to LTE transmitters (IZMF, 2010). Five test transmitters and two pilot transmitters were assessed in cities in Germany. The results showed that the field emissions from LTE transmitters were well below the limits set by the German BImSchV (26th Federal Emission Protection Ordinance), which is based on the ICNIRP guidelines (see Appendix B).

In Sweden, exposure contributions due to different RF sources were compared with exposure to LTE base stations at 30 locations throughout Stockholm (Joseph et al, 2010b). The total exposure was reported to be in the range 0.2–2.6 V m^{-1}, of which an average of 4% was due to LTE exposure.

2.4.3.3 Terrestrial and satellite microwave links

Frequencies used by fixed-site telecommunications services range from the VLF band to the high microwave region. Services include public and private communications networks, satellite ground stations and control/telemetry services to remote sites. The majority of these are point-to-point microwave communications links, but the principles of exposure assessment would apply equally to mobile communications systems.

A summary of fixed microwave links is given in Table 2.12. Most of these systems use parabolic dish reflectors up to 3.7 m in diameter, mounted on towers or on buildings.

Satellite uplink services are detailed in Table 2.13. The Very Small Aperture Terminal (VSAT) systems are transportable. A theoretical assessment of the power density from a typical 14 GHz VSAT terminal has shown that the power density rises along the axis in front of the dish for about 40 m but then starts to fall off.

These systems generally use parabolic reflectors of circular cross-section with diameters varying from 1 or 2 metres to tens of metres, with many falling in the range 5–15 m. Since these diameters are much

TABLE 2.12 Fixed microwave links in the UK

Band (GHz)	Power to antenna (W)	Number of installations
1.7–2.45	5	250
4	20	1200
6	10	3000
7	–	500
11	10	1800
13	10	1500
15	3	500
18	0.4	1600
23	1	4500

TABLE 2.13 Satellite TV uplinks

Type	Band (GHz)	Power (W)	Dish (m)	Number
Broadcast uplink	14	600	3–5.5	12
VSAT	14	2–5	1.8	200

greater than the 2 cm wavelength, the antenna gains are very large, ranging from 30 to 80 dB, so that line-of-sight communication is possible over large distances. The power output normally varies from less than a watt to a few watts but may be in excess of a kilowatt for satellite links. Various approaches have been used to estimate the potential exposure to fields from such antennas (Hankin, 1974; Ministry of Defence, 1989). Although, in principle, it is possible to be exposed to power densities of a few hundred watts per metre squared (a few hundred volts per metre) near these high power antennas, this is most unlikely to be the case for members of the public. The antenna is directed at a satellite so, since nearby buildings need to be avoided, exposure to the main lobe is unlikely to arise. Only people who have access to the vicinity of the reflector or approach the useful beam at low elevation angles are likely to be materially exposed and their exposure will be to fields around a few tens of watts per metre squared, below the ICNIRP reference level for occupational exposure (ICNIRP, 1998 – see Appendix B). Public exposure at normally accessible positions will be typically below 10^{-4} W m^{-2} (0.2 V m^{-1}) at distances in excess of 100 m measured along the axis of the dish.

2.4.3.4 Cordless phones

Both analogue cordless phones and digital cordless phones have average output power levels of around 10 mW. However, while analogue phones produce continuous signals, digital systems can involve time sharing and pulse modulated signals so their peak powers can be higher than the 10 mW average. Digital Enhanced Cordless Telecommunication (DECT) phones operating at 1880–1900 MHz offer voice

communication with a peak power of 250 mW but, in contrast to mobile phones, there is no adaptive power control. Emissions during calls are in the form of 400 μs bursts produced once every 10 ms, ie there are a hundred bursts per second, giving an average power of 10 mW. The average powers are thus 10 or more times smaller than those from mobile phones operating at their highest power level. Most DECT base stations on standby (when not making a call) transmit an 80 μs pulse every 10 ms, ie they transmit for 0.8% of the time on average. Hence, the average power level on standby is 2 mW.

Kramer et al (2005) assessed the exposure at a distance of 1 m from DECT devices, and found maximum electric field strengths of the order of approximately 1% of the ICNIRP reference levels (Appendix B). Assuming far-field conditions this value corresponds to 0.01% of the reference level for power flux density (which is a more relevant comparison in the context of the underlying SAR-based basic restriction). They also reported a maximum 10 g averaged spatial peak SAR value of 0.06 W kg^{-1} when devices were placed in close proximity to a flat homogeneous phantom, which is clearly below the ICNIRP basic restriction of 2 W kg^{-1} for localised exposure.

2.4.3.5 Terrestrial trunked radio (TETRA)

Terrestrial trunked radio (TETRA) is a specially designed mobile communications standard for the emergency services, offering higher reliability and enhanced security compared with other older analogue technologies. TETRA devices operate at frequencies of 380–470 MHz. The features of the system, in particular the discontinuous nature of the waveform, which is similar to GSM in that TDMA is used, and similar to older mobile radio in that it is produced by the handset when the user pushes a button (push-to-talk mode), have been considered in depth in an earlier report by AGNIR (2001). The 25% duty factors of the hand-portable equipment mean that average powers for the 1 and 3 W transmitters are reduced to 0.25 and 0.75 W, respectively, but could increase if additional available channel space (more than one of the four slots available) were to be used, eg for data transmission. A comparison of output powers for different types of phones used near the head is given in Table 2.14.

Exposures have been estimated for maximum power transmission using experimental modelling (Gabriel, 2000b) and the SAR produced in a phantom head is given in Table 2.15. Increases due to additional channel utilisation would in theory increase the SAR by a factor of four, but in practice the phone is likely to be held further from the body when data rather than speech are being transmitted.

Dimbylow et al (2003) developed a numerical model of a commercially available TETRA handset with helical and monopole antennas, and calculated SARs in a 2 mm resolution anatomically realistic numerical model of the head. For the handset held vertically in front of the face in the position that was considered to be most representative of practical use, the 10 g averaged SARs were 0.42 and 0.59 W kg^{-1} with the monopole and helical antennas, respectively, and based on 0.25 W average radiated power (class 4). Various positions were considered with the handset held to the side of the head and the maximum SARs with the two antennas were 0.59 and 0.98 W kg^{-1}, again based on 0.25 W radiated power.

2.4.3.6 Bluetooth devices

Bluetooth devices operate at 2.45 GHz, and provide short range wireless connectivity between mobile communications devices. The majority of mobile phones, computers and their peripheral accessories are equipped with Bluetooth capability. The peak power of a Bluetooth device used for distances up to

TABLE 2.14 Peak and time-averaged output powers for various types of different handheld radio terminals when operating at their maximum power level (the average figures for TETRA are for one time-slot)

	Maximum output power (W)		
System	**Peak**	**Average**	**APC available**
Analogue police radio (450–460 MHz)	1.5	1.5	–
TETRA* Class 3 radio (380–385, 410–415 MHz)	3	0.75	✓
TETRA* Class 4 radio (380–385, 410–415 MHz)	1	0.25	✓
GSM900 (890–915 MHz)	2	0.25	✓
GSM1800 (1710–1785 MHz)	1	0.125	✓
DECT (1880–1900)	0.25	0.01	–

* APC is available for TETRA handsets in their usual trunked mode of operation, but not when they are used in direct mode (AGNIR, 2001).

TABLE 2.15 Measured SARs produced in a phantom head exposed to radio signals from 1 W and 3 W TETRA hand portables

	SAR (W kg^{-1}) for 1 W radio			SAR (W kg^{-1}) for 3 W radio		
	Spatial peak	**1 g averaged**	**10 g averaged**	**Spatial peak**	**1 g averaged**	**10 g averaged**
Left ear	1.40	1.16	0.89	5.07	3.92	2.88
Right ear	1.72	0.94	0.88	5.07	2.74	2.33
Front	0.35	0.28	0.24	0.92	0.72	0.53

around 1 m, eg for a wireless hands-free kit used with a mobile phone, is usually 1 mW, although 2.5 and 100 mW devices are also available. While the 100 mW devices have similar powers to mobile phones and therefore can produce similar exposures, the low power outputs of most devices will give rise to correspondingly low exposures, well below guideline levels (see Appendix B).

Consistent with powers of the order of 1 mW, an assessment of exposure to Bluetooth devices at 1 m found maximum electric field strengths of the order of 0.5% of the electric field reference level recommended by ICNIRP (Kramer et al, 2005). Assuming far-field conditions this value corresponds to 0.0025% of the reference level for power flux density. The same study reported a maximum 10 g SAR of 0.5 W kg^{-1} for a nominally 100 mW power device, which is clearly below the ICNIRP basic restriction of 2 W kg^{-1} for localised exposure. Martínez-Búrdalo et al (2009) assessed human exposure to electromagnetic fields from Bluetooth devices in some operating situations and showed that the exposure levels in the worst-case situations studied are lower than those obtained when analysing exposure to

mobile phones, with both field and SAR values being far below guideline levels, even when considering the combined exposure to both a GSM and a Bluetooth antenna. The authors concluded this was to be expected because of the low power of the signals and the distance between the person and the antennas.

2.4.3.7 Hands-free kits

An important feature of hands-free kits for use with mobile phones is that they move the major source of exposure to RF fields, the antenna, away from the head and sometimes also from other parts of the body. The kits consist of an earpiece and a microphone connected to the phone either with wires or with a wireless Bluetooth radio link.

The use of a hands-free kit would be expected to reduce the SAR in the head because of the increased distance between the antenna and the head and because connecting wires would not be expected to form an efficient RF waveguide. Nevertheless, it has been claimed that, under certain conditions, the SAR near to the earpiece of a wired hands-free kit can exceed the SAR at the same point from the phone when that is held next to the head (Consumers' Association, 2000). However, the methodology used for this work has been criticised (Bit-Babik et al, 2003).

As part of the MTHR Programme, further studies have been carried out to determine the level of SAR associated with the use of hands-free kits with GSM mobile phones and to identify the factors that influence these levels (Porter et al, 2004). The results showed that, for the combinations tested, use of a hands-free kit resulted in a lower peak 10 g averaged SAR value within the head. The authors also indicated that the layout of the hands-free kit with respect to the phone has a very significant effect on the coupling and movement of the hands-free kit away from optimal coupling geometries with the wire reducing the SAR greatly. The phone and hands-free kit geometries were deliberately chosen to enhance the current and hence the SAR. Thus, the SAR values represent an approximation to the worst case; in typical use the SAR values would be expected to be significantly lower (Porter et al, 2004). In a separate study, Kühn et al (2009a,b) developed procedures for the testing of hands-free kits under worst-case and realistic usage conditions and applied these to a set of devices. The authors concluded that the use of hands-free kits reduces the exposure of the entire head compared to the mobile phone operated at the head, but there might be very localised exposure enhancement in the ear. The authors also concluded that specific compliance testing of hands-free kits is not necessary.

2.4.3.8 Radio-controlled toys

Radio-controlled toys include cars, boats, planes, helicopters and scale railway locomotives. Radio-controlled devices often have a transmitter that is the controller and have control sticks, triggers, switches and dials at the user's finger tips. The receiver is mounted in the toy itself and receives and processes the signal from the transmitter, translating it into signals that are sent to the servos, which are automatic devices that use error-sensing feedback to correct the performance of a mechanism. Typically the transmitter multiplexes all the channels into a single pulse-position modulation radio signal. The receiver demodulates and demultiplexes the signal and translates it to the pulse-width modulation used by standard servos. More recently, high-end toys use pulse-code modulation (PCM) to provide a computerised digital bit-stream signal to the receiving device, instead of analogue-type pulse modulation.

There is a large range of operating frequencies and output powers for the radio-controlled toys available in the market. In terms of exposure assessment, each device needs to be considered on the basis of its own output power and frequency of operation.

2.4.3.9 Baby monitors

Baby monitors are radio systems used to monitor remotely the sounds made by an infant. The transmitter, equipped with a microphone, is placed near to the child and the receiver equipped with a speaker, is carried by, or near to, the person caring for the infant. Baby monitor devices operate at 40, 466, 864 and 2450 MHz and can have peak transmit powers up to 500 mW.

A study carried out by Kramer et al (2005) assessed the exposure at a distance of 1 m from selected products including baby monitor devices and found maximum electric field strengths of the order of approximately 11% of the ICNIRP reference levels, which corresponds to 0.0025% of the reference level for power flux density (assuming far-field conditions). The study also reported a maximum 10 g averaged spatial peak SAR of 0.08 W kg^{-1}, which is much lower than the ICNIRP basic restriction of 2 W kg^{-1} for localised exposure.

2.4.3.10 Wireless local area networks

WLAN technologies operating in certain frequency bands near 2.4 and 5 GHz are 'licence exempt', and the bandwidth is shared between multiple users. The most widely used technical standards are produced by the Institute of Electrical and Electronic Engineers (IEEE). The IEEE802.11x family of standards specifies the technical configuration of Wi-Fi technology, and the original 802.11 document specified the standard for WLANs, providing for data rates of 1 and 2 Mbps (IEEE, 1999, 2000). However, to address the need for supporting higher data transmission rates, the IEEE introduced 802.11b for rates of up to 11 Mbps in the 2.4 GHz band. Standards 802.11a, 802.11g and 802.11n were later developed to attain even higher data rates (up to 72 Mbps) in a single channel, and exploit the 5 GHz band to avoid overcrowding in the 2.4 GHz frequency band.

In WLANs, the most popular technology used for the wireless portion of the network is known as Wi-Fi. Through the use of this technology, devices and computers are connected to the local area network (LAN) wirelessly, eliminating or reducing the need for wired Ethernet. In such set-ups all devices must be equipped with antennas that transmit and receive radio waves in order to allow wireless connection. Terminal devices such as laptop computers are known as 'clients' and the point of entry to the wired network is referred to as an 'access point', usually located within a few tens of metres and in the same building.

In Europe, the European Telecommunications Standards Institute (ETSI) develops standards for harmonising the equipment in terms of compliance with regulatory requirements in relation to emissions and the use of the radio spectrum. For example, the ETSI harmonised standard EN 300 328 limits the maximum power for any system operating in the 2.4 GHz band to 100 mW. In the UK, Ofcom requires compliance to the Interface Requirement (IR), which limits the maximum transmit power in the 2.4 GHz frequency band to 100 mW and stipulates that devices operating in the lower frequencies of the 5 GHz band may only be operated indoors and have a maximum power of 200 mW (Ofcom, 2006a,b). A higher

maximum output power of up to 4000 mW is acceptable for devices operating at the higher frequencies in the 5 GHz band (Ofcom, 2007).

Typical public exposure to WLAN in the environment has been assessed by Foster (2009) and Schmid et al (2007a). In addition, compliance with exposure guidelines has been tested under scenarios that produce higher-than-typical exposures, eg with the antennas transmitting continuously and within a few centimetres of the body (Kramer et al, 2005; Kühn et al, 2007; Schmid et al, 2007b; Martínez-Búrdalo et al, 2009). These studies found exposures well within the guidelines set by ICNIRP and the most pessimistic scenarios found exposures comparable to those from mobile phones, although still within exposure guidelines.

In a more recent study by the HPA (Peyman et al, 2011b), laboratory measurements have been carried out with examples of Wi-Fi devices (laptops and access points) used in UK schools to evaluate the RF power densities around them and the total radiated powers. The total radiated power emissions from the laptops were evaluated by summing the power flowing through a spherical surface enclosing the laptops. For 15 laptops and 12 access points operating at 2.4 GHz, the maximum integrated radiated powers (IRP) recorded at 1 m were 17 and 28 mW, respectively. The maximum power density values for the laptops and access points at 0.5 m were 22 and 87 mW m^{-2}, respectively, decreasing to 4 and 18 mW m^{-2} at 1 m distance. Consistent with the low radiated powers, these power density values are well below the ICNIRP reference level of 10 W m^{-2}.

A parallel study by the HPA considered the absorption of RF energy in the body of a person near the devices and calculated the localised SAR arising from Wi-Fi equipment in models of adults and children. At 2.4 GHz, using a power of 100 mW and a duty factor of one (100%), the highest localised SAR value in the head was calculated as 5.7 mW kg^{-1}. This represents less than 1% of the SAR previously calculated in the head for a typical mobile phone exposure condition (Findlay and Dimbylow, 2010).

The above calculations were based on the assumption of a duty factor of one (100%). However, in reality, it is highly unlikely that a duty factor of one will be achieved, especially for the 6-minute time-averaging period relevant to assessments in the context of the ICNIRP guidelines. The duty factor would have to be much less so that multiple users could access the system simultaneously. A range of technical factors, including the quality of the air interface, signal strength, interference from other devices, modulation scheme and the performance of the hardware, would affect the duty factor in practice. Recently the HPA carried out a series of on-site measurements in a selection of UK schools to record the proportion of the time that individual Wi-Fi computers transmit during typical school lessons. For every 30-minute recording session, the total transmission time for laptops was of the order of a few tens of seconds, corresponding to a duty factor of about 1% for laptops and 10% for access points (Khalid et al, 2011). A detailed description of the HPA Wi-Fi study, and its results, is included in Appendix A.

In May 2010, the Wi-Fi Alliance (an international trade association of companies) announced that the industry is working on a 60 GHz technology that will be an expansion to the family of Wi-Fi technologies. This is planned to deliver very high throughput, measured in gigabits instead of megabits per second, with a smaller coverage footprint than traditional forms of Wi-Fi. The typical applications for this high frequency Wi-Fi technology will include streaming of high definition video and audio, display and latency-free gaming.

Another WLAN technology known as Worldwide Interoperability for Microwave Access (Wi-Max) has become available in recent years. Wi-Max is a wireless broadband access technology that provides performance similar to 802.11/Wi-Fi networks with the coverage and quality of service of cellular networks. The Wi-Max range is considerably longer than that of Wi-Fi, and can be up to 50 km for fixed stations, and 2–15 km for mobile stations. Wi-Max technology operates at licence-exempt frequencies of 2–5 GHz and is governed by the IEEE 802.16.X family of standards. Recently, an evaluation of exposure levels generated by Wi-Max systems has been carried out by scientists at the University of Bologna in Italy (Barbiroli et al, 2009). The results demonstrated that the Wi-Max installations in Italy are generally compliant with the exposure limits provided by the regulations, which in Italy include lower restriction values than those in the ICNIRP guidelines.

2.4.3.11 Smart meters

Smart meters are communication devices that allow remote readings of gas and electricity meters. The parameters monitored include location, consumption units, time and frequency of usage. At regular intervals usage data are transmitted from the device to the utility company, eliminating the need for estimated or manual meter readings. The technology used to monitor the utility meters is commonly called home area networking (HAN), which involves networking several devices in the household premises. Smart meters also transmit and receive data wirelessly between the meter and a central server. There are a number of existing wireless technologies that can be used to enable this connectivity. These technologies include GSM, GPRS, CDMA, 3G, LTE and Wi-Fi.

Recently, three separate reports have been published in the USA on the potential health effects associated with smart meter use (EPRI, 2010; Maine CDC, 2010; CCST, 2011). All three concluded that RF emissions from smart meters are well within the US Federal Communications Commission (FCC) public exposure limits. According to EPRI (2010), the estimated maximum exposure from a typical embedded 1 W transmitter at a distance of 30 cm in front of a meter is about 18 μW cm^{-2}. This value is only 3% of the exposure standard set by the FCC in the USA, it is also significantly lower than the ICNIRP reference level of 10 W m^{-2}. EPRI (2010) concluded that even if a meter malfunctioned and transmitted constantly, ie with a duty factor of 100%, exposure levels would still be well within the FCC standards. The effect of cumulative exposure was also studied by EPRI (2010) in situations where multiple meters are located together – for example, in an apartment complex. The results indicated that exposure levels are only 0.6% of the FCC limits under the worst-case scenario (duty factor of 100%).

In the UK, a national roll-out of smart meters is currently being planned, involving a visit to every home and the replacement of around 50 million gas and electricity meters (Ofgem, 2010). There are many manufacturers of smart devices, and so far a technology-neutral approach has been adopted. The details of the technology to be deployed in the UK are therefore not yet known but, given the low output power of typical devices, it is not expected that people's exposure will exceed the ICNIRP restrictions.

2.4.3.12 Ultra-wideband (UWB) applications

Ultra-wideband technology uses a wide range of frequencies between 0.96 and 29 GHz, transmitting information spread over a large bandwidth (over 500 MHz). The main applications of UWB include medical imaging, through-wall sensing, ground penetrating radar (GPR), precision location and tracking,

sensor networks and wireless personal area networks (WPAN). Although UWB was traditionally accepted as a pulsed radio system, the FCC now defines a UWB device if its fractional bandwidth is greater than 0.2 or if it occupies 500 MHz of the spectrum (FCC, 2002). In terms of transmission, this means that the emitted signal bandwidth exceeds the lesser of 500 MHz or 20% of the centre frequency.

The FCC applies a power spectral density emission limit for UWB devices of −41.3 dBm MHz^{-1}, corresponding to 75 nW MHz^{-1}. This is the limit that applies to unintentional emitters in the UWB band, called the Part 15 limit. However, the emission limit can be significantly lower (as low as −75 dBm MHz^{-1}) in other segments of the spectrum.

2.4.4 Industrial applications

High power RF and microwave energy sources are used extensively in a range of industrial and some domestic equipment. Under normal conditions, users of such equipment are shielded from exposure to the fields it produces. However, given the very high powers in use, and sometimes the open nature of a particular application, it may be difficult to shield fully all body-parts of the operator from stray fields and leakage emissions.

Industrial and domestic uses of RF and microwave energy, together with detailed reports of measured fields for some equipment, have been well described elsewhere (AGNIR, 2003; ICNIRP, 2009). This section presents an overall summary of these previous reports, updated where appropriate. Table 2.16 presents a summary, including example applications, commonly used frequencies and powers, and an overview of experimentally determined exposures.

2.4.4.1 Microwave ovens

Microwave ovens are manufactured to standards that require leakage levels to be kept below specified emission limits. In the UK, the relevant British Standard, EN 60335-2-25 (IEC 60601-2-33) (BSI, 1997), requires that microwave leakage should not exceed 50 W m^{-2} (140 V m^{-1}) at 5 cm from the external surface of the appliance.

The UK maximum leakage value is greater than the ICNIRP reference level for the public, ie 10 W m^{-2} (ICNIRP, 1998). If any leakage were to occur it would normally be from a small area, such as a slot in the region of the oven door, from where the emission would spread and reduce rapidly in strength with distance. Whilst power densities very close to the slot might approach the UK limit, and so exceed the ICNIRP reference level, people behaving normally in the vicinity of the oven would never be exposed at levels exceeding the ICNIRP reference level.

Microwave energy is also used in industrial heating and drying processes for many materials, including foodstuffs, building materials, paper, medical supplies and chemical mixtures (Osepchuk, 2002). In some processes, the exposure is through open applicators applied over a moving surface, such as in asphalt processing. In others, small coaxial antennas are inserted within the material, as for moisture-drying buildings. In the latter case, power densities exceeding 1000 W m^{-2} may be reached on the back surface of the wall being dried.

TABLE 2.16 Summary of the industrial and domestic applications of high power RF and microwave energy

Equipment/process	Example applications	Frequencies used	Power (kW)	Approximate exposures
Microwave ovens (industrial and domestic)	Cooking	2.45 GHz	0.5–1.5	Leakage <50 W m^{-2} at 5 cm (maximum SAR <0.256 W kg^{-1})
RF processing and drying	Wall-drying Asphalt curing	2.45 GHz, 915 MHz	1– 600	May reach 1000 W m^{-2} for wall-drying
Dielectric heating	Glue drying, plastic welding	13.56, 27.12, 40.68 MHz	1–100	Commonly 100 V m^{-1}, maximum 1000 V m^{-1} at the operator
Induction heating (industrial)	Zone refining, annealing, hardening, brazing Cooking	0.1–3 MHz	1–100	2–8000 V m^{-1}, 0.1–20 A m^{-1} at the operator (SAR is lower than that from dielectric heating, for same field)
Induction heating (domestic)	Cooking	20–60 kHz	1–3	10 V m^{-1} at 10 cm
Plasma discharge etching and sputtering	Semiconductor fabrication	13.56 MHz (also 0.14, 0.28, 0.38 MHz)	Up to 1000	<10 V m^{-1} at 10 cm, <0.07 A m^{-1} at 30 cm (at 13.56 MHz)
Plasma torch	In mass spectrometers	27 MHz	14	<30 V m^{-1}, <0.07 A m^{-1} at the operator

2.4.4.2 Induction heating

RF induction heaters are used extensively in industry for a variety of purposes such as surface hardening, zone refining, annealing and brazing. The frequency and power used depend upon the process requirements, but an important parameter in the choice of frequency is the depth of penetration of the field or skin depth. The powers range from about 1–10 kW and the coils may be small single-turn devices of a few centimetres in diameter, used for heating localised regions of a product, or larger multi-turn systems. Fields may be highly localised and the rapid variation in field strength at close distances to small coils is an important factor in determining exposure.

Coil impedance rises with frequency and at frequencies of several hundred kilohertz and above electric field strengths may become of greater relevance than magnetic fields when compared to exposure guidelines. Estimates of exposure based on electric and magnetic field strength alone suggest that induction heating gives rise to comparable exposures to dielectric heating. However, since the coupling to the human body is not as efficient at the lower frequencies used for induction heating, the energy deposition in the body is lower. The current density arising from induction heater exposure is lower by a factor of 10, and for the SAR by 100, in comparison with that for a dielectric heater generating the same external field.

Domestic and commercial cooking hobs have been developed using the induction heating principle, eddy currents being induced in pans using flat coils or rings placed beneath the pans. The frequencies used are in the 20–50 kHz range (below the lower limit specified for this report, but included here for completeness) with powers usually ranging from about 1–3 kW. More recent developments have enabled the use of aluminium cookware at frequencies over 60 kHz (Suzuki and Taki, 2005). Measurements of electric and magnetic fields in the vicinity of such equipment under conditions of maximum power show that electric field strengths at distances of 25 and 30 cm can range from 4.3–50 V m^{-1} and magnetic field strengths from 0.7–3.8 A m^{-1} depending upon the circumstances of use, including the number of rings activated (AGNIR, 2003).

2.4.4.3 Plasma discharge equipment

Plasma etchers are used in various stages of the semiconductor fabrication process to break down polymer etch-resistant coating, etch metals deposited on the semi-conductor wafer, or assist in building up deposits on the wafer through plasma-assisted chemical vapour deposition (PACVD). The technique involves the delivery of RF energy to a pair of electrodes inside an evacuated reaction vessel, in which the wafers to be etched are placed, in order to establish and maintain a plasma discharge.

RF sputtering is similar to plasma etching in that the process applies coatings to components placed inside an evacuated chamber by means of a plasma discharge. It is unlikely that parts of the body such as the head or torso would be substantially exposed close to such devices.

Plasma torches are used as part of mass spectrometry systems. The torch assembly comprises a glass cylinder that contains the discharge electrodes.

2.4.4.4 Dielectric heating

Machines used for RF dielectric heating have been identified as potentially one of the most important sources of RF field exposure amongst the working population and have been the focus of some attention (AGNIR, 2003). The wavelength range in air of this type of equipment is 3–30 m, thus exposure occurs well within a wavelength of the source where complex field distributions occur. Dielectric heaters have output powers ranging from less than a kilowatt to tens of kilowatts and may be completely shielded and automated or be unshielded and operated manually. In general, the greatest exposure arises from machines of a few kilowatts used for welding PVC where, in particular, operators of machines using C-frame presses to weld PVC often sit 30–50 cm from the welding electrodes.

The RF grounding of the frame of the machines can substantially affect the current distribution on the machine and therefore the magnetic field generated. In addition, the spatial distribution of electric field strength at positions occupied by the operators is highly non-uniform, resulting in a reduced energy absorption rate in the near field.

The problems of evaluating exposure to this type of equipment are complicated by the nature of the work. The weld cycle is usually a matter of seconds and the duty factor (RF-on-time to total-cycle-time) can vary from about 0.1 to 0.5. During each weld cycle the field strengths vary and the operators may need to place their hands in regions of high field strength.

2.4.4.5 Wireless power transmission (WPT)

The concept of wireless transport of electrical energy is being actively explored for the specific purpose of using satellite-borne solar panels to supply electrical energy to the Earth. Lin (2002) has reviewed these systems, together with their biological implications. Current designs by NASA in the USA and by the Japanese Aerospace Exploration Agency have been summarised by ICNIRP (2008). The satellites, operating at 2.45 or 5.8 GHz, would emit up to about 6 GW total power, giving an estimated maximum power density at the receiving antenna of 1800 W m^{-2} for one of the proposed systems.

For domestic uses, devices using WPT operate only over very short distances, typically using mutual induction. WPT is used in items such as electric toothbrushes and convection ovens, and in charging pads for mobile phones or laptops. Power coupling can only be achieved efficiently if the charger and device are in very close proximity. For medium to long range power transmission, evanescent wave coupling (or resonant non-radiative energy transfer) is currently being explored. This offers the prospect of lossless power transfer, with associated minimal hazard from exposure to RF fields.

2.4.5 Medical applications

2.4.5.1 Magnetic resonance imaging and magnetic resonance spectroscopy

Magnetic resonance imaging (MRI) uses the nuclear magnetic resonance of protons in order to obtain images of human anatomy and function in three dimensions for diagnostic and research purposes. These images can achieve a spatial resolution of better than 1 mm and a high degree of differentiation between adjacent soft tissues. Such is its diagnostic value that the use of MRI for medical purposes is rapidly expanding. At the time of writing, the rate of increase in use of MRI in England shows a doubling in about 5 years, and reached over 2 million scans in 2010/11 (Figure 2.7).

Magnetic resonance spectroscopy (MRS) derives metabolic information from the nuclear resonance of a wider range of nuclei, including those of hydrogen, phosphorus and sodium. Its use is also increasing, but is largely restricted to major academic and research centres.

In order to excite nuclear resonance, the body is exposed to repeated pulses of an RF field whilst placed in a strong magnetic field. The frequency used is selected to match the magnetic field strength used, depending on the gyro-magnetic ratio of the particular nucleus. All clinical MRI systems derive images from proton magnetic resonance. By far the largest number of clinical scanners currently in use operate at a magnetic field of 1.5 T, for which the resonant frequency is 63.86 MHz. Open-bore scanners commonly use fields below 0.35 T, and some high field systems operating up to 11.7 T are being installed for experimental studies (HPA, 2008). The frequency used in each case is proportional to the magnetic field and may be calculated using the gyro-magnetic ratio for hydrogen, 42.58 MHz T^{-1}. So patients in open-bore scanners are exposed to frequencies below 15 MHz, whilst very high field research systems use 200–400 MHz RF pulses. At these frequencies, the body is of the same order of magnitude as the wavelength, and field inhomogeneity becomes more likely.

Several different coil designs are used. The main transmitter coil is commonly a birdcage body coil that is integrated into the scanner. It is usually driven in quadrature, creating a circularly polarised RF field that has the advantage of reducing the RF power deposited in the patient from that in an equivalent but linearly

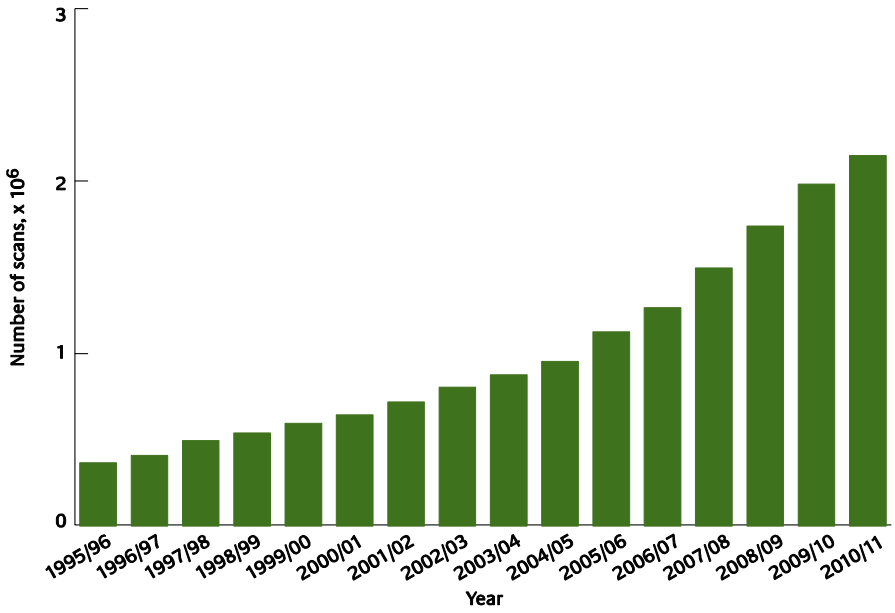

FIGURE 2.7 Annual totals of MRI scans carried out in NHS trusts in England from 1995/96 to 2010/11 (Department of Health, 2011)

polarised field. Specialised RF coils may be used to enclose the head or knee, or a surface coil may be used for superficial tissues. Exposure is limited to the imaged volume, but field uniformity may be compromised.

Commercial MRI scanners make available to the operator calculated whole-body SAR values for the selected magnetic resonance sequences. In practice, these vary from less than 0.1 W kg^{-1} for a number of commonly used sequences to about 4 W kg^{-1} whole-body SAR for more complex settings (HPA, 2008). In order to operate with SAR values higher than 4 W kg^{-1}, BS EN60335-2-25 specifies two levels of operational control, a limit of 20 W kg^{-1} for exposure of extremities and a 10 s limit for even higher exposures (BSI, 1997). A number of methods exist to compute the temperature rise in realistic body models, and these predict steady-state maximum increases of about 2°C under these conditions. Such models have also been used to predict local SAR hot-spots (HPA, 2008). Recent studies have emphasised issues for local fetal heating (Gowland and Wilde, 2008; Pediaditis et al, 2008; Dimbylow et al, 2009).

2.4.5.2 Other RF imaging techniques

In a few academic centres, RF imaging systems are being developed – and are undergoing clinical evaluation – that image the dielectric properties of body tissues. Applications have focused on breast imaging, but include cardiac and intracranial haemorrhage imaging. Cross-sectional imaging is achieved either by using ultra-wideband pulses in echo mode, similar to radar (see, for example, Li X et al, 2004, and Sill and Fear, 2005) or by the reconstruction of cross-sectional dielectric images from multiple transmission measurements (Li D et al, 2004). Contrast-enhanced imaging, using micro-bubbles or carbon nanotubes, may improve diagnostic contrast in the future (Shea et al, 2010).

One pulsed experimental system, for which information is available only on a commercial website (so-called MARIA), currently in clinical trials, uses 31 antennas emitting pulses with a bandwidth of 4–10 GHz and operates with a peak output power of less than 1 mW. Zastrow et al (2007) carried out a safety evaluation on another system intended for breast imaging, which uses 120 ps pulses with a 6 GHz carrier frequency, and with a frequency range of 1–11 GHz. Using finite difference calculations for 11 different phantom conditions, the peak un-averaged specific absorption during a 1 mJ single-pulse exposure was predicted to be in the range 95.46–108.6 mJ kg^{-1}. The highest energy absorption is in the skin layers. For this system, 50 antennas are used and each contributes to the overall exposure. The authors concluded that exposures needed for a successful clinical system lie well within current safety guidelines.

The alternative approach (Li D et al, 2004) uses a ring of 16 monopole antennas surrounding the breast, driven in sequence, with the RF field at each of the other antennas being measured. A cross-section of the dielectric properties of the tissue is reconstructed from these received signals. The scanner operates in the frequency range 0.5–2.1 GHz. Other sections may be reconstructed by moving the ring array with respect to the breast.

Another experimental form of microwave imaging is thermoacoustic tomography. Energy is delivered to the body tissues by the absorption of a microwave pulse. Transient thermal expansion generates an acoustic wave that is then detected by an ultrasonic transducer (Xu and Wang, 2006).

2.4.5.3 Diathermy and RF ablation

Short-wave and microwave diathermy is used as an adjunct to physiotherapy to alleviate acute or chronic conditions of the muscles, ligaments, tendons and joints by heating tissue using RF energy. At higher powers and energy densities, RF and microwave currents are used to cause tissue destruction as an adjunct to surgery. Both areas of application are in widespread use. There is also some clinical use of RF- or microwave-induced tissue heating (hyperthermia), in conjunction with chemotherapy and/or radiotherapy, for the treatment of cancer, but this is considerably less common. In each case the intention is to cause a temperature rise in the tissue, sufficient to cause an intended therapeutic or destructive outcome.

Power levels used by the clinical operator are sufficient to cause the desired outcome at the site of therapy or surgery for the benefit of the patient. There are no regulatory limits to the use of such equipment, and exposure is entirely at the professional judgement of the clinical operator. Neither are there regulated limits to the stray exposure to other parts of the patient's body.

The operator will generally be exposed to, and absorb, RF energy during the treatment. In the case of directed microwave energy it is possible that part of the useful beam that does not irradiate the patient could be intercepted by the clinical operator.

Short-wave diathermy

Short-wave diathermy operates at 13.56 or 27.12 MHz. The electrodes are 'close coupled' to the treatment area. Exposure to operators, standing in their normal treatment positions in front of their equipment console, may exceed 60 V m^{-1} and/or 0.16 A m^{-1}. At 0.2 m from the electrodes, field strengths exceeding 1000 V m^{-1} and up to 11 A m^{-1} have been reported. Leakage from cables may ultimately give rise to the greatest local exposure to the operator unless care is taken to avoid proximity to this source.

Microwave diathermy

The frequency used for microwave diathermy is 2.45 GHz. Typically the operating power of such equipment is around 200 W and energy is directed to the patient using reflector-type antennas, but the design and field characteristics of each type of applicator vary considerably. In one report, power densities measured at distances varying from 0.3–1.2 m from five different applicators ranged from 0.3–100 W m^{-2}. Power densities can exceed reference levels close to applicators. On the basis of stray field measurements made on available microwave equipment, parts of the body may be exposed transiently to power densities in excess of 50 W m^{-2} if the operator is in front of the plane of the front surface of the applicator.

Surgical diathermy and RF ablation

RF techniques are very widely used during surgical procedures. The technique, known as surgical diathermy or electrosurgery, uses a small active electrode as a source of high current density to act as a cutting or coagulation instrument. Current densities as high as 10 A cm^{-2} may be generated with a total source power up to 200 W. The fundamental operating frequency is typically around 500 kHz, but RF emissions may include a wide range of spectral harmonics up to at least 20 MHz (IPEM, 2010). Depending on the application, the electrode may be pointed or blunt, and be placed in contact with, or a few millimetres above, the tissue. The RF drive may be continuous or pulsed, with pulsing ratios from 50%-on/50%-off to 5%-on/95%-off. When a single active electrode is used, a large ground electrode is placed typically beneath the patient. Alternatively, a pair of small electrodes may be used.

The operation of an electrosurgical unit gives rise to RF field exposure, and it is well documented that such fields are of sufficient strength to interfere with the operation of electro-medical monitoring equipment. Reports of field measurements under typical conditions are sparse, however. One study has reported measured electric fields at the position of the surgeon's hand (Edwards, 2003; IPEM, 2010). For five units, electric field exposure, averaged over 6 minutes, varied from 81.9–430 V m^{-1}, with the greatest instantaneous electric field being 770 V m^{-1}. Electric field contours gave the average distance for the 3 V m^{-1} contour as being typically between about 1.3 and 1.7 m from the electrode.

More recently, RF ablation techniques have been introduced clinically for minimally invasive surgery. For example, a catheter-tip electrode can be used to destroy abnormally-conducting cardiac tissues (Williams et al, 2002). The power delivered to the tissue is typically about 20 W. For cancer treatment, a small needle electrode may be inserted within a tumour to create sufficiently high temperatures to kill the local cancer cells. Similar methods are being developed for the treatment of varicose veins and uterine fibroids. In order to overcome problems associated with unwanted heating from stray currents at lower frequencies, small interstitial microwave antennas (9.2 GHz) can deliver sufficient power through a waveguide to destroy tissue, and have been used successfully in the treatment of menorrhagia by endometrial ablation.

2.4.5.4 Telemetry

RF telemetry can be used for monitoring bodily activities. One application uses a telemetry pill with a pH sensor to measure the gastrointestinal acidity profile. The use of such pills may have reduced somewhat with the advent of sophisticated endoscopic probes. Telemetric devices require a frequency band and power sufficient to propagate through body tissues, whilst avoiding interference with any other

communications systems. Since the required range is always short, the radiated power is limited to a few milliwatts. Selection of the frequency band is subject to current bandwidth controls, which vary between countries. The Wireless Medical Telemetry Service in the USA has set preferred bands for medical devices to be 608–614 MHz, 1395–1400 MHz and 1429–1432 MHz, to replace the previously used 402–406 MHz band which has become subject to interference from other users.

2.4.5.5 Wireless transcutaneous power transmission

Battery life limits the longevity of active implanted devices. A number of systems are in use and under development to allow such devices to be powered from an external source using RF power transmission. Transmitted power for most commercial systems are a few tens of milliwatts, but the development of very low power microelectronic components promises systems requiring only about 1 mW (Baker and Sarpeshkar, 2007). The coupling is typically by paired flat coils, one internal and one external, separated by a skin flap of no more than 10 mm thickness. Systems may include status telemetry as well as power input. Widespread use includes power for cochlea implants, and periodic external monitoring and reprogramming for implanted cardiac pacemakers. Implantable drug delivery systems require more power. One such system (Smitha et al, 2005) was designed to couple up to 500 mW at 433 MHz in order to drive an implanted micro-miniature infusion pump. Similar powers would be expected to be required for future retinal implants.

2.4.6 Security and navigation applications

2.4.6.1 Full-body scanners (millimetre wave scanners)

Both ionising and non-ionising radiations are utilised in imaging devices that are used to enhance the security screening of public places – in particular, airports. Millimetre wave body scanners operate in the extremely high frequency (EHF) region (30–300 GHz), just below the sub-millimetre range, which is known as the terahertz range. At these frequencies, the absorption of electromagnetic fields by the human body is very superficial and mainly confined to the skin area. Little information is available about technical specifications of these scanners and the levels of exposure. However, the manufacturers claim that the signals created by the scanners are thousands of times less powerful than those from other commercial RF devices such as mobile phones, wireless handsets and other standard household devices.

2.4.6.2 RF identification (RFID)

RF identification (RFID) technology uses radio waves for the purpose of identification and tracking. RFID devices are usually made of two main components: readers and labels (tags). The tags are made of an integrated circuit that stores and processes information and an antenna for receiving and transmitting signals. Depending on the frequency of operation, tags can be read from several metres away and beyond the line of sight of the reader. Table 2.17 summarises the available RFID technologies and their applications (Finkenzeller, 2006).

2.4.6.3 Electronic article surveillance (EAS)

Electronic article surveillance (EAS) equipment is used to prevent theft from establishments such as shops and libraries. EAS systems comprise a detection unit, a tag to be detected and sometimes a tag deactivator. The principles of operation are similar to those of metal detectors and RFID systems in that an

TABLE 2.17 Different RFID technologies and their applications

Frequency range	Maximum allowed transmission power	Applications
Up to 135 kHz	72 dB μA m^{-1} max	Low frequency, inductive coupling Access control Item and animal identification Near-contact range
3.1–8.8 MHz	13.5–42 dB μA m^{-1}	EAS, medium frequency (ISM), inductive coupling
13.56–27.28 MHz	42–60 dB μA m^{-1}	Medium frequency (13.56 MHz, ISM), inductive coupling, widespread usage for contactless smartcards, smartlabels and item management, eg library systems Typically 1 m range
433 MHz	10–100 mW	UHF (ISM), backscatter coupling Asset tracking Up to 100 m range
860–960 MHz	Up to 4 W EIRP	UHF/supply chain and logistic purposes
2.4 GHz	0.5 W EIRP, outdoor 4 W EIRP, indoor	SHF/logistic purposes Factory automation applications Active tag
5.8 GHz	4 W USA/Canada, 0.5 W Europe	SHF/road traffic Road tolling systems

electromagnetic field is produced over a defined volume. If a tag that has not been deactivated, or removed from the item to which it is attached, enters the detection region, the resulting characteristic perturbation of the field is detected. As with RFID systems, a broad range of frequencies is used by different types of EAS equipment, from sub-kilohertz frequencies to microwave frequencies.

EAS detectors typically contain two or more elements for the generation and detection of fields, which have the appearance of flat panels, loops or pillars and are positioned either side of the customer exit of the shop or library, etc. At least one of the elements contains transmitter coils; the other element or elements contain receiver coils, and possibly transmitter coils too if a Helmholtz configuration is employed. Systems also exist that employ a single antenna containing coils that are connected to the transceiver.

Deactivators are generally desktop devices installed at the customer checkout. Disposable tags containing resonant circuits may be deactivated by overloading the circuit using a pulsed RF magnetic field at the resonant frequency.

Measurements of electric and magnetic field strength close to EAS equipment and of the contact current from some devices have been carried out; the results are summarised in Tables 2.18 and 2.19. The field strength values given in these tables are the maximum ones measured at a given distance from the device. In the case of exposures to pulsed fields, the displayed field strengths are the maximum rms field strengths during a pulse.

TABLE 2.18 Electric field strengths from EAS detectors and tag deactivators at specified distances from the plane of the antenna casing of each device (the detectors were dual antenna systems unless noted otherwise)

Device	Frequency (MHz)	Transmission characteristics	Distance (cm)	Electric field strength (V m^{-1})
Detector	7.4–9.1	Continuous, swept frequency	10	4.0
Detector (single antenna)	7.4–8.8	Continuous, swept frequency	2.5	<1
Detector	7.4–8.8	Continuous, swept frequency	2.5	<1
Deactivator (detection mode)	7.4–8.6	Pulsed, frequency stepped	10 20	89 21
Deactivator (detection mode)	7.4–8.8	Continuous, swept frequency	2.5	<1
Deactivator (deactivation mode)	7.4–8.6	Pulsed, fixed frequency	10 20	86 20
Deactivator (deactivation mode)	7.4–8.8	Pulsed, fixed frequency	5 10 20	190 60 9

TABLE 2.19 Magnetic field strengths from EAS detectors and tag deactivators at specified distances from the plane of the antenna casing of each device (the detectors were dual antenna systems unless noted otherwise)

Device	Frequency (MHz)	Transmission characteristics	Distance (cm)	Magnetic field strength (A m^{-1})
Detector	0.001953	Pulsed, fixed frequency	25 100	350 30
Detector	7.4–9.1	Continuous, swept frequency	15 20	0.09 0.06
Detector (single antenna)	7.4–8.8	Continuous, swept frequency	0 10 20	2.0 0.39 0.18
Detector	7.4–8.8	Continuous, swept frequency	15 35	0.12 0.03
Deactivator (detection mode)	7.4–8.6	Pulsed, frequency stepped	3 10 50	12.3 3.1 0.18
Deactivator (detection mode)	7.4–8.8	Continuous, swept frequency	2.5	0.12
Deactivator (deactivation mode)	7.4–8.6	Pulsed, fixed frequency	3 10 30 50	58 2.7 0.34 0.13
Deactivator (deactivation mode)	7.4–8.8	Pulsed, fixed frequency	5 10 20	10 3 0.8

2.4.6.4 Radar

The term radar covers a wide range of applications from low power Doppler systems to large air and space surveillance systems. The majority of radars operate in the UHF and SHF regions and most employ pulsed transmissions with duty factors in the range 0.0001–0.01, and pulse lengths of the order of microseconds. Most radars employ highly directional, high gain antenna systems.

It is possible to calculate the on-axis peak and average power densities of a radar system. Table 2.20 illustrates the application of such calculational techniques applied to two systems: air traffic control (ATC) radar and tracking radar. It can be seen that the power density in the near field of the tracking radar is higher than those from ATC radars because of the smaller antenna aperture, even though it is a lower power system.

TABLE 2.20 Typical characteristics of two radar systems

Parameter	ATC radar	Tracking radar
Wavelength	23 cm	3 cm
Peak power	2.3 MW	200 kW
Average power	3.4 kW	300 W
Aperture	10 m	1 m
Near-field boundary	154 m	12 m
Distance to 100 W m^{-2}	132 m	33 m
Distance to 10 W m^{-2}	553 m	102 m
Maximum power density in near field	173 W m^{-2}	1528 W m^{-2}

2.4.6.5 Traffic radar

Radars for traffic speed assessment generally use frequencies of around 10.5 or 24 GHz, although some operate at about 35 GHz. The radars operate under continuous wave conditions using the Doppler frequency shift of the reflected signal created by a moving object. The powers used by the radars are in the 10–100 mW range and measurements summarised by NIOSH of several investigators (Lotz et al, 1995) for both fixed and handheld systems indicate that the power densities measured at 5 cm from the radar apertures range from 1.4–64 W m^{-2}. The mean power density measured by NIOSH was about 10 W m^{-2} and exposures outside the 30° cone from the antenna aperture less than 0.1 W m^{-2}.

2.4.6.6 Air traffic control (ATC)

Responsibility for civil ATC radars within the UK is undertaken by National Air Traffic Services (NATS). This includes primary (surveillance), approach, ground movement and secondary (transponder) radars. A summary of civil ATC radars is given in Table 2.21.

TABLE 2.21 UK air traffic control radars

Operating wavelength (cm)	Radar type	Maximum peak power (kW)	Maximum average power (W)	Number of units
50	S264	70	150	5
50	S264A	500	1000	9
23	HSA/ARJ	75–2200	120–3300	12
10	Various	60–650	125–600	43
3	Various	20–150	10–230	38
2	ASTRE	20	6.5	3

For most radar systems there is a high peak power in the pulse compared with the average power determined from the pulse repetition rate and pulse width. In addition to the reduction in average power due to the pulse characteristics, surveillance radar systems such as ATC frequently use a narrow beam of only a few degrees (typically about 3°) which is rotated several times per minute and this reduces the average power by a further factor. The beams are highly directional and, outside the main beam, the power density decreases by several orders of magnitude. Measurements at several hundred metres from such systems indicate average field strengths of tens of millivolts per metre (around 10^{-5} W m^{-2}) and peak field strengths of several volts per metre (around 10^{-1} W m^{-2}).

At an ATC test facility with the antenna stationary, measurements have been made in the vicinity of a radar operating at a frequency of 2.8 GHz and peak power output of 650 kW (Allen et al, 1994). At ground level between 100 and 250 m from the antenna and in the equipment cabin at a height of 9 m above the ground and 60 m from the antenna, electric field strengths were less than 14 V m^{-1} (0.5 W m^{-2}). At about 19 m from the antenna, the power density at a height of 9 m above the ground was 87 V m^{-1} (20 W m^{-2}). Under normal operating conditions with the antenna rotating, the time-averaged power density would be considerably lower.

2.4.6.7 Weather radar

In UK, the Met Office operates a network of radars that provide precipitation data for weather forecasters. Weather radar systems are usually optimised for transmission in the frequency range 5.6–5.65 GHz. Typical peak and average output power values for these systems are about 250 kW and 150 W, respectively. Some wind profiling radars operate at 1.29 GHz, with maximum peak and average powers of 600 and 72 W, respectively. The weather radars are usually mounted on securely fenced high towers, over hills, and away from residential areas. A few on-site exposure measurements have been carried out by the HPA on a selection of weather radar sites; all the measured power density values were below the ICNIRP guideline levels for occupational and public exposure. Typical peak power densities measured at several locations were about 0.055% and 0.23% of the ICNIRP peak power density reference levels for occupational and public exposures, respectively.

2.5 Summary and Conclusions

Exposure of the general public from low level man-made RF electromagnetic radiation is now essentially universal, arising from a wide range of devices operating over a range of frequencies and signal characteristics. Sources are used for communications, medical diagnosis, treatment and surgery, and a wide range of industrial applications.

The widespread introduction of RF devices for public use has resulted in a general increase in the average exposure of the general public above natural background. Nevertheless, exposures remain below internationally accepted guideline levels.

Modern communications protocols use power control and spectral efficiency methods to reduce interference between devices using the same frequency channels at distant locations, and also to maintain battery life. As a result, the trend in instantaneous exposure to a member of the public from mobile communications devices will probably be downward.

Short-range wireless local area networks are being established in homes, public places and educational institutions. The personal exposure from the associated group of sources is expected to be very low, but generalisations are very difficult, depending on locations and synchronisation of the aerials and their emissions.

Standard computational models for dosimetry are now available for adults, but have been shown to be inadequate for age-dependent studies, and for fetal dosimetry. New models, together with improved measurements of dielectric properties, are improving knowledge in this area.

Mild, localised hyperthermia is the most likely mechanism for any biological response. Whilst many new modulation and pulsing methods are being introduced, it is extremely unlikely that demodulation of the carrier frequency, under such conditions, causes any independent biological response.

Industrial procedures, including sputtering, welding and induction heating, are well established, of which RF dielectric heating gives rise to the highest occupational exposures.

In a medical context, the operators of both surgical and medical diathermy devices may be exposed to high levels of RF fields. For individual members of the general public, by far the highest single-event exposures to RF fields arise during medical applications, including those associated with surgical diathermy, medical diathermy and magnetic resonance imaging.

For overall, long-term exposure of the general public, mobile phone handsets are not only highly prevalent, but they also produce the highest exposures encountered during everyday life, primarily of cranial tissues. Public exposure levels from other man-made sources such as Wi-Fi and monitoring equipment, and other digital communications devices including radio/TV masts and microwave link antennas, are considerably lower than those from mobile phone handsets.

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3 Cellular Studies

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

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

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

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

Additionally, if a pulse-modulated signal is applied the cells will only receive an exposure during the pulse. For GSM transmissions the pulse cycle is one in eight, so that the cells will only be exposed to RF fields for one-eighth of the total exposure time, and the mean SAR will be one-eighth of the peak SAR. As a general guideline, the experiments in which the exposure to RF fields has an SAR of less than 1 W kg^{-1} are less likely to involve heating of the cells, although there are some suggestions in the literature that even at low SAR levels there could be micro hot-spots (Liu and Cleary, 1995; Holtze et al, 2006). Heat is known to cause many biological changes and the heating effect of exposure to high intensity RF fields is well established. However, there are claims that exposure to RF fields could also have non-thermal effects on biological systems. Hence the exposure conditions used in the experiments become very important in trying to establish the difference between thermal and non-thermal effects.

Some papers only quote the exposure to RF fields as a power density, which is not necessarily a good indicator of the energy that the cells absorb, as similar power densities can give rise to markedly different SARs depending on the exposure system employed. The better experiments have good dosimetry, thus allowing the exposure to be properly assessed; they also have appropriate experimental controls, so that the size of the cellular response to RF field exposure can be compared to known cellular stimulators or inhibitors. Many of the published studies can be criticised for poor dosimetry and inadequate experimental controls. All results from studies should be regarded as preliminary until independently verified; at present such verification is rare as most replication studies do not support the original findings. This inability of studies to stand up to independent replication casts doubt on the robustness of the findings.

The *in vitro* biological changes due to RF field exposure reported so far are relatively small, which makes experimental confirmation difficult. Even if these changes were confirmed the health implications would be hard to assess and would require further studies using experimental animals or humans. However, the results from *in vitro* studies can be useful to suggest possible mechanisms and indicate areas of further research.

The AGNIR 2003 report on the health effects of exposure to RF fields, based on the published *in vitro* literature, concluded that there was insufficient evidence and no known mechanism to support a direct or indirect effect of RF field exposure on carcinogenesis. Reported effects were not confirmed by independent studies and some apparently similar experiments had contradictory results. A similar confused pattern of results was seen in studies of non-carcinogenic effects, so that no general conclusions could be drawn. The scope of this review has been mainly limited to new evidence published since the previous AGNIR report on RF fields (AGNIR, 2003).

3.1 Genotoxic Effects

Genotoxic effects can be divided into three areas: mutation studies, chromosomal damage and DNA damage. Many studies use several techniques that look at these different aspects within the same experiment.

In vitro mutation studies are a rapid method to assess genotoxicity and are normally undertaken in bacteria or yeast. Most previous reports of low intensity RF field exposure found no change in the rate of mutation; however, at higher intensities where heating cannot be excluded rates can be increased (IEGMP, 2000).

Since 2003, there have been only a few mutation studies published. None has shown increased mutation rates. Bacteria were exposed to 900 MHz with SAR values from 0.22 mW kg^{-1} to 4 W kg^{-1} for up to 48 hours (Belloni et al, 2005; Chang et al, 2005) and to 2.45 GHz at SAR values ranging from 5–200 W kg^{-1} (Koyama et al, 2007) without increasing the mutation rate.

The main methods used to investigate chromosomal damage are chromosomal aberrations, micronucleus formation and sister chromatid exchange; these methods detect fairly gross changes to the chromosomes. Chromosomal aberrations can be seen using light microscopy and are thought to be indicative of genotoxicity. They can accumulate in non-dividing cells but may be lost in cells undergoing division. The consequence of these aberrations is unclear, but they may be associated with cancer, developmental abnormalities or miscarriage. Micronucleus formation, the occurrence of cells with additional, unusually small nuclei, is thought to be the consequence of breaks in the DNA. Estimation of the frequency of micronucleus formation as a result of chromosomal damage is quite sensitive as micronucleus formation can accumulate, particularly in non-dividing cells. However, micronuclei also occur in normal cells, making the interpretation of experiments more difficult. Sister chromatid exchange, the switching of DNA from one part of a chromosome to another, is an early marker of genotoxic effects and is believed to be due to the replication of damaged DNA. It is a widely used and accepted test of genotoxicity.

The favoured procedure for assessing DNA damage was the comet assay (single cell gel electrophoresis assay), but more recently the detection of gamma-H2AX histone has proved a useful and sensitive technique. These techniques detect more subtle changes of DNA strand breaks. The comet assay is a method for measuring DNA strand breaks in individual cells and is used to assess DNA damage. The damaged DNA migrates during electrophoresis out of the nucleus towards the anode; the resulting comet-like appearance is visualised microscopically by fluorescent staining of the DNA. Detection of gamma-H2AX, a phosphorylated histone, is an early indicator of DNA double strand breaks. Gamma-H2AX is required for the repair of double strand DNA breaks and its presence is detected by specific antibodies; this method is a more sensitive detector of damage than the comet assay.

AGNIR (2003) concluded that there was no overall, convincing evidence to support the view that exposure to RF fields was directly carcinogenic or that it promoted other carcinogenic agents. The results of experiments used to assess for genotoxicity were mostly negative, in that there was no increase in the rate of cell proliferation, cell transformation, mutation rate or sister chromatid exchange. Only one study found an increase in chromosomal aberrations and another reported that there was DNA damage through synergy with a genotoxic agent, although surprisingly only at one dose of the agent. The results from the micronucleus assays were variable, with no consistent pattern of results. Even in experiments where micronuclei occurred their importance to human health was unclear as there is a natural incidence of micronuclei in normal cells.

Since 2003 many new studies have been published (Table 3.1); several use the same type of cells and similar exposures thus allowing comparison between results. Some studies have used human lymphocytes to investigate RF field exposure. These cells are easy to obtain by venipuncture from the peripheral blood supply and can be maintained in culture for a few days. Their involvement in the immune system and their role in leukaemia make them suitable targets for studying the effects of exposure to RF fields.

TABLE 3.1 Genotoxic effects

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

TABLE 3.1 *Continued*

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

TABLE 3.1 *Continued*

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

(h) = human, (m) = mouse, (r) = rat, (ch) = Chinese hamster

HL60 – human acute myeloid leukaemia cells, v79 – Chinese hamster fibroblast cells

BBB – blood-brain barrier, CW – continuous wave

Several of the studies using lymphocytes found no genotoxic effects of exposure to RF fields. These studies cover a wide range of exposure parameters in terms of SAR (from a few milliwatts per kilogram to tens of watts per kilogram), duration (from minutes to days), and frequency (800 and 1900 MHz) (McNamee et al, 2003; Zeni et al, 2003, 2005, 2008; Wang B et al, 2005; Sannino et al, 2006; Scarfi et al, 2006; Stronati et al, 2006; Vijayalaxmi, 2006; Kim et al, 2008; Manti et al, 2008; Chen et al, 2009, 2010). However, there are also studies that used similar exposures of SAR, duration and frequency that did show potential genotoxic effects (Sarimov et al, 2004; Markova et al, 2005; Zotti-Martelli et al, 2005; Mazor et al, 2008; Gajski and Garaj-Vrhovac, 2009; Sannino et al, 2009b). There is no apparent difference between the experiments that show effects and those that do not. This discrepancy makes interpreting the results difficult, as there appear to be contradictory data. So, despite having many more experiments on which to base a conclusion, a clear answer is still elusive.

Results from studies using other cell types are also contradictory. Epithelial cells exposed to 1800 MHz for 2 or 24 hours showed DNA damage as measured by the comet and gamma-H2AX assays at SAR values of 3 W kg^{-1} or more (Sun et al, 2006; Yao et al, 2008a). A further paper (Yao et al, 2008b) was retracted. Exposure of fibroblasts to 1800 MHz at 1 to 2 W kg^{-1} for up to 24 hours caused DNA damage (Diem et al, 2005; Schwarz et al, 2008). There was some scientific concern about the validity of these data but even if taken at face value the strength of the data was undermined by a replication study that could not confirm this DNA damage (Speit et al, 2007). Nor did a study of fibroblasts exposed to 900 MHz at 1 W kg^{-1} for 24 hours find any effect on DNA damage as measured by the comet assay and micronuclei counts (Sannino et al, 2009a). A study on stem cells found them to be more sensitive than fibroblasts to exposure to RF fields but not all frequencies caused DNA damage; 915 MHz did cause damage, whereas 905 MHz did not (Markova et al, 2010). Such specific frequency dependence is difficult to explain and seems unlikely unless there is some form of specific tuning. DNA in mouse auditory hair cells (Huang et al, 2008) and some mammalian cell lines (L5178Y and CHL) were unaffected by exposure to mobile phone frequencies (Kim et al, 2008) as were human trophoblasts cells (Valbonesi et al, 2008), neuroblastoma cells (Luukkonen et al, 2010) and isolated sperm (Falzone et al, 2010); sperm were also exposed to 5.7 W kg^{-1} without any adverse effects. However, another study on trophoblasts (Franzellitti et al, 2010) found no effect for continuous wave exposure but pulsed wave exposure at 1800 MHz caused DNA damage after 16 hours of exposure, although recovery was rapid. Astroglial cells were similarly unresponsive to continuous wave exposure but 20 minutes of pulsed wave exposure at 900 MHz caused DNA damage (Campisi et al, 2010). In contrast, amniotic cells exposed to pulsed wave exposure at 900 MHz for 24 hours showed no cytogenetic effects (Bourthoumieu et al, 2010).

At other frequencies the data are more consistent in showing no genotoxic effects of exposure to RF fields. Leukaemia cells (HL60) exposed to 400 MHz at 500 V cm^{-1} for 6 minutes showed no adverse response (Port et al, 2003) and lymphocytes exposed to 2.3 GHz showed no chromosomal damage (Hansteen et al, 2009). The effects of exposure to 2.14 and 2.45 GHz have been extensively studied by one particular research group (Miyakoshi et al, 2002; Koyama et al, 2004; Komatsubara et al, 2005; Wang J et al, 2005; Hirose et al, 2006; Sakuma et al, 2006; Koyama et al, 2007; Hirose et al, 2008). At 2.14 GHz, exposures up to 800 mW kg^{-1} have been tested from hours to weeks with no adverse effect on DNA. A variety of cells from ovary to brain have been exposed to 2.45 GHz at up to 200 W kg^{-1} for 2 hours with no chromosomal or DNA damage.

There have been very few studies at higher frequencies. A study exposing epithelial cells to 35 GHz found that 30 W cm^{-2} caused chromosomal damage (Shckorbatov et al, 2009).

In general, the evidence that exposure to RF fields has a direct genotoxic effect is fairly weak in that there are no consistent effects between laboratories and many conflicting results. However, one of the concerns is that exposure to RF fields could enhance the effect of other known genotoxic agents, such as X-rays or chemical carcinogens. Only a relatively few studies have addressed this concern.

Human lymphocytes exposed to X-rays (1 Gy) before or after exposure to an RF field had no additional effect on chromosomal aberrations, micronucleus formation or sister chromatid exchange (Stronati et al, 2006; Chen et al, 2009). However, another study exposing lymphocytes to X-rays (4 Gy) before RF field exposure found increased chromosomal aberrations (Manti et al, 2008); the authors suggested that the exposure to an RF field had affected DNA repair mechanisms. A similar conclusion was reached by authors of a study that exposed whole blood whilst inhibiting DNA repair. They found an increase in the number of DNA breaks, implying that the RF field exposure was causing repairable DNA damage in normal cells (Tiwari et al, 2008). An effect on DNA repair was also the conclusion in a study that showed synergistic effects of RF field exposure and doxorubin, an inhibitor of lymphoblastoid cells (Chen et al, 2010).
The effect of combining exposure to RF fields and chemical carcinogens was variable. In one study two chemical carcinogens (mitomycin c, 4-nitroquinoline 1-oxide) caused enhanced DNA damage when RF field exposure was applied at the same time; however, two other chemicals (bleomycin and methyl methanesulfonate) showed no enhanced effects (Wang B et al, 2005). In a separate study, DNA damage was enhanced by combined exposure to RF fields and 4-nitroquinoline 1-oxide or cyclophosphamide but not by ethylmethanesulfonate (Kim et al, 2008). Another known mutagen (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone) was tested in combination with RF fields but no enhanced effect was found (Sannino et al, 2009a). At higher frequencies (2.45 GHz) synergistic effects of bleomycin (Koyama et al, 2004, 2007) and metylcholanthene (Wang J et al, 2005; Hirose et al, 2008) were apparent at high SAR values (over 50 W kg^{-1}) and is likely to be due to a thermal effect.

3.2 Effects that could Potentially Lead to Carcinogenesis

3.2.1 Cell transformation

Cell transformation is one stage on the multistage path to malignancy and involves the release of cells from contact inhibition. Transformed cells, in contrast to normal cells, continue to proliferate despite the close contact of other cells. Although there is no convincing evidence that RF field exposure has a direct carcinogenic effect, it might act synergistically in combination with known mutagens or promoting agents to enhance their effect.

The previous review (AGNIR, 2003) found only a few studies had investigated cell transformation and there was no strong supporting evidence that RF field exposure caused cell transformation. The position since then has not changed; there have been only a few new studies and no evidence of effects. Mouse fibroblasts exposed to 2.45 GHz at a wide range of SAR values (5–200 W kg^{-1}) for 2 hours had no increase in cell transformation (Wang J et al, 2005). Similarly, BALB and 3T3 cells exposed to 2.14 GHz at SARs from 80 to 800 mW kg^{-1} for up to 6 weeks showed no effects (Hirose et al, 2008).

3.2.2 Cell proliferation

Many studies on cell proliferation have been added to the literature since 2003. Most looked at the effect of exposure to RF fields on the rate of cell proliferation or programmed cell death (apoptosis). Factors that alter the rate of cell proliferation or apoptosis may play a role in carcinogenesis. The possibility that RF field exposure may cause an increase in the rate of cell proliferation of normal and transformed cells is an important concern and some studies have tried to address this question. Most of the initial findings were summarised by the Royal Society of Canada Expert Panel Report (Royal Society of Canada Expert Panel, 1999) and the IEGMP report (IEGMP, 2000). In general, the results were mixed; there were some modest increases in proliferation rate, but there were also studies showing no effect or even a decreased rate. There were very few additional studies in the AGNIR 2003 report. One study at mobile phone frequencies found no effect of exposure, another at 42.2 GHz found a decreased proliferation rate and increased apoptosis, and yet another found that at 50–80 GHz only cancer cells were affected. No conclusions could be drawn from these few and diverse studies.

Several newer studies have measured the rate of cellular proliferation (Table 3.2). Again the results are mixed; several show no effect on proliferation rate (Yu et al, 2002; Capri et al, 2004b; Miyakoshi et al, 2005; Takashima et al, 2006; Tai-Qin et al, 2008), but these are matched by studies that do show changes. However, none of these new studies shows an increase in the rate of proliferation when cells are exposed to mobile phone frequencies. A concern is that transformed cells (cancer cells) might be potentially more susceptible to RF field exposure and their rate of growth enhanced. Based on the results of the latest studies this concern does not seem to be warranted. However, there is no clear pattern emerging from these studies on a decreased rate of proliferation. The ability to cause a decrease does not appear to depend on whether the cells are derived from normal tissue or cancer cell lines, or whether they are from animals, plants or bacteria. Human lymphocytes exposed to 900 MHz at 70 mW kg^{-1} showed no effect (Capri et al, 2004b), whereas human keratinocytes (skin cells) exposed to 900 MHz at 80 mW kg^{-1} showed a decrease (Duranti et al, 2005). Duckweed had a decreased rate of growth (Tkalec et al, 2005), as did parasitic amoeba (Aksoy et al, 2005) and mung bean seedlings (Sharma et al, 2010), whereas bacteria showed no effect (Cranfield et al, 2003b). An effect was shown in human neuroblastoma cells exposed to 900 MHz at 1 W kg^{-1} (Buttiglione et al, 2007), and human glioma cells (Cao et al, 2009), but human glioma cells exposed to either 1950 MHz at 1–10 W kg^{-1} (Miyakoshi et al, 2005) or 2000 MHz at up to 800 mW kg^{-1} (Sekijima et al, 2010) showed no effect, nor did cholinergic cells exposed to 900 MHz at 1 W kg^{-1} for up to 144 hours (Del Vecchio et al, 2009b). Even using the same cell type did not produced consistent results: mouse fibroblasts exposed to 849 MHz with a range of SAR values from 2–10 W kg^{-1} showed no effect (Lee et al, 2008); however, hamster fibroblasts exposed to 864 or 935 MHz at SARs ranging from 0.08 to 12 W kg^{-1} consistently showed a reduction in rate of proliferation for one research group (Pavicic and Trosic, 2006, 2008a,b; Pavicic et al, 2006; Trosic and Pavicic, 2009).

Only a few studies have been undertaken at higher frequencies. One study at 41.32 GHz found an increased rate of proliferation (Lai et al, 2008), but another study looking at the range 50–80 GHz found a decrease in melanoma cells (Beneduci et al, 2005), and a third using 42 GHz found no effect (Beneduci, 2009). Chinese hamster ovary cells and human glioma cells exposed to 2.45 GHz at 0.05–200 W kg^{-1} for 2 hours showed only thermal effects (Takashima et al, 2006). At a higher frequency of 99 GHz no biological effect was found in bacteria exposed for 19 hours (Cohen et al, 2010).

TABLE 3.2 Possible carcinogenic effects

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

TABLE 3.2 *Continued*

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

TABLE 3.2 *Continued*

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

TABLE 3.2 *Continued*

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

(h) = human, (m) = mouse, (r) = rat, (ch) = Chinese hamster

HL60 – human acute myeloid leukaemia cells, TK6 – lymphoblastoma cells, v79 – Chinese hamster fibroblast cells, L929 – mouse fibroblasts

CW – continuous wave

3.2.3 Apoptosis

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

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

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

Exposure to continuous wave 900 MHz at 2 W kg^{-1} for 24 hours caused increased apoptosis in rat neuronal cells by activation of a pathway that does not use caspase (Joubert et al, 2008). However, this effect was not seen in the same cells when a pulsed signal at 0.25 W kg^{-1} was used (Joubert et al, 2007). This difference was not seen in a study of neurons from mice where a pulsed wave at 1900 MHz (no SAR information provided) caused an increase in gene expression related to apoptosis (Zhao T et al, 2007) nor did it support the caspase-independent route to apoptosis. The results from human neuroblastoma cells exposed to RF fields are more consistent in that all the studies show a lack of response (Joubert et al, 2006; Merola et al, 2006; Höytö et al, 2008a; Moquet et al, 2008). The possibility that continuous wave exposure is required to elicit a response was not confirmed by other studies.

Several other cell types have been tested at various frequencies, SAR levels, pulsed and continuous wave exposure, and durations ranging from minutes to hours; the results have been mixed, with no pattern of exposure emerging that can always cause an effect. Exposure to pulsed 1800 or 1900 MHz at 1–10 W kg^{-1} for up to 12 hours had no effect on apoptosis in human monocytes (Lantow et al, 2006c), acute myeloid leukaemia cells or lymphoblastoma cells (Chauhan et al, 2007a). Increasing the exposure period to 44 hours and making it intermittent with a regimen of 10 minutes on and 20 minutes off also had no effect on apoptosis or heat shock protein expression (Capri et al, 2004a). However, exposure to 900 MHz increased apoptosis in similar cell types, human lymphocytes and lymphoblastoid cells, using continuous wave exposure at 3.5 mW kg^{-1} (Marinelli et al, 2004) or 1.35 W kg^{-1} (Palumbo et al, 2008), although continuous or pulse wave was not specified in the latter study. Also, leukaemia cells exposed to 2.45 GHz at 10 W kg^{-1} had increased gene expression related to apoptosis, which was claimed to be a non-thermal effect (Lee et al, 2005). Mouse stem cells have also been shown to respond to RF field exposure with increased apoptosis, although this was only seen after 6 hours and not after 48 hours (Nikolova et al, 2005). An apoptopic response was found in epidermoid cancer cells when exposed to 1950 MHz at 3.6 mW kg^{-1} for 1–48 hours (Caraglia et al, 2005), but no similar response was found in glioma cells exposed to 900 MHz at 2.6 mW cm^{-2} for 2 hours each day for 3 days (Cao et al, 2009). Neither human glioma cells (A172) nor fetal-lung fibroblasts (IMR90) underwent apoptosis when exposed to 2.14 GHz at a range of SAR values (0.08– 0.8 W kg^{-1}) for up to 48 hours (Hirose et al, 2006).

Two studies found synergistic effects when RF field exposure was combined with other forms of electromagnetic radiation. Exposure to RF fields before gamma radiation (5 Gy) caused increased apoptosis in glioma cells; neither exposure alone caused an effect (Cao et al, 2009). Ultraviolet radiation exposure together with exposure to RF fields caused increased apoptosis in mutant yeast that was more susceptible to apoptosis but no increase in normal yeast (Markkanen et al, 2004). Initially, bacterial death was reported to increase when exposed to 900 MHz (Cranfield et al, 2003a), but in a later study this effect was discounted as being due to the exposure to RF fields (Cranfield et al, 2003b).

In summary, the data on apoptosis are not consistent and the results somewhat confusing. There is approximately an equal distribution of findings showing increased apoptosis and studies showing no effect of exposure to RF fields. This equal split between effect and no effect is also true of the cell types that might be expected to receive most of the RF field exposure in the body during mobile phone use, namely nerve-related cells and blood cells. The difficulty in interpretation is that the reported effects cannot be linked to particular cell types, frequency or levels of exposure (SAR and time). Other suggestions such as a requirement for continuous wave or for intermittent exposure were not confirmed.

3.2.4 Ornithine decarboxylase

Ornithine decarboxylase (ODC) is a key enzyme required for cells to grow and divide. Its activation is related to cell proliferation and most tumour promoters, although not all, increase the activity of ODC. In this regard ODC activity has been used in cells to test for tumour-promoting agents. The effect on ODC of exposure to RF fields was extensively reviewed by the Royal Society of Canada Expert Panel (1999) and updated by the IEGMP (2000). They concluded that exposure to RF fields may cause a slight increase in ODC levels but the changes were small compared to those of chemical promoters, where there can be up to a 500-fold increase. These small changes were unlikely to have an effect on tumour promotion either alone or in synergy with other agents. There were no new studies at the time of the previous AGNIR review (2003).

More recently, there have been several studies on ODC activity; most have investigated the effect of RF field exposure on L929 mouse fibroblast cells (Table 3.2). This particular cell type was chosen because of a report that exposure to 835 MHz at an SAR of 2.5 W kg^{-1} for up to 24 hours caused an increase in ODC activity in L929 fibroblasts (Penafiel et al, 1997). However, none of the seven new studies from three independent research groups has been able to repeat that finding (Desta et al, 2003; Höytö et al, 2006, 2007a,b, 2008a,b; Billaudel et al, 2009b). Although no effect on ODC activity in L929 cells was found, a small decrease in ODC activity was seen in primary astrocytes when exposed to 872 MHz at 1.6 and 6 W kg^{-1} applied for up to 24 hours (Höytö et al, 2007a). The authors commented that ODC activity was particularly temperature sensitive and small temperature increases of less than 1°C decreased ODC activity. Thus, there is a critical necessity that exposed and control cells are tested at exactly the same temperature. Combined effects with other agents were also investigated; menadione was used to induce reactive oxygen species and tertbutylhydroperoxide to induce lipid peroxidation. Menadione combined with RF field exposure induced increased caspase activity (an indicator of apoptosis) in L929 cells but not in SH-SY5Y neuroblastoma cells; tertbutylhydroperoxide combined with RF field exposure increased lipid peroxidation in human SH-SY5Y neuroblastoma cells but not in L929 cells (Höytö et al, 2008a). The implication of these studies was that cells might need to be sensitised to make an effect of RF field exposure apparent, but not all cells are sensitive to the same agents. Billaudel et al (2009a) also investigated effects on SH-SY5Y cells using both 835 and 1800 MHz, with SARs ranging from 1–2.5 W kg^{-1} for 24 hours, but found no effect on ODC activity.

3.2.5 Reactive oxygen species

Reactive oxygen species (ROS) are molecules containing oxygen that are highly chemically reactive because they contain free radicals. The generation of ROS is a naturally occurring process in cell metabolism and ROS levels are normally controlled by specific enzymes and antioxidants. Although ROS are required by cells, an excess can be damaging and they have the potential to damage DNA. Only a few papers have looked directly at ROS production, but the effects, if they occur, may also be detected in studies of DNA damage.

Neither lymphocytes nor fibroblasts responded to 900 MHz exposure with an increase in ROS production. However, if lymphocytes were also stimulated by the addition of iron ions then ROS was increased more than with iron ions alone (Zmyslony et al, 2004). This was not the case for lymphoblastoid cells exposed to

1950 MHz (Brescia et al, 2009) or neuroblastoid cells exposed to 872 MHz (Luukkonen et al, 2010). Nor was it the case for fibroblasts where the addition of a mutagen and RF field exposure had no more effect on ROS production than with the mutagen alone (Zeni et al, 2007). Neurons exposed to 1800 MHz at an SAR of 2 W kg^{-1} for 24 hours using an intermittent exposure of 5 minutes on and 10 minutes off showed oxidative damage (Xu et al, 2010), and mung beans exposed to 900 MHz for up to 4 hours had increased ROS production (Sharma et al, 2009). At the higher frequency of 9.71 GHz, yeast responded with an increase in ROS at exposures of 4 W kg^{-1} or greater (Crouzier et al, 2009).

3.3 Other Changes in Cellular Processes

3.3.1 Gene expression

Chromosomes contain genes, and genes require activation for the production of proteins. Activation of a gene is referred to as gene expression; this expression can be switched on or off. In response to stimulation, genes known as early genes are switched on; the expression of these genes is a sensitive early marker of adaptive cellular changes. The expression of these early genes can be caused by a variety of stimuli, those that have normal cellular functions but also by potentially harmful agents. Particular genes are activated in response to stress experienced by the cell – for example, the genes that produce heat shock proteins. These protective proteins are formed to safeguard the cell and its functions not only in response to heat but also in response to other physical and chemical agents that cause cellular stress.

There were only a few new studies of gene expression in the earlier AGNIR report (2003). However, the results were intriguing in that most studies showed an increase in expression of genes for heat shock protein, but the exposure conditions and the type of response were too inconsistent to be able to draw any conclusions.

More recent investigations looking at gene expression have reported effects in some studies but not in others using apparently similar RF field exposures; this makes drawing any conclusions from the few published papers difficult (Table 3.3). Effects have been found using SAR values ranging from 2 W kg^{-1} (Capri et al, 2006) to 20 W kg^{-1} (Lee et al, 2007), but equally a lack of effects has been reported with SAR values ranging from 1 W kg^{-1} (Tuschl et al, 2006) to 25 W kg^{-1} (Thorlin et al, 2006) or even 60 W kg^{-1} (Im et al, 2010b). Effects do not appear to show a dependence on frequency (900 or 1900 MHz) (Whitehead et al, 2005; Zeng et al, 2006), intermittent exposure (Zeng et al, 2006; Zhao R et al, 2007) or FDMA versus CDMA (Whitehead et al, 2006a,b). There are insufficient numbers of studies to draw conclusions about which types of cells may be sensitive to RF field exposure, apart to say that fibroblasts (Whitehead et al, 2005, 2006a,b; Im et al, 2010b) and glial cells (Thorlin et al, 2006; Nicolaz et al, 2009; Hirose et al, 2010) appear to be insensitive to RF field exposure, since the studies that used these cell types found no effect of exposure. Other cell types lack a sufficient number of studies to make even a preliminary judgement (Capri et al, 2006; Tuschl et al, 2006; Zeng et al, 2006; Lee et al, 2007; Zhao R et al, 2007; Gerner et al, 2010; Im et al, 2010a).

Most of the studies (Table 3.4) that have investigated heat shock protein in haematologically related cells (lymphocytes, monocytes and macrophages) have done so at mobile phone frequencies and have found

TABLE 3.3 Gene expression

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

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

no effect. The studies use frequencies between 800 and 1900 MHz but with a wide range of SAR values and durations as well as pulsed and continuous wave exposure (Hook et al, 2004; Chauhan et al, 2006a,b, 2007b; Gurisik et al, 2006; Lantow et al, 2006a,b; Lee et al, 2006; Simko et al, 2006). Similarly, no effect was found in neurons or other nerve-related cells over a wide range of frequencies (900 MHz – 60 GHz), SAR values (0.1–100 W kg^{-1}) and various durations including intermittent exposures (Gurisik et al, 2006; Qutob et al, 2006; Wang et al, 2006; Chauhan et al, 2007b; Hirose et al, 2007; Zhadobov et al, 2007). Nor were fibroblasts responsive in the exposure range from 836 MHz to 2.14 GHz (Laszlo et al, 2005; Hirose et al, 2007; Sanchez et al, 2007; Im et al, 2010a). Skin cells (keratinocytes) responded to exposure to 900 MHz at 2 W kg^{-1} for 48 hours with a slight increase in HSP70 expression (Sanchez et al, 2006), but this was not found at 1800 MHz with the same SAR and duration (Sanchez et al, 2007) or at the higher frequencies of 42.25 and 61.2 GHz using very high SAR values (up to 770 W kg^{-1}) for up to 60 minutes (Szabo et al, 2003). The changes in heat shock expression previously reported for the nematode *C. elegans* were reinterpreted, when an improved exposure system was employed, as being due to thermal effects (Dawe et al, 2009). Embryonic cells deficient in p53 (p53 is a protein that prevents cancer by tumour suppression) responded to exposure to 1710 MHz at 0.4–2 W kg^{-1} using an intermittent exposure regimen of 5 minutes on and 30 minutes off for 6–72 hours (Czyz et al, 2004). An intermittent exposure regimen of 5 minutes on and 10 minutes off was also effective in trophoblast cells exposed to 1800 MHz at 2 W kg^{-1}, for 4–24 hours (Franzellitti et al, 2008). However, using an intermittent exposure regimen was not a generally applicable method to make cells respond, as neither glioma nor monomac cells were stressed by 1900 MHz at SARs of 0.1–10 W kg^{-1}, cycled 5 minutes on and 10 minutes off for 24 hours (Chauhan et al, 2007b). At higher frequencies (8.15–18.0 GHz), 1 hour of RF field exposure caused stimulation of a stress signalling pathway in lymphocytes (Cherenkov et al, 2009).

3.3.2 Intracellular signalling

Cells receive information via external signals and many cell-signalling pathways include a transient increase in intracellular calcium. This increase can be due to release from internal stores or an influx of calcium ions across the cell membrane from the surrounding fluid. Intracellular calcium concentrations are tightly controlled by the cell and are maintained at a level approximately 1000-fold less than the surrounding fluid. Transient increases in the concentration of calcium in the cell act as a trigger for various other cellular processes. This mechanism is common to many types of cells and hence factors that change the intracellular calcium concentration can have a diverse range of effects depending on the type of cell affected. Much of the early work on exposure to RF fields focused on calcium movement in brain tissue.

3.3.2.1 Calcium flux

The IEGMP report (2000) concluded that that the evidence that RF field exposure caused calcium release from brain tissue was contradictory. The suggestion that these effects occur specifically with pulse-modulated RF signals was intriguing but the implication for cell function was unclear and there was no obvious health effect. A further review of the literature was undertaken (AGNIR, 2001) which examined the evidence for a role of pulse-modulated RF fields (in particular, 16 Hz modulation) in causing an increased efflux of calcium from tissue and cells. That report found that the existence of changes in

TABLE 3.4 Stress effects, expression of heat shock protein

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

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

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

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

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

TABLE 3.5 Intracellular signalling

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

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

3.3.3 Membrane effects

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

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

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

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

barrier due to better cell culture techniques. The later study showed that the effects they reported in their initial paper were due to a poor model rather than to exposure to RF fields. The same group also found no effect of 966 MHz at 1.8 W kg^{-1} for up to 84 hours (Franke et al, 2005b). However, Kuo and Kuo (2008) used a similar frequency (915 MHz at 5 mW for 90 minutes) as a potential clinical application to enhance the transfer of antiviral drugs in to the brain across the blood-brain barrier. As yet, the few *in vitro* models of the blood-brain barrier have not provided a better understanding of what might occur *in vivo* and there are divergent findings in these *in vitro* models. Looking at higher frequencies to investigate junctions between cells, a study using keratinocytes showed no effect of exposure to 30.16 GHz until the cells had been stimulated (Chen et al, 2004).

Other studies have investigated the effect of exposure to RF fields on the membranes of individual cells. One function of cell membranes is their involvement in cell movement and this was shown to change following exposure to RF fields, although the direction of this change was not consistent between cell types; the motion of neutrophils increased (Aly et al, 2008), whereas the reverse effect was seen in sperm, where motility decreased in response to exposure to mobile phone frequencies (Erogul et al, 2006; Falzone et al, 2008; Agarwal et al, 2009; De Iuliis et al, 2009). One suggested cause of this decreased motility was the increase production of reactive oxygen species (ROS); this was also proposed as the mechanism by which yeast exposed to 971 MHz had decreased membrane fluidity (Crouzier et al, 2009). However, in another study of human sperm no increase in ROS production was found after exposure to 1800 MHz for 60 minutes nor were there changes to the cell membrane (Falzone et al, 2010). The rate at which cell membranes can engulf substances (endocytosis) was shown to increase; this effect was reported as due to the electric field component and was independent of frequency and duration of exposure (Mahrour et al, 2005; Moisescu et al, 2009). In cholinergic cells exposure to 900 MHz at 1 W kg^{-1} had an inhibitory effect on the membrane and reduced the number of outgrowths (Del Vecchio et al, 2009a). In keratinocytes and melanoma cells, exposure to 2.25 GHz fields affected the cell membrane by causing increased externalisation of the phospholipid phosphatidylserine (Szabo et al, 2006). In a phospholipid model of an artificial membrane, exposure to 60 GHz at less than 0.9 W cm^{-2} caused an increase in lateral pressure but was insufficient to cause disorganisation of the membrane (Zhadobov et al, 2006).

Using a different model of an artificial lipid membrane, exposure to 985 MHz altered the membrane dynamics and conformation of the porin channel; however, the authors raised the possibility that the effect was due to microsecond heating (Mohammadzadeh et al, 2009). The result of heating was also concluded for the changes in bilayer permeability in vesicles exposed to 900 MHz at 12 W kg^{-1} for 5 hours (Gaber Mohamed et al, 2005). Stankiewicz et al (2006) reported that receptors within the normal membrane became more responsive when exposed to RF fields; lymphocytes exposed to 900 MHz at an SAR of 0.024 W kg^{-1} had an increased response to mitogens (agents that trigger cell division) such as phytohaemagglutinin (PHA) or concanavalin A (con A). In trophoblast cells, exposure for 1 hour to 1817 MHz at 2 W kg^{-1} caused the increased expression of membrane proteins (Cervellati et al, 2009). Not all reported effects were stimulatory; rat neurons taken from the hippocampus exposed to 1800 MHz at 2.4 W kg^{-1} showed a reduced synaptic activity and a reduced number of synapses (Xu et al, 2006). Additionally there are studies that show no effect; rat neurons in preparations of hippocampal slices showed only effects consistent with heating on synaptic transmission when exposed to 9.3 GHz at a wide range of SAR values (0.25–360 W kg^{-1}) (Pakhomov et al, 2003).

TABLE 3.6 Membrane effects

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

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

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

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

3.3.4 Direct effect on proteins

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

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

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

TABLE 3.7 Direct effect on proteins

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

(h) = human

CW – continuous wave

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

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

3.4 Summary

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

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

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

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

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

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

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4 Animal Studies

Animal studies are usually performed using inbred strains of mice or rats and where all animals are genetically identical to ensure a relative consistency of response and absence of confounding, and all variables can be well quantified and precisely controlled (but see Taft et al, 2006, for a discussion of genetic drift in strains of mice). A distinct advantage of *in vivo* experiments is that they provide information concerning the interaction of the agent in question with living systems that display the full repertoire of physiological functions in a way that may not be achievable with *in vitro* studies, such as investigating effects on operant behaviours, and over a timescale that is not usually possible with epidemiological studies, allowing the possibility of multigenerational studies. In addition, transgenic or gene knockout models of many disorders are further increasing the value of animal studies to reveal and understand disease pathogenesis (Bradley, 2002).

Extrapolation of the results of animal studies to humans is not necessarily straightforward, and this is particularly true regarding cancer (Anisimov et al, 2005). Although there are many similarities between processes in humans and other mammals at a molecular level, there are obvious differences in anatomy and physiology between species, as well as differences in variables such as life expectancy and DNA repair capacity. Nevertheless, animal studies are expected to provide qualitative information regarding potential outcomes in humans. The possibility that exposure may cause an effect through a species-specific mechanism that does not operate in humans also has to be considered.

As with cellular and human studies, research using RF fields with animals has continued to focus on the signals associated with mobile phones and base stations, with particular emphasis on investigating whether low intensity exposures that do not cause substantial heating may impair brain and nervous system function; lead to an increased risk of cancer, either directly or indirectly; or reduce fertility or cause an effect on development. Many studies have been published on each of these topics since the previous review by AGNIR in 2003. Also, reflecting concerns about the sensitivity of children to mobile phone signals (Kheifets et al, 2005), more information has been published in the last few years on the responses of immature and juvenile animals to RF fields. In addition, some studies have used sub-mammalian species, but because of their less obvious relevance to human health, these studies have not been included in this review.

Each study has to be evaluated critically, and this includes assessing the adequacy of the experimental design, statistical analysis and the absence of confounding (Repacholi and Cardis, 1997). For example, several types of exposure system have been specially developed for rodents, including different types of carousel and reverberatory chambers (Chou et al, 1999; Balzano et al, 2000; Wake et al, 2007; Jung et al, 2008; Arima et al, 2011), all of which attempt to maximise the welfare of the animals as well as offering good control of metrology, dosimetry and environmental conditions, and these systems have been widely used. However, other studies have simply put a mobile phone into the cage with the animals, and while this simplicity is appealing, the resulting exposures are very poorly controlled and ill-defined and do

not meet the current recommended minimum requirements for quality exposure assessment. Detailed and precise dosimetric information, preferably including a measure of uncertainty and variability, is an essential prerequisite for accurate interpretation of experimental results (Ardoino et al, 2005; Kuster et al, 2006).

It is clear that exposure to RF fields at sufficient intensity will induce heating in animals, the magnitude of which depends on the intensity of the field and the duration of exposure, and also on the environmental conditions and the species exposed. Two recent studies provide further insights into these responses. Ebert et al (2005) investigated the thermoregulatory responses in two strains of mice (B6C3F1 and NMRI) exposed to 905 MHz fields using a 'Mini-wheel' exposure system. Differences in thermal response thresholds were seen that depended on the metabolic rate and on the size of the mouse: under the conditions tested, core temperature was maintained with whole-body SARs between 2 and 5 W kg^{-1}, whereas using SARs between 6 and 10 W kg^{-1} resulted in runaway increases in core temperature. Masuda et al (2011) investigated the effects of very localised exposure of the rat cortex to RF fields on cerebral blood flow and temperature rise. Using a figure-of-eight loop antenna, a small, predefined target area of the parietal cortex was exposed to 1950 MHz fields for 18 minutes at local SARs between 10 and 263 W kg^{-1} (averaged over 4.04 mg). Measurements were made on 35 anaesthetised rats using non-perturbing probes (a Doppler blood flow meter and optical fibre thermometer) inserted into the brain. All exposures caused significant elevations in cerebral temperature and blood flow, and both parameters increased linearly with increasing SAR and exposure duration. In addition, steady-state blood flow in the cortex was significantly correlated with local temperature rise of the target area. However, thresholds for these effects were not determined.

4.1 Brain and Nervous System

The brain and nervous system have long been considered sensitive targets for the effects of low level RF fields, and many studies have been carried out using a range of animal models. Overall, AGNIR (2003) concluded that despite some reports of acute biological changes, no field-dependent effects on the brain and nervous system had been firmly established in the absence of heating. However, it was noted that the available evidence was limited, and it did not rule out the possibility of subtle changes, particularly in young and immature animals (Sienkiewicz et al, 2005). More recent studies are reviewed below.

4.1.1 Cellular physiology

AGNIR (2003) concluded that while some studies had found various changes in acute genomic responses in the rodent brain, the most consistent effects had been reported on stress-related genes and proteins following exposures that caused hyperthermia. Such effects may also occur as a consequence of the immobilisation of animals, which is often necessary to ensure a tight control on absorbed energy. Since 2003, a growing number of studies have explored effects on cellular metabolism, or events associated with injury or apoptosis in animals (Table 4.1). Specific effects on vascular permeability in the brain are considered in Section 4.1.4.

Text continues on page 124

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

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

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

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

TABLE 4.1 *Continued*

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

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

TABLE 4.1 *Continued*

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

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

Several studies by Finnie and colleagues have detected no consistent evidence of any field-induced changes in gene and protein expression following low level exposures. Using a dipole antenna system, Finnie (2005) found acute exposure of restrained mice to pulsed 900 MHz fields did not cause activation of *c-fos* expression in five cortical areas. However, expression was significantly greater compared with freely moving animals, indicating the effects of immobilisation stress. A similar lack of field-dependent effects was reported by Finnie et al (2007) following long-term, repeated exposure. Similarly, there was no evidence that short- or long-term exposure to 900 MHz fields produced microglial activation in the cortex or hippocampus of mice (Finnie et al, 2010). In addition, no field-dependent changes in either *c-fos* expression (Finnie et al, 2006a) or heat shock proteins (Finnie et al, 2009) were found in brains of fetal mice following daily exposures of pregnant animals to 900 MHz throughout gestation.

Using microarray technology, Paparini et al (2008) found no evidence that acute exposure of mice to 1800 MHz fields was associated with major transcriptional changes. Changes in the expression of various genes were observed, but none of these was confirmed using more specific, quantitative techniques.

Following intermittent exposure of heads of mice to CDMA signals at 7.8 W kg^{-1} for up to 12 months, Kim et al (2008) found no evidence of injury or increased cell death in the brain. Grafström et al (2008) examined whether long-term, repeated exposures to pulsed 900 MHz fields affected the histopathological changes associated with injury or ageing in the rat brain: no field-dependent changes were seen. Using a rat model of multiple sclerosis, Anane et al (2003) found that exposure to 900 MHz signals had no effect on the onset, severity or progression of the induced responses.

Two independent studies (Masuda et al, 2009; Poulletier de Gannes et al, 2009a) found no evidence of apoptosis and/or increases in degenerating ('dark') neurons in the brains of juvenile rats after acute, low level exposure to pulsed 900 MHz fields. (Previously, Salford et al, 2003, had reported that an equivalent exposure had caused widespread damage to neurons: AGNIR (2003) noted a number of technical weaknesses with this study.) Similarly, Kumlin et al (2007) found repeated, daily exposures to 900 MHz fields caused no signs of neuronal degeneration in the hippocampus or dentate gyrus of immature rats. No increase in apoptosis was reported in the brains of *hsp*70.1-deficit mice following repeated exposure to 849 or 1762 MHz fields (Lee et al, 2005).

Other studies have reported a variety of field-dependent effects using a number of different models. Belyaev et al (2006) reported modest effects on gene expression in the cerebellum of rats exposed to pulsed 915 MHz signals at 0.4 W kg^{-1} for 2 hours. The genes encoded proteins with no obvious commonality in function. In addition, no significant changes in hsp70 were detected using Western blot. López-Martin et al (2006, 2009) found short-term exposure to pulsed 900 MHz signals increased *c-fos* expression (and seizure activity) in an animal model of epilepsy; however, no effects were seen without pre-treatment with a subconvulsive dose of picrotoxin.

As an indicator of potential damage to neural tissues, de Sèze and colleagues have investigated changes in expression of glial fibrillary acidic protein (GFAP) in the rat brain following head-only exposure to GSM signals. Acute exposure at 6 W kg^{-1} resulted in significant increases in GFAP which were detectable in the frontal cortex and basal ganglia up to 3 days after exposure (Mausset-Bonnefont et al, 2004; Brillaud et al, 2007). Changes were also noted on neurotransmitter receptors (see Section 4.1.2), although there were no effects on behaviour (see Section 4.2.2). Repeated, daily exposures over a 2-month period were

effective in causing significant increases in GFAP expression in several areas of the brain (Ammari et al, 2008a, 2010). Changes in regional neural activity in the rat brain were reported following short-term, repeated exposure at 6 W kg^{-1} but not at 1.5 W kg^{-1} (Ammari et al, 2008b), raising the possibility of a heating effect. Another group reported an increase in GFAP in the mouse hippocampus following daily exposure to 835 MHz signals at 1.6 W kg^{-1} for 3 months (Maskey et al, 2010a). This exposure also resulted in a decreased expression of a calcium binding protein, and an increase in the numbers of apoptotic cells.

Maskey et al (2010b) also investigated the effects of acute and repeated exposures on calcium binding proteins in the mouse hippocampus. Expression of calretinin and calbindin D28-k were significantly increased by acute exposure, while repeated exposure for 1 month produced an almost complete loss of pyramidal cells in area CA1.

One group has reported that acute, daily exposure of young adult, female rats for 1 month caused substantial losses of neuronal cell populations in the brain. Bas et al (2009a) reported significantly decreased pyramidal cell numbers in the hippocampus, and Sonmez et al (2010) reported a similar effect on Purkinje cells in the cerebellum. The stage of development of the brain in these rats was considered comparable to that seen in teenagers.

Nittby et al (2008a) reported that exposure of rats to very weak 1800 MHz fields did not produce significant changes in the expression of individual genes in either the hippocampus or the cortex, although gene ontology analysis indicated highly significant changes in various functional categories of genes in both the cortex and hippocampus; however, the vast majority of the genes in each category were changed by only very small values (between 0.95- and 1.05-fold). Several of these gene categories were associated with membrane functions or cellular signalling.

Several studies have used a mobile phone as an exposure system: some allowed the animals to roam freely, while others held the animals at a set distance and orientation to the handset. Yan et al (2008, 2009) reported that long-term exposure of rats increased the mRNA levels of four proteins associated with injury and cellular repair. However, the local SARs in the brain were very variable. Sokolovic et al (2008) reported low intensity RF fields increased oxidative stress in the brain following daily exposure of rats for up to 60 days. It was found that measures of lipid and protein oxidation were increased by exposure, and the activities of two antioxidant enzymes were significantly changed: catalase was reduced and xanthine oxidase (XO) was increased. However, as groups of animals were free to roam around the mobile phone, the local SAR within the brain would have been highly variable both during and between each exposure; the whole-body SAR was estimated to be between 0.04 and 0.13 W kg^{-1}. Further, it was found that the changes in lipid oxidation and XO were prevented by daily intraperitoneal injection of melatonin. Previously, Ilhan et al (2004) reported changes in markers of oxidative stress in the brains of restrained rats following repeated exposures over 7 days.

Çetin Sorkun et al (2009) reported that repeated, daily exposures to the fields from a mobile phone increased proliferation and protein synthesis, particularly in glial cells of the rat brain. Exposure for 2.5 hours per day to a phone in talk mode produced significantly greater effects than 2.5 minutes per day from a ringing phone, although sham exposure using a switched-off phone (even for 2.5 minutes per day) produced greater effects than those in a group of cage controls.

İmge et al (2010) investigated the effects of fields from an active mobile phone on purine metabolism and antioxidant enzyme activity in freely moving rats. Significant reductions in two enzymes were reported after daily exposures over 3 weeks, although many other measured parameters were unaffected. The absence of any dosimetry, especially to the brain, renders these results largely uninterpretable.

Other studies using mobile phones have reported no statistically significant effects. Yimaz et al (2008) exposed rats for a short period each day for a month and found no changes in Bcl-2, an apoptosis-regulating protein, and Daşdağ et al (2008) reported no change in p53 activity. More recently, and using a head-only exposure system, Daşdağ et al (2009) reported that daily exposure of rats for1 month resulted in decreased caspase-3 expression and no effect on p53 in glial cells, suggesting that exposure was not associated with an increase in apoptosis.

As part of a study investigating effects on neurodegenerative changes, Arendash et al (2010) found that twice-daily exposure of young transgenic mice to 918 MHz GSM signals for 7 months had no significant effects on DNA repair enzymes, antioxidant enzymes or protein oxidative damage in the brain.

Seaman and Phelix (2005) examined the combined effects of acute exposure to a pulsed radar signal and a mitochondrial toxin on the ultrastructure of the caudate-putamen in rats. Injection of the toxin alone caused signs of neuronal injury (evidenced as changes in the endoplasmic reticulum and elsewhere) as did exposure at 6 W kg^{-1} alone; combined exposure significantly increased these changes. Exposure at 0.6 W kg^{-1} alone did not affect ultrastructure, and combined exposure with the toxin reduced the signs seen with the toxin alone. The higher SAR increased colonic temperature by about 3 to 4°C. It was not clear whether the observed changes in neuronal ultrastructure would lead to changes in information processing, but permanent damage or cell death were considered unlikely.

Tarantino et al (2005) investigated the delayed effects of long-term, continuous, whole-body exposure of rabbits to 650 MHz, typical of some broadcasting signals. No effects were seen on body weight, and the health of the animals did not decline, but progressive changes were seen in brain morphology with a gradual increase in apoptosis. Animals were exposed in their home cages within a shielded room, but the basis of the SAR used (quoted at 4.8 W kg^{-1}) was not explained.

Although they did not use brain tissue, Ozgur et al (2010) investigated the effects of exposure to GSM signals on oxidative damage and antioxidant enzyme status in guinea pigs. Significant increases in malondialdehyde and total nitric oxide, and decreases in the activities of superoxide dismutase and glutathione peroxidise, were reported in the liver following exposure at 0.38 W kg^{-1} for 10 or 20 minutes each day for 7 days. There was some evidence of a dose response, as oxidative damage was significantly increased by longer exposures.

4.1.2 Neurotransmitters

Interest in the effects of RF fields on chemical transmission in the brain and nervous system has been sporadic at best, and much work was performed using 2.45 GHz, before the advent of modern mobile phones. AGNIR (2003) concluded that there was some evidence that exposure to RF fields may cause changes in neurotransmitter activity, with studies suggesting that exposure may induce changes in cholinergic function, particularly following hyperthermic exposures. It is also possible that, in some cases, inadvertent stress may have contributed to the observed responses.

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

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

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

More recent studies are sparse (Table 4.2). Using sensitive molecular techniques, Mausset-Bonnefont et al (2004) investigated the effects of acute exposure of the heads of rats to high power (but not hyperthermic) 900 MHz fields on the levels and binding properties of *N*-methyl-D aspartate (NMDA) and $GABA_A$ receptors and dopamine transporters in the cortex, striatum and hippocampus. Significant changes were reported, particularly for decreased levels of $GABA_A$ receptors in the hippocampus, increased dopamine transporters in the striatum, and decreased NMDA receptors in the cortex. In addition, the expression and phosphorylation state of NMDA receptor subunits at the postsynaptic membrane were investigated using immunohistochemistry. It was found that exposure reduced the expression of one receptor subunit (NR1) in the cortex and another subunit (NR2A) in the cortex and hippocampus. Further, at the level of the synapse, the expression of all three subunits was significantly reduced in the striatum and cortex, and the phosphorylation of the NR1 was significantly decreased in the cortex, prompting suggestions that the changes in the NMDA receptors may have been driven by de-phosphorylation mechanisms. The functional significance of the observed molecular changes was investigated by measuring behaviour in an open field. However, no effects were observed on activity or grooming either immediately or 24 hours after exposure.

Using a microdialysis technique, Crouzier et al (2007) measured the release of acetylcholine (ACh) from the hippocampus of freely moving rats during exposure to pulsed 900 MHz signals. No field-dependent effects were found.

4.1.3 Electrical activity

Studies investigating effects on the spontaneous and evoked electrical activity in the brain present some difficult technical challenges in order to avoid the possibility of field-induced artefacts or causing localised heating of electrodes and leads. Interpretation of the results may also not be straightforward: thermophysiological effects, orientation or arousal responses from auditory perception of the applied field, or stresses associated with exposure, also may contribute to any observed response. The quality of many of the early studies is highly variable, and the most consistent effects have been seen following exposures inducing 1°C or more rises in core temperature, but a few studies suggest changes in certain frequency bands may occur during exposure (AGNIR, 2003). ICNIRP (2009) concluded that effects on the electroencephalogram (EEG) in animals were rather variable and the possibility of uncontrolled artefacts could not be ruled out. Recent studies have not provided clear evidence of field-dependent effects, although few studies have been undertaken (Table 4.3).

Vorobyov et al (2004, 2010) exposed freely-moving rats to pulsed 915 MHz fields and recoded changes in the beta frequency band in the hypothalamus, with less consistent effects seen in the cortex. These effects were associated with changes in cholinergic activity. However, it is possible that these changes in the EEG may reflect to some extent either local thermal effects or thermophysiological responses by the hypothalamus.

Crouzier et al (2007) measured the EEG and other physiological variables in freely moving rats during exposure to pulsed 900 MHz signals. No field-dependent effects were found.

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

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

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

Lipping et al (2009) used the paradigm of burst-suppression as an indicator of pulsed 900 MHz signals on the EEG. Pigs were heavily anaesthetised to produce a relatively flat EEG that alternated with high amplitude, mixed frequency bursts; in this state a burst can be provoked by mild somatosensory and other stimuli. However, acute exposure to repeated, short duration signals was not correlated with triggering burst activity. In addition, under lighter anaesthesia, no effects were seen on the relative power of the major EEG frequency bands using exposures that increased local temperature in the head.

López-Martin et al (2006, 2009) used an animal model of epilepsy to investigate the effects of RF fields on seizures. They found short-term exposure of rats to pulsed 900 MHz (but not continuous wave) signals induced seizures following pre-treatment with a subconvulsive dose of picrotoxin, and resulted in generalised continuous spike and wave trains in the EEG. Exposure without pre-treatment had no effect. This suggests that exposure triggered epileptic episodes, but whether (human) epileptics may be more vulnerable to the effects of pulsed fields remains to be determined.

Although the EEG was not measured, Erdinc et al (2003) explored the effects of 900 MHz signals on pentylenetetrazole-induced seizure behaviour in young mice. Acute exposure had no effect, but the onset of mild limb movements was reduced following exposure for 20 hours. Onset of more severe movements and mortality were not affected.

4.1.4 Blood-brain barrier

One of the most controversial areas of study concerns effects of RF fields on the blood-brain barrier. A few studies have reported that exposures of rodents to very low level fields may alter the permeability of the blood-brain barrier and cause leakage of molecules from the blood into the cerebrospinal fluid. Such responses could produce severe and lasting adverse consequences, and changes in permeability also occur in brain trauma and during hyperthermia. However, other studies have not replicated these results with very low level fields, and consistent changes in permeability have only been found using hyperthermic exposures. AGNIR (2003) concluded that well-conducted studies have not reported any effects on the blood-brain barrier unless exposures increased core body temperature. Recent studies on this topic and associated studies investigating changes on the microcirculation in the brain have mostly been negative, but a few positive studies have been reported (Table 4.4).

Kuribayashi et al (2005) investigated the effects of repeated exposure to PDC signals in immature and young rats. No significant effects on vascular permeability of the blood-brain barrier were seen, nor did exposure result in any pathological changes. In addition, exposure had no consistent effect on the expression of three genes involved in the regulation of barrier function.

In a novel approach, Cosquer et al (2005a) assessed the effects of microwaves on the blood-brain barrier using a rat behavioural model. The performance of animals in a radial arm maze was measured following daily exposure to pulsed 2.45 GHz fields and injection of a derivative of scopolamine, a drug known to affect maze performance, but in a form that only poorly crosses the blood-brain barrier. Injection of the drug either before or after exposure had no significant effect on performance, suggesting the permeability of the blood-brain barrier was not altered. In addition, exposure was not associated with increased leakage of albumin into the brain.

The effect of daily exposure to GSM signals on the integrity of the blood-brain barrier in fetal and neonatal mice was investigated by Finnie et al (2006b,c). No effects on albumin extravasation were seen. Kumlin et al (2007) found repeated exposure of immature rats to GSM signals did not increase leakage to Evans blue dye. In addition, no degenerative changes were seen in the hippocampus or dentate gyrus.

Highlighting potential differences in gender response, Sirav and Seyhan (2009) reported acute exposure to continuous wave 900 or 1800 MHz fields increased the permeability of the blood-brain barrier to albumin in anaesthetised male, but not female, rats. However, limitations of the study include inadequate descriptions of the exposure system and incomplete dosimetry. More importantly, it is possible that the changes seen in the males are more attributable to a depressed value for the sham-exposed control group.

Their earlier studies were reviewed by AGNIR (2003) and in recent years Salford and colleagues have continued to explore effects on the permeability of the blood-brain barrier. In contrast to their other studies using shorter exposures, Grafström et al (2008) reported no increase in albumin extravasation (nor other histopathological changes) following long-term, low level exposure of rats to GSM signals. Eberhardt et al (2008) reported that acute exposure to GSM signals reversibly increased albumin extravasation after 14 days post-exposure, and increased dark neurons after 28 days. Further, these effects showed evidence of an inverse dose-response relationship: no explanation could be offered for this result. Nittby et al (2009) examined the lasting effects of exposure. Seven days after exposure, albumin extravasation was greatest in rats exposed at 0.012 W kg^{-1}.

The potential importance of the results originating from Salford and colleagues suggesting that low level exposures may affect the integrity of the blood-brain barrier has prompted three independent research groups to try to confirm the findings. These investigations used the same strain of rat as used previously, but they avoided some of the technical weaknesses in the original studies, which included using rats of widely different ages, and the later groups habituated their animals to the exposure systems.

Firstly, McQuade et al (2009) used a similar transverse electromagnetic transmission line (TEM) exposure cell and similar exposure parameters to those used by Salford and colleagues. Rats were exposed for 30 minutes to continuous and pulsed 915 MHz fields over a wide range of SARs. However, no increase in albumin extravasation was found in the brain at any intensity.

Next, Masuda et al (2009) examined the effects of exposure for 2 hours to pulsed 915 MHz fields at up to 2.0 W kg^{-1}. The effects on albumin leakage and on the appearance of dark neurons were evaluated 14 and 50 days after exposure. Using improved staining techniques, no evidence of increased albumin extravasation was found in the brain, nor was the incidence of dark neurons significantly increased.

Finally, Poulletier de Gannes et al (2009a) also used improved staining techniques to identify albumin leakage and the presence of dark neurons 14 or 50 days after head-only exposure of rats to a GSM signal. In addition, a more specific marker for neuronal degeneration was used, and apoptosis was measured. No evidence of increased albumin extravasation, neuronal degeneration, numbers of dark neurons or apoptosis was found in any of 12 selected regions of the brain. The lack of effect on albumin leakage is shown in Figure 4.1.

One group has used the closed cranial window model to observe the effects of RF fields on cerebral microcirculation directly in rats (Masuda et al, 2007a,b; Hirota et al, 2009). Neither single nor repeated exposure over 4 weeks to PDC signals produced any significant effects on cerebral haemodynamics, leukocyte behaviour or blood-brain barrier permeability.

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

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

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

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

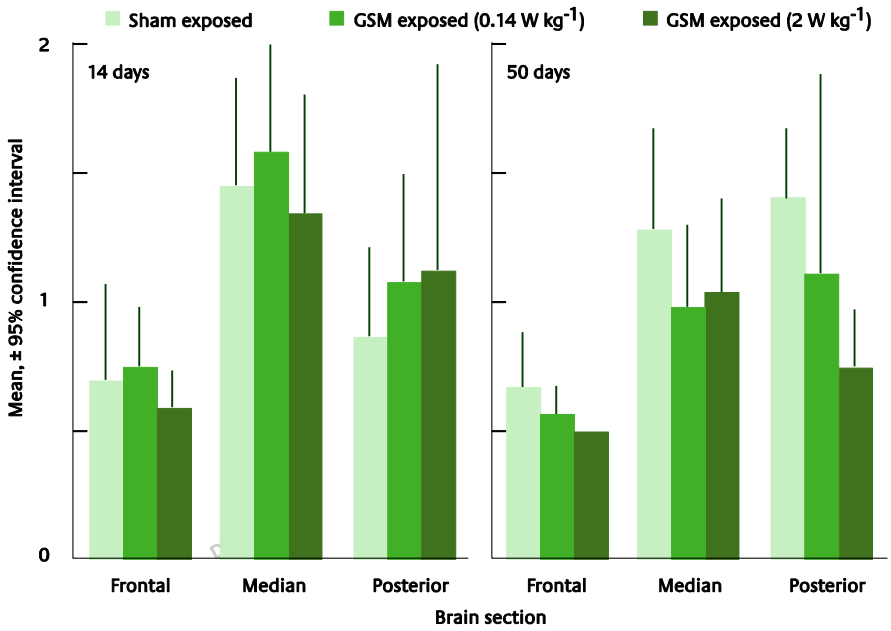

FIGURE 4.1 Albumin extravasations in the brain of rats at 14 or 50 days after a single 20-hour exposure to 900 MHz GSM fields or sham exposure (*n* = 8, in all groups). Three cross-sections of the brain were analysed, indicated by frontal, median or posterior. Numbers of extravasations are low for all groups, and there are no significant differences between exposed and sham-exposed animals. Redrawn with permission from Poulletier de Gannes et al (2009a)

4.1.5 Autonomic functions

Some studies have investigated the effects of RF fields on autonomic function, such as heart rate and blood pressure. AGNIR (2003) noted possible effects on long-term systolic hypotension in rats from ultra-wideband signals, which were below the threshold for auditory perception of pulsed microwave fields. There is a paucity of recent work (Table 4.5).

It is generally accepted that RF-field-induced cardiovascular responses are consistent with those associated with thermoregulation to conventional heating. However, new and emerging technologies are using frequencies of around 30 GHz and more (millimetre wavelengths). Fields at these frequencies will cause greater heating in the skin compared with longer wavelengths. Millenbaugh et al (2006) found that only exposure to severely hyperthermic fields at 94 GHz significantly decreased the time taken to reach circulatory collapse in anaesthetised rats compared with animals exposed to warm environments, while core temperatures at this point were significantly reduced. It was concluded that core temperature remained the major determinate of the induction of collapse, and the influence of heating of the skin only becomes of biological significance when a certain threshold rate of heating in these tissues has been exceeded.

Li et al (2007) investigated the effect of electromagnetic pulses (EMP) on delayed cardiovascular responses in rats. Heart rate was not affected by exposure, but blood pressure showed a biphasic response, being increased for up to 6 hours post-exposure, then being decreased for 1 month.

TABLE 4.5 Animal studies investigating effects on autonomic function

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

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

4.1.6 Summary

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

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

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

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

4.2 Behaviour

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

4.2.1 Spatial memory tasks

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

Text continues on page 140

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

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

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

TABLE 4.6 *Continued*

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

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

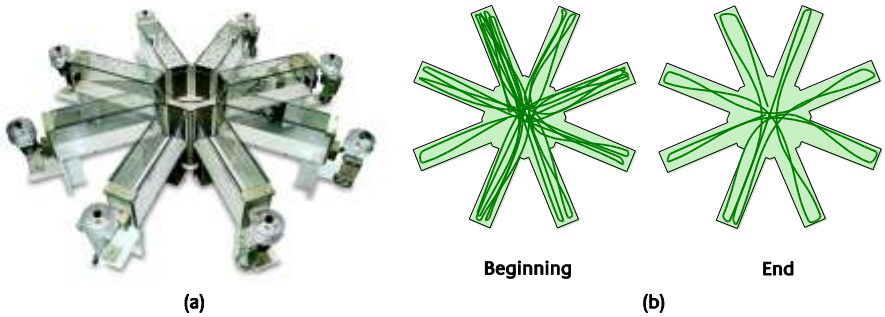

FIGURE 4.2 (a) Radial arm maze (courtesy of Med Associates, Inc) – food is available at the ends of each of the arms and animals are required to forage for this food
(b) Typical paths taken by animals in the maze during the test: at first (left) an animal makes many errors (repeat entries into an arm) to obtain all the food, but gradually learns to make few errors (right)

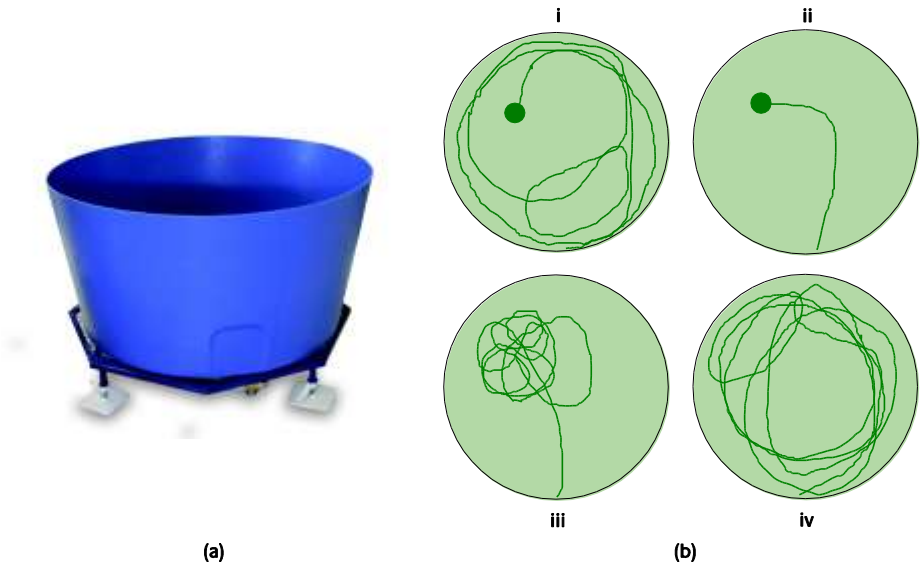

FIGURE 4.3 (a) Water maze (courtesy of Med Associates, Inc) – the maze has a diameter of about 100–200 cm depending on the species tested
(b) A small circular platform (shown in grey) is submerged beneath the surface of the water in the maze and animals are required to find the location of this platform to escape from the water. Typical swim paths taken by an animal (i) early and (ii) late in testing. The platform is removed during the probe trial and typical swim paths of an animal are illustrated, showing (iii) good and (iv) poor acquisition of the task

In an attempt to replicate the deficits in behaviour reported by Lai and colleagues, Cobb et al (2004) exposed rats to pulsed 2.45 GHz fields and tested spatial learning in a 12-arm radial maze. All animals acquired the food-reinforced task over 10 days, and no field-dependent deficits in performance were seen. In a commentary on the study, Lai (2005) suggested that methodological differences may explain

these different outcomes: among other minor differences between studies, Lai limited the number of choices his animals could make each day to 12, whereas Cobb et al allowed an unlimited number of choices (both within a 10-minute trial duration) which would support increased performance of the task. However, it is not apparent from an inspection of the data that the animals used by Cobb et al showed over-learning compared with those of Lai et al (1994), and so they are unlikely to have been more resistant to any RF-field-induced disruptions in acquisition. Also the rates at which both sets of animals reduced errors in the task were very similar, suggesting equivalent rates of learning in both studies.

Cassel and colleagues also did not confirm the results of Lai et al (1994). In a series of studies, exposure had no significant effects on maze performance at either 0.6 W kg^{-1} (Cassel et al, 2004) or 2.0 W kg^{-1} (Cosquer et al, 2005a). The maze used in these studies had small, transparent side walls, and so provided access to distal visual cues, but using a maze with high opaque walls (as used by Lai and colleagues) did not affect the result (Cosquer et al, 2005b). Cassel et al speculated that the results reported by Lai et al may have been more attributable to stress or anxiety than to memory per se; however, exposure had no significant effects on anxiety as measured in an elevated-plus maze under low or high levels of ambient light (Cosquer et al, 2005c; see Table 4.7).

Ammari et al (2008c) explored the effects of long-term, head-only exposure to GSM signals on spatial memory in rats. No significant differences in acquisition of a radial arm maze task were seen following repeated, daily exposures for 2 or 6 months or on subsequent performance following the introduction of delay during testing (which would have increased the difficulty of the task).

Nittby et al (2008b) investigated the effects of long-term exposure to GSM signals on a recognition memory task. Over three trials, rats were presented with four black blocks arranged in a square, then with four grey cylinders arranged in a T-shape, and finally with two black blocks and one grey cylinder in their previous locations and one grey cylinder in a novel location. Exploration of the objects (defined as closely approaching and attending) was measured on each trial. Rats normally have a preference to explore less recently seen (older) objects or recently seen (familiar) objects in novel locations. However, exposed animals showed significantly less preference to explore older objects compared with more familiar ones, although the magnitude of this effect was far smaller than that shown by the cage control animals. Exposure had no effect on remembering object location, and all animals showed the expected preference to explore objects in novel locations.

Other studies have reported deficits in spatial memory following exposure to RF fields, but none offers unequivocal evidence for field-dependent effects. Narayanan et al (2009) placed a mobile phone in silent but vibratory mode beneath a cage containing young adult rats. Each day for 4 weeks, these animals were exposed to the fields associated with 50 missed calls and then their spatial learning capabilities were tested using a water maze. Significant differences in behaviour were seen. Exposed animals initially took far longer to locate the escape platform during acquisition trials and, although their latencies improved, they remained slower than controls. During the probe trial, the exposed animals took significantly longer to reach the target quadrant and spent less time in that quadrant. However, no estimate of the SAR from the phone was given, although the emissions from the phone would be negligible under these circumstances (see Chapter 2). The authors conceded that the vibrations made by the phone could have been responsible for the observed responses.

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

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

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

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

Fragopoulou et al (2010a) reported subtle deficits in a water maze task in young adult mice exposed to fields from a commercial mobile phone sending a continuous audio signal. Animals were exposed for 1 hour before testing, as well as for 15 minutes between each trial, for 10 minutes after testing, and again for 2 hours before the probe trial. This protocol did not result in any overall changes, either in latency to find the hidden platform or in the mean distance swam for all days, but both latency and distance were significantly increased in the first trial on days 2, 3 and 4, and exposed animals did not show the expected preference for the target quadrant during the probe trial. It was suggested that exposure had interfered with memory retrieval or consolidation. However, there are a number of caveats with this study, including the over-complicated exposure protocol, exposing the animals between trials and before the probe trial, using the same start position for the first trial each day, and not randomising the order of the trials. Further, while a mobile phone offers a readily available source of RF fields, it does not allow any knowledge or control of individual exposures, particularly in a group of freely moving animals.

Testing ideas originally proposed by Litovitz and colleagues, Lai (2004) reported that deficits in task performance caused by exposure to microwaves could be inhibited by simultaneous exposure to a temporarily incoherent magnetic field. In this study, rats were exposed to continuous wave 2.45 GHz fields using a cylindrical waveguide system placed inside a set of Helmholtz coils that generated a highly complex magnetic signal between 30 and 100 Hz at 6 μT ('magnetic noise'). Acute exposure to microwaves before testing resulted in a significant increase in time taken to locate the escape platform, but simultaneous exposure to microwaves and magnetic noise attenuated this difference; magnetic noise alone had no effect. These results are shown in Figure 4.4. During the probe trial, and consistent with earlier studies from this laboratory, the animals exposed to microwaves also spent significantly less time in the quadrant of the maze that previously held the platform compared with the other treatment groups.

Two studies have exposed young or immature animals to RF fields and measured the effect on their behaviour. Kumlin et al (2007) exposed rats to GSM signals at 0.3 or 3 W kg^{-1} from about 3 weeks of age for 5 weeks and found improvements in performance of the water maze task, with significantly decreased latencies to locate the escape platform at both SARs. During the probe trial, animals exposed at the higher SAR also spent significantly more time in the quadrant of the pool that previously contained the platform. No significant effects were seen on open field behaviour. Interestingly, comparable changes have been reported by Takahashi et al (2010) following prenatal and early postnatal exposure of male rats to pulsed 2.14 GHz signals (see Section 4.7.2).

Daniels et al (2009) reported a lack of effect on spatial memory function in adult rats following early postnatal exposure to 840 MHz 'equivalent to … exposure from mobile phones'. However, an increase in freezing behaviour in the maze was seen in exposed males, and a significant decrease in locomotion and an increase in grooming were observed in males in an open field. No morphological changes were seen in the hippocampus or cortex. Overall, these results were taken as evidence that exposure had acted as an environmental risk factor in the development of abnormal behaviour. However, the usefulness of this study is limited by the lack of dosimetry, and the protocol used for the water maze seems less than ideal.

Using a transgenic mouse model of Alzheimer's disease, Arendash et al (2010) reported that the expected deficits in behaviour normally displayed by adult mice in a cognitive interference version of the water maze task could be significantly reduced by long-term exposure to 918 MHz GSM signals

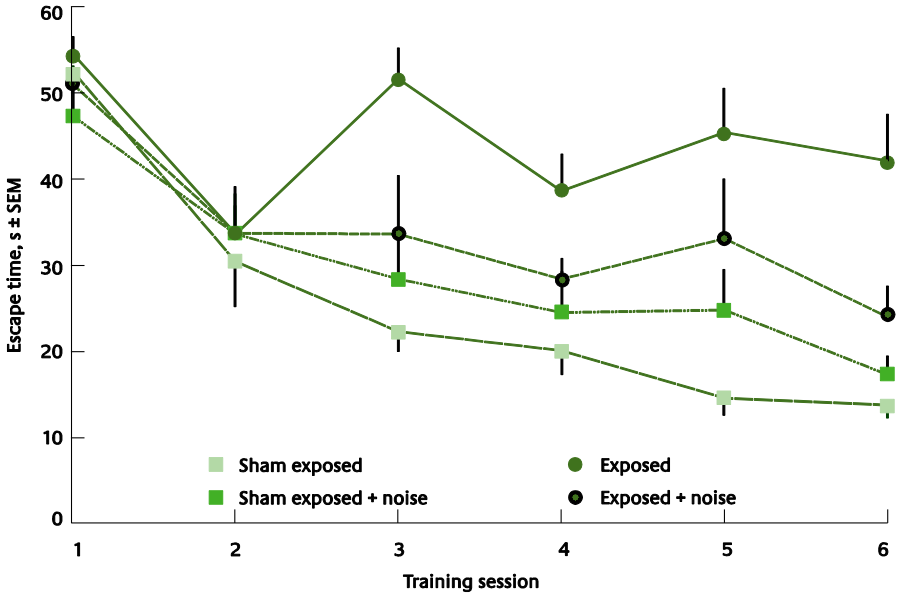

FIGURE 4.4 Mean swimming times of rats to locate an escape platform during the six training sessions in a water maze (n = 8, in all groups). Compared with sham-exposed animals, exposure to continuous wave 2.45 GHz microwaves significantly increased escape times. This effect was attenuated by simultaneous exposure to microwaves and a 30–100 Hz magnetic field at 6 μT (noise). Redrawn with permission from Lai (2004)

(Arendash and Cao, 2010). Starting at 2 months of age, animals were exposed at about 0.25 W kg^{-1} twice a day (morning and late afternoon) for up to 7 months, and their performance in the water maze task was measured at set intervals. For this task, the swimming pool was divided into a central area and six radial arms, and the escape platform was placed at the end of one of the arms. A second maze in a different laboratory and a Y-maze provided interference and distraction between the trials. Animals had five trials each day to find the location of the platform, the position of which was changed each day. Performance was measured as the numbers of errors made and the escape latencies. The task was considered analogous to a human cognitive test that can be used to discriminate between patients with Alzheimer's disease, those with mild cognitive impairment and non-demented individuals. After 4–5 months of exposure, the performance of the transgenic mice was not significantly different from that of sham-exposed animals, but after a further 2 months of exposure, their performance was significantly improved compared with sham-exposed animals, resulting in a level of performance comparable to that of non-transgenic littermates. The results of a battery of sensorimotor and anxiety tests largely ruled out non-cognitive influences on behaviour. Levels of soluble amyloid-β (Aβ) protein in the hippocampus and frontal cortex were (non-significantly) increased in transgenic animals, and there were no consistent effects on measures of oxidative stress.

Arendash et al (2010) also investigated the effects of repeated exposures on slightly older animals (beginning at 5 months of age). The same tasks and exposures were used. At first, the transgenic animals

showed an impaired performance of the task irrespective of their exposure status. However, after 8 months of exposure, the performance of the transgenic mice improved, and they made significantly fewer errors in the maze than the sham-exposed transgenic animals. These results are shown in Figure 4.5. The performance of the non-transgenic animals also improved with exposure, and they made significantly fewer errors than their sham-exposed counterparts after 5 or more months of exposure. In addition, significant reductions were seen in exposed transgenic mice in levels of Aβ deposition in the hippocampus and cortex, both *in vivo* and *in vitro*, and nearly-significant increases in levels of soluble Aβ.

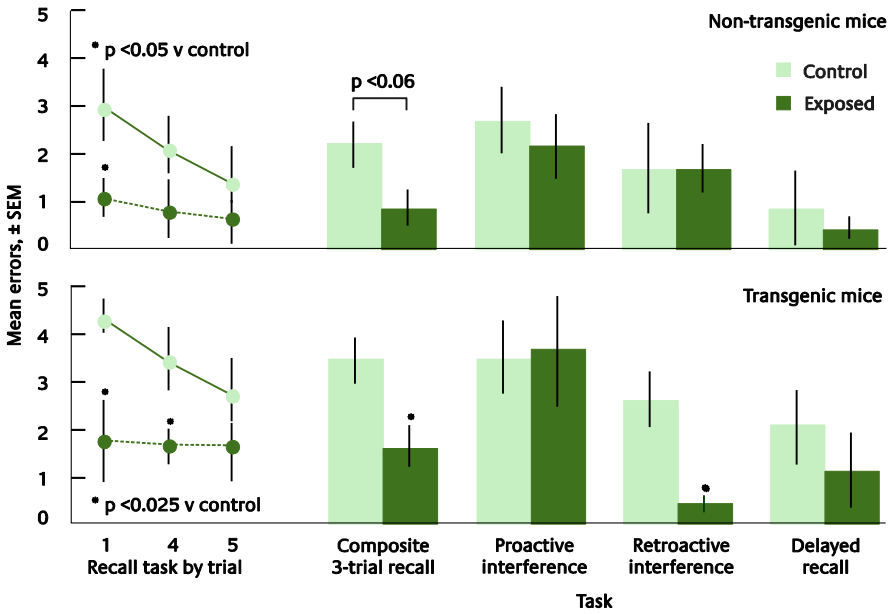

FIGURE 4.5 Cognitive interference testing after 8 months of exposure to a 918 MHz GSM signal at 0.25 W kg^{-1} in 13 month old non-transgenic (NT) and AβPPsw transgenic (Tg) mice. Errors made in locating an escape platform in a radial arm water maze in each of the four component tasks are shown (n = 5–8, in all groups). Exposed NT mice exposed showed significantly better recall performance than NT controls, particularly early in testing. Exposed Tg mice were significantly superior to Tg controls in both three-trial recall and retroactive interference tasks. Data for the final 2-day block of testing are shown. Redrawn from Arendash et al (2010) with permission from IOS Press

The authors noted an elevation in both body and brain temperature during irradiation following repeated, but not single, exposure of transgenic, but not other, animals, and suggested (among other possibilities) that an increase in cerebral blood flow resulting from exposure may have suppressed Aβ aggregation. The measured increase in rectal temperature exceeded 1°C, which seems high given the estimate of the SAR used, although the thermoregulatory responses of transgenic animals to repeated exposure to RF fields have not been explored. An increase in cerebral blood flow resulting from field-induced hyperthermia may provide some explanation of the observed results in the transgenic animals.

A simple exposure system was used in this study, with the animal cages being arranged in a circular pattern around the antenna within a Faraday cage, but few other details of the exposure system were given. The local SAR in the brain appears to have been derived from measurements of the (external) electric field strength (Arendash and Cao, 2010), but no information on the probes used or the techniques employed was given. Measurements in the near field are difficult to interpret because of complex field components and coupling relationships with probes and any surrounding objects which are hard to predict. The external fields are likely to be only loosely related to the SAR under these conditions. The SAR predictions are also uncertain because the animals were free to move within their cages.

This study is the first to suggest that long-term, repeated exposure to RF fields may lessen or reverse the impact of age-related behavioural deficits in a transgenic mouse model of Alzheimer's disease, and also to improve performance in non-transgenic animals. However, with some uncertainties surrounding the exposure set-up and dosimetry, and given the possibility that field-induced hyperthermia may be key, replication of this study is essential before any conclusions can be drawn. Such a replication should include the use of a well-characterised exposure system and incorporate modern experimental or computational methods to determine the average SAR in the brain, and possibly in other major organs, for both young and older animals. In addition, the use of more than one exposure level would allow the dose-response relationship to be investigated.

In a follow-up study by the same group, repeated exposure of both normal and transgenic mice was associated with a significant increase in mitochondrial function, especially in the cerebral cortex and hippocampus (Dragicevic et al, 2011). Using the same system as previously, the animals were exposed to pulsed 918 MHz fields at 0.25 to 1 W kg^{-1} for 1 hour twice a day for 1 month. Rectal temperatures of the exposed animals were increased by exposure by about 1°C, although temporal muscle temperatures (used as a surrogate for brain temperatures) did not significantly increase (which was ascribed to an increase in cerebral blood flow). Although behaviour was not investigated in this study, the enhancements in cognitive behaviour previously seen in transgenic mice following exposure to pulsed RF fields were attributed to the observed changes in mitochondrial function.

4.2.2 Other tasks

Relatively few studies have investigated effects on innate behaviour or on non-spatial learning tasks (Table 4.7). Mausset-Bonnefont et al (2004) reported no significant effects on open field behaviour of rats following acute, head-only exposure; similarly, Nittby et al (2008b) reported an absence of effects following low level, long-term exposures. However, Daniels et al (2009) reported changes in activity of adult male rats in an open field following early postnatal exposure to very low level 840 MHz fields; no effects were seen in females.

It has been postulated that exposure to RF fields might influence cognitive function and behaviour by increasing the levels of stress or anxiety. Cosquer et al (2005c) investigated this possibility in rats using an elevated-plus maze to measure anxiety responses. Following acute exposure to pulsed 2.45 GHz fields, no changes in behaviour were observed in the maze, even under conditions of low ambient light which should have shown any anxiogenic response. As part of a study investigating effects on the developing brain, Kumlin et al (2007) exposed juvenile animals to GSM signals from about 3 weeks of age for 5 weeks.

Exposure was without significant effect on behaviour in an open field or an elevated-plus maze, or on an acoustic startle response test.

Two additional studies have explored effects on anxiety in rats using the elevated-plus maze, but neither is particularly informative of possible effects. Kumar et al (2009) reported that exposure to a daily cohort of missed calls from a GSM mobile phone increased levels of anxiety in rats. Behavioural changes were seen both immediately and 24 hours after the last exposure. The phone was silent, but was kept in vibratory mode, suggesting low frequency vibrations could have contributed to the observed changes. Rocha et al (2009) reported that long-term, daily exposures of male and female rats to continuous wave 850 MHz fields from gestation until adulthood resulted in lower levels of anxiety, and exposure was also associated with increased water consumption. These changes were attributed to heating, although body temperatures were not recorded, and no significant effects were seen on water maze performance. However, this study has several conspicuous limitations, particularly in dosimetry, such that nothing can be deduced with any certainty.

Narayanan et al (2010) reported significant effects on passive avoidance learning in rats. A group of rats was exposed to RF fields using a commercial mobile phone placed in their cage in silent (but vibratory) mode. Animals were exposed to the fields associated with 50 missed calls each day for 4 weeks. Passive avoidance was tested using latency to enter a small, dark compartment from a large, bright one. The exposed animals took significantly longer to enter the dark compartment on the second and third of three habituation trials, and during the retention trials performed 24 and 48 hours after associating the small compartment with electrical foot shock. However, no estimate of the SAR from the phone was given, and it is likely to have been very variable between animals. The contribution of the vibrations made by the phone was also not considered.

Ntzouni et al (2011) investigated the effects of GSM signals on the performance of an object recognition task in mice. The task was conducted in a dedicated arena, with animals exploring two identical objects on one trial, and after an inter-trial interval (ITI) of 10 minutes, the animals explored one of the objects from the previous trial as well as a new object. Animals were exposed using a working mobile phone that had been placed under the arena or home cage. Exposures during the trials resulted in a non-significant decrease in discrimination. After an interval of 8 days with no procedures, the same animals were exposed in their home cages for 90 minutes each day for 17 days. Another object recognition task was conducted, during which animals were exposed in their home cages for 60 minutes immediately before testing, during the ITI and for 20 minutes after testing. Under these conditions, the animals showed a significant reduction in discrimination. Daily home cage exposures of 90 minutes were reinstated for a further 11 days. One day later, a third object recognition task was begun, and this resulted in a non-significant decrease in discrimination. While the authors suggested that exposure to mobile phone signals had affected short-term memory, perhaps through interference with some consolidation process, the use of a mobile phone as a signal source, and the complex exposure schedule (with animals being exposed either during a trial, during the ITI, or before and after a trial) complicates interpretation of these data. Further, a radio was played to simulate speech during exposures in both the arena and home cage, so the experimental conditions under which the three sets of trials were conducted appear to be different in the various parts of this study.

4.2.3 Summary

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

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

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

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

4.3 Endocrine System

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

4.3.1 Melatonin

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

TABLE 4.8 Animal studies investigating effects on endocrine function

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

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

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

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

4.3.2 Other hormones

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

4.3.3 Summary

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

4.4 Auditory System

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

4.4.1 Experimental studies

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

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

Text continues on page 156

TABLE 4.9 Animal studies investigating effects on auditory function

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

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

TABLE 4.9 *Continued*

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

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

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

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

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

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

4.4.2 Summary

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

4.5 Cancer Studies

The possibility that low level exposure to RF fields may increase the risk of cancer has received much attention. Laboratory studies have addressed this possibility using well-established animal models. AGNIR (2003) concluded that there was no direct evidence to suggest that exposure to RF fields was genotoxic or increased the risk of cancer, and several large, well-performed animal carcinogenicity studies had reported that exposure to mobile phone or other signals was without significant effect on longevity and survival, or on the incidence of spontaneous or induced tumours.

4.5.1 Genotoxicity

Although there are studies showing positive effects, particularly that exposure of rats may cause an increase in DNA strand breaks in brain cells, the overall evidence to suggest that low level RF fields can reliably affect the integrity of DNA is inconsistent and not strong (AGNIR, 2003). Nonetheless, given the importance of this possibility, studies have continued to look for evidence of genotoxicity. These have used several reliable monitors of measuring *in vivo* genotoxic effects, including the induction of micronuclei, and the comet assay (single cell gel electrophoresis assay). Most of these studies used rodent somatic cells, but a very few have used germ cells.

Several studies using different signals and exposure conditions have reported no significant changes in micronucleus formation (Table 4.10). Vijayalaxmi et al (2003) found that late prenatal and long-term postnatal exposure of rats to 1.6 GHz Iridium signals had no effect on bone marrow cells. In 2004 the same group reported a similar lack of effect in mice following acute exposure to extremely high frequency fields at 42 GHz (Vijayalaxmi et al, 2004). Görlitz et al (2005) found that exposure of mice to GSM or DCS signals for 1 week or 6 weeks had no effect on bone marrow or other tissues, even using whole-body SARs as high as 25–30 W kg^{-1}. In this extensive study, all low frequency signal modulations that would occur during a typical mobile phone conversation were applied, including DTX and power control. Juutilainen et al (2007) reported that long-term exposure of either normal mice to NMT signals or ODC-transgenic and non-transgenic mice to GSM or D-AMPS signals did not increase the frequency of micronuclei in peripheral red blood cells. Similarly, Ziemann et al (2009) reported an absence of changes in the frequency of micronuclei in blood cells of mice following long-term exposure to either GSM or DCS signals at up to 4 W kg^{-1}. Again, all low frequency modulations that occur using handsets were applied during exposure. The latter two studies should have been able to detect both acute and chronic DNA-damaging effects by evaluating micronucleus frequency in polychromatic and normochromatic erythrocytes, and both would have been able to detect possible delayed effects (genomic instability). In addition, Gurbuz et al (2010) reported that the repeated exposure of anaesthetised rats to 1800 MHz GSM fields at 4.5 V m^{-1} (SAR not given) did not significantly increase the numbers of micronuclei in exfoliated bladder cells.

Independent replication of reported positive effects remains an important goal in this area. However, three attempts did not substantiate earlier results of Lai and Singh (1996) (suggesting that acute exposure may cause DNA damage in rat brain cells). No effects were reported by Lagroye et al (2004) in brain cells following exposure to pulsed 2.45 GHz signals using two versions of the alkaline comet assay, or by Belyaev et al (2006) using GSM signals. In addition, Verschaeve et al (2006) reported that long-term co-exposure to pulsed 900 MHz signals had no additional genotoxic effects in brain and other cells

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TABLE 4.10 Animal studies investigating effects on genotoxicity and mutagenicity

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

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

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

TABLE 4.10 *Continued*

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

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

compared with those caused by a chemical mutagen alone; this study also reported no enhanced effects on micronuclei induction in peripheral blood cells.

Investigating possible mutagenic effects, Ono et al (2004) found that intermittent exposure of *lacZ*-transgenic Muta™ mice to 2.45 GHz fields during most of gestation had no significant effect on mutation frequency at the *lacZ* gene in a range of tissues, including the brain and testes. However, group numbers were very small in this study and comparisons were made with historical controls.

Together, these studies suggest that neither acute nor long-term exposure to RF fields, including the fields used by mobile phones, induce genotoxicity in rodents. However, other studies have reported clastogenic effects, but none of these studies is particularly robust. Investigating effects on micronucleus formation in bone marrow cells in rats, Trosic et al (2004a) reported a transient increase following daily exposure to 2.45 GHz fields after 15 days, whereas Demsia et al (2004) reported an increase following daily exposure to 910 MHz fields for 30 days. Using the signal from an analogue mobile phone in test mode, Ferreira et al (2006) reported an increased incidence of micronuclei in red blood cells of rats exposed during gestation, and Kumar et al (2010) reported a significant increase in micronuclei in red blood cells of adult rats following repeated exposure to high frequency fields (10 and 50 GHz) at very low intensities. The latter study also reported significant increases in antioxidant enzyme activities and in the production of reactive oxygen species (ROS), although the value of ROS for the animals exposed to 10 GHz was the same as that for the animals sham-exposed to 50 GHz.

A few studies have reported increases in DNA fragmentation*. Paulraj and Behari (2006) reported increases in single strand breaks and Kesari et al (2010) reported increases in double strand breaks in brain cells of young adult rats following repeated, daily exposures to 2.45 or 16.5 GHz. Lai and Singh (2005) observed significant increases in DNA single and double strand breaks in rat brain cells caused by exposure to a continuous wave 2.45 GHz field, and reported that these could be blocked by simultaneous exposure to a temporally incoherent magnetic field. Since other authors have not reported RF-field-induced effects on strand breaks, this particular result requires independent replication.

Finally, Aitken et al (2005) examined the impact of low level 900 MHz fields on the DNA of developing sperm of mice. Sperm count and morphology were not affected and there was no evidence of increased DNA fragmentation, but significant changes in gene-specific DNA damage were observed, suggesting that exposure had caused an increased frequency of lesions at two specific loci. As yet, there appear to have been no attempts to replicate this particular result.

4.5.2 Cancer assays

AGNIR (2003) concluded that RF fields were unlikely to have a major impact on carcinogenesis. A number of well-performed studies using standard rodent models of cancer reported that various mobile phone signals had not affected the incidence of X-ray-induced lymphomas in mice, spontaneous and chemically induced brain tumours, or chemically induced mammary and skin tumours.

* Garaj-Vrhovac et al (2009) reported increased DNA strand breaks in white blood cells of rats exposed to 915 MHz, but this article was retracted by the journal because the statistical methods were inappropriate: significance had been calculated using the numbers of cells counted (800) and not the numbers of animals used (8).

Recent studies investigating the carcinogenic potential of RF fields tend to fall into one of four categories: long-term rodent bioassays using conventional animal strains (Table 4.11); promotion studies with animal models prone to developing tumours (Table 4.12); co-promotion or co-carcinogenesis studies with known mutagens/carcinogens (Table 4.13); or progression studies involving implanted tumour cells (Table 4.14).

4.5.2.1 Long-term rodent bioassays

Classical long-term bioassays are considered a cornerstone in assessing the potential of agents to induce malignancies. Anderson et al (2004) reported that long-term exposure of rats to 1.6 GHz Iridium signals had no significant effects on survival, growth or longevity, or on various types of brain and other tumours. Daily, whole-body exposure was started during late gestation and continued through weaning, with head-only exposures then continuing until the animals were 2 years old. Exposures were well controlled in both types of exposure regime to ensure an average SAR in the brain of 0.16 or 1.6 W kg^{-1}.

In a US National Toxicology Program type toxicity and carcinogenicity study, Smith et al (2007) exposed male and female rats to GSM or DCS signals at up to 4 W kg^{-1} every day (excluding weekends) for 2 hours per day for 2 years. All low frequency modulations and power control functions that occur during a typical mobile phone conversation were simulated during exposure. No significant effects were seen on weight, mortality or clinical signs and, compared with sham-exposed animals, there were no significant increases in the incidence, latency or multiplicity of primary tumours or metastases. Sporadic differences between treatment groups were observed, but nothing outside historical norms for this strain of rat. In a companion study using mice, Tillmann et al (2007) reported an identical lack of field-dependent effects. Particular highlights of both of these studies include the size of the groups, a very detailed dosimetric analysis, working to good laboratory practice standards, and the comprehensive pathology assessments.

Bartsch et al (2010) examined the effects of near-continuous, long-term exposure to low intensity 900 MHz GSM signals on health and survival in female rats. Weight was monitored at regular intervals and an extensive post-mortem examination was carried on most animals. No significant changes in weight gain or on the incidence of mammary or pituitary tumours were seen in two groups of 12 animals exposed for up to 24 months. No significant effects on weight gain were seen in two groups of 30 animals given exposure until death (at about 36 months of age), but their lifespan was significantly shortened. The incidence of mammary tumours was also reduced, possibly due to a relative increase in pituitary tumours in these animals. It was suggested that previous rodent studies had not used a sufficiently long exposure period to enable the effects of the RF field to be seen. Significant differences in survival were also noted between groups (including the sham-exposed animals), which were attributed to differences in the time of year the animals were born: those animals born in the spring had a significantly longer survival compared with those born in the autumn.

Jin et al (2011) exposed young rats to combined CDMA and WCDMA signals at a combined SAR of 4 W kg^{-1}, 5 days per week for a year. No significant effects on weight or on spontaneous tumour rates were found, and post-mortem analysis showed no significant pathological differences that could be related to exposure. In addition, analysis of blood and urine revealed no significant field-related effects, apart from a few sporadic changes.

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

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

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

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

Taken together, these rodent studies provide strong evidence that exposure to RF fields at up to guideline values for up to 2 years has no adverse effect on health, nor does such exposure increase the risk of cancer.

A full US National Toxicology Program project entitled 'Studies to Evaluate the Toxic and Carcinogenic Potential of Cell Phone Radio Frequency Radiation in Laboratory Animals' was initiated in 2003 at the Illinois Institute of Technology (IIT) Research Institute. This project uses well-characterised reverberation chambers to expose animals to intermittent fields (10 minutes on/10 minutes off) for 18.5 hours per day, 5 days per week, without the need for restraint. Following studies exploring thermal effects, and a pre-chronic study investigating effects on *in utero* and post-weaning exposures, a chronic toxicity/carcinogenicity study will be undertaken. It is planned to expose rats and mice for 2 years to GSM or CDMA signals at 900 and 1900 MHz at three SARs, the highest of which is expected to induce an increase in body temperature of 1°C. Previous studies (reviewed by the World Health Organization, 1993) have shown that long-term absorption of RF energy at that level will have a considerable impact on thermoregulation, and induce compensatory changes in metabolism, as well as reducing food consumption and spontaneous activity. This project is expected to be completed by the end of 2012, with the results published in late 2014 (http://ntp.niehs.nih.gov).

4.5.2.2 Tumour-prone models

Some strains of mice show increased sensitivity to the development of certain tumours, either naturally or through selective breeding, or by gene manipulation. Sommer and colleagues investigated the potential of RF fields to promote cancer using a strain of mice that is genetically predisposed to developing a high incidence of lymphoblastic lymphoma. No significant effects on lymphoma development, survival times or blood cell counts were found in these animals following continuous, long-term exposure to either GSM (Sommer et al, 2004) or UMTS signals (Sommer et al, 2007). Differences were apparent between the cage controls and the other groups of animals, due to differences in housing conditions. Sommer et al (2007) also reported that metastatic infiltrations in mice that developed lymphoma were not increased by exposure. In contrast, using another strain that develops a high incidence of lymphoma, Anghileri et al (2005) reported that lymphocyte infiltration was increased following repeated, acute exposure from a mobile phone. Survival rate was also decreased in exposed animals. The effects were attributed to changes in calcium haemostasis. However, the complete lack of dosimetry, and other shortcomings with the study, render the results uninterpretable.

Repacholi et al (1997) reported a field-dependent increase of lymphoma in transgenic mice. They found a significant doubling in the incidence of non-lymphoblastic lymphoma in *Eμ-Pim1* transgenic female mice following long-term, daily exposure to 900 MHz GSM fields. An attempt to replicate these results, but using refined methods, did not confirm the original results (Utteridge et al, 2002). However, this study itself has been the subject of much scrutiny and criticism as to whether it constitutes a valid replication (Goldstein et al, 2003a,b; Kundi, 2003a,b; Lerchl, 2003). Oberto et al (2007) represents a second attempt to confirm these results. No increases in lymphomas were found in *Pim1* transgenic mice following long-term, daily exposure to GSM signals, and no trends were seen, so the original results were not supported. As with the other attempted replication, more than one SAR value was tested and dosimetry was significantly improved compared with the original, although animals had to be restrained to achieve this,

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

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

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

and Oberto and colleagues used both sexes. Survival was significantly reduced in exposed male animals, and in one group of exposed female mice, but these findings were classified as incidental as the histopathology provided no evidence that exposure was associated with any particular cause of early death. Comparing between studies, the differences in lymphoma reported by Repacholi and colleagues were attributed to an anomalous decrease in lymphoma in their controls, not an increase in their exposed animals.

Saran et al (2007) exposed neonatal *Patched1* knockout mice to GSM fields for 30 minutes twice a day for 5 days and examined the incidence of medulloblastomas, rhadbomyosarcomas and early signs of basal cell carcinomas. These mice show an increased predisposition for these tumours, and cerebellar and skin tumours are greatly accelerated by early exposure to ionising radiation, while the muscle tumours are unaffected. However, no significant increases were seen for either tumour following exposure to RF fields, and there was no evidence of an excess of preneoplastic lesions in the skin. In addition, survival was unaffected compared with that of sham-exposed animals (Figure 4.6). This study suggests that RF fields have no effects on tumour promotion or progression, or on cell proliferation or malignant conversion. Further, the lack of a tumorigenic effects argues against the possibility that RF fields may act as an epigenetic carcinogen.

4.5.2.3 Co-carcinogenic studies with known carcinogens

Several studies have investigated the effects of long-term exposure to RF fields on the promotion of central nervous system tumours in rats initiated by prenatal (maternal) administration of *N*-ethylnitrosourea (ENU). Neither exposure to 1.4 GHz TDMA (Shirai et al, 2005) nor exposure to 1.9 GHz WCDMA signals (Shirai et al, 2007) significantly increased the incidence of brain and spinal cord tumours, although some differences between treatments were noted, and the incidence of pituitary tumours was decreased in male rats exposed to TDMA signals (but within the historical range of tumour incidence for these animals). Similarly, no significant effects on any type of neurogenic tumour were seen with exposure to pulsed 860 MHz signals (Zook and Simmens, 2006). In contrast, Tillmann et al (2010) found that lifetime exposure to UMTS signals (beginning before birth) increased the incidence and multiplicity of lung carcinomas in female mice compared with animals treated with ENU alone. Significant effects were also seen on liver tumours, but these were discounted due to possible confounding caused by bacterial infection. UMTS exposure on its own had no tumorigenic effect. Due to limitations in the design of the study, the authors considered this a pilot, so more extensive studies using this model would be informative.

No effects on tumour incidence were reported by Heikkinen et al (2006) following repeated exposure to GSM signals in rats that had been given a carcinogen and mutagen in their drinking water. The only statistically significant increase reported was in the combined frequency of vascular tumours of the mesenteric lymph nodes in the animals exposed to the highest SAR, and this was attributed by the authors to a low value in the sham-exposed group, rather than to an increase per se in the exposed animals.

Two studies with similar designs have investigated the effects of RF fields on the promotion of chemically induced mammary tumours in rats (Yu et al, 2006; Hruby et al, 2008). Both studies reported sporadic

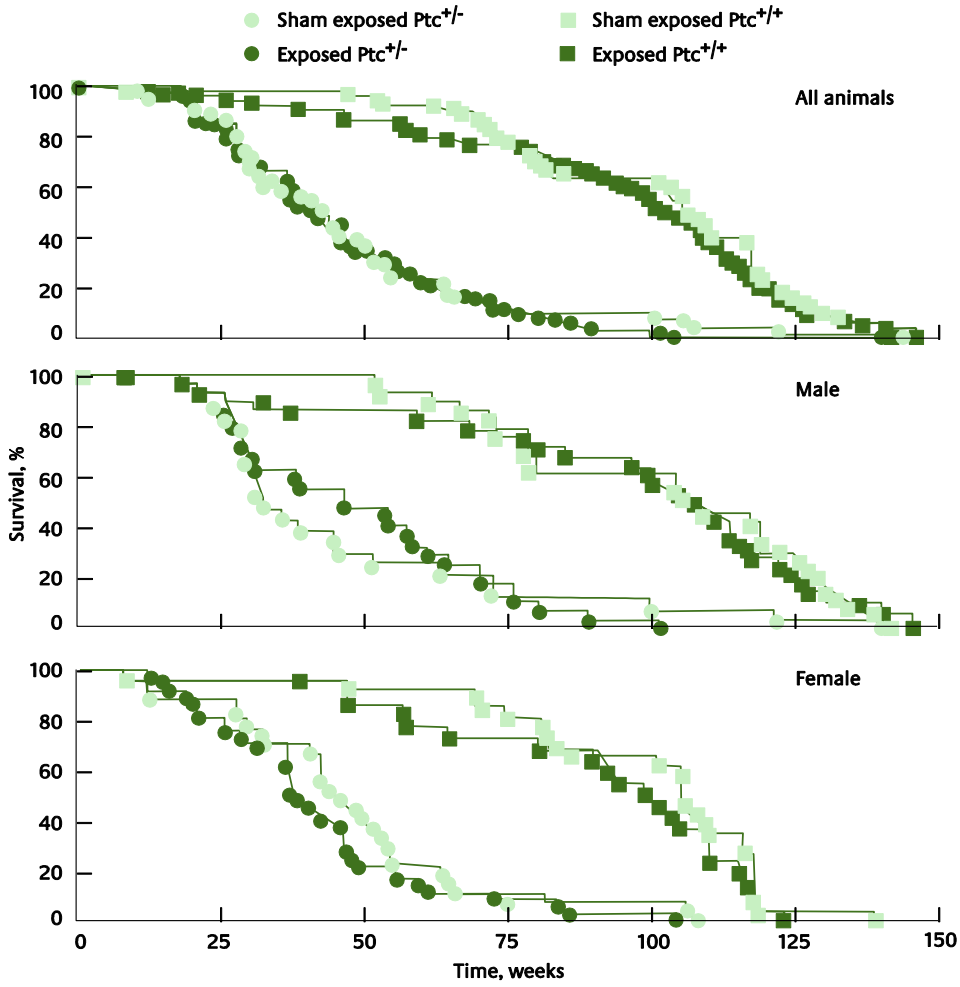

FIGURE 4.6 Tumour-free survival of *Patched1* (*Ptc1*$^{+/-}$) mice and wild-type (*Ptc1*$^{+/+}$) siblings following early postnatal exposure to 900 MHz GSM fields at 0.4 W kg^{-1} or sham exposure. Data are shown as Kaplan-Meier survival curves for all animals, for male mice, and for female mice. All survival curves are clustered in two groups that separate *Ptc1*$^{+/-}$ from *Ptc1*$^{+/+}$ genotypes, but exposure had no significant effect on mean survival. Redrawn with permission from Saran et al (2007)

differences between treatment groups, some of which were statistically significant, but there were no overall trends or consistency between the studies, with the exception that both studies reported the highest incidence of tumours in the cage control groups.

Huang et al (2005) investigated whether repeated exposure to two CDMA signals could promote chemically induced skin tumours in mice. No tumours were seen with either frequency after 20 weeks, and skin histology was unaffected.

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

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

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

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

4.5.2.4 Implanted tumour cells

Extremely high frequency fields, or millimetre waves, are used as a therapeutic agent in some countries to treat cancer and other conditions. In humans, absorption is largely confined to the skin, but these fields will penetrate into muscle in mice. Three studies by Ziskin and colleagues have investigated the effects of exposure to millimetre waves on the development of tumours following injection of melanoma cells into mice. Radzievsky et al (2004) reported exposure mainly of the head to 61 GHz reduced or had no effect on melanoma growth depending on when irradiation was started. Logani et al (2004) reported exposure to 42 GHz had no significant enhancement on anti-cancer drug-induced inhibition of tumour growth. Logani et al (2006) found that the number of metastatic lung colonies caused by injection of an anti-cancer drug could be decreased by exposure to 42 GHz; natural killer cell activity was also significantly increased. In these three studies, the local temperatures in the region of the nose were increased by about 1°C or more.

4.5.3 Summary

While some studies have reported clastogenic effects, and observed increases in DNA strand breaks in rat brain cells, other well-conducted studies have been unable to replicate or confirm the effect. In addition, a number of studies using different animal models and signals have reported no effects on micronucleus formation in haematopoietic and other tissues. However, one study has reported that RF fields are capable of inducing lesions at specific loci in DNA, and these would not have been detected using conventional genotoxicity assays. Even so, the overall evidence for genotoxic effects in animals remains weak.

Recent animal studies have produced no consistent evidence that RF fields cause or increase the risk of cancer. Five long-term rodent bioassays have indicated no adverse health effects with exposure to GSM, DCS or other signals at up to 4 W kg^{-1} for up to 2 years, although one study reported a reduction in survival with near-continuous, low level, lifetime exposures. Other studies have used animal models genetically predisposed to develop certain tumours, including the use of transgenic animals, and these have also found no evidence of decreased survival or of increased incidence of tumours in lymphoma or multiple tumour models. Recent long-term studies with known carcinogens have also produced no evidence that RF fields are co-carcinogens, although one pilot study using UMTS signals indicated an increased risk of lung tumours in female mice treated with ENU during gestation and after weaning. Lastly, three studies involving implanted melanoma cells in mice suggest that short-term exposures to extremely high frequency fields (millimetre waves) may generally inhibit tumour growth, possibly through changes in natural killer cell activity. However, these particular studies may have limited relevance to exposures outside clinical situations.

Taken together, these studies have produced no compelling evidence that RF fields are genotoxic or cause robust carcinogenic effects with exposures below guideline values.

A similar conclusion was reached by Repacholi et al (2011a) who conducted a systematic review of animal laboratory studies and investigated the risks of exposure to RF fields associated with mobile phones on brain cancers or other tumours of the head. No statistically significant relationship was found between

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

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

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

exposure to RF fields and genotoxic damage to the brain or the incidence of brain cancers or other neoplasms of the head. However, a significant increase in spontaneous pituitary tumours was found in female rats and mice at SARs below 2 W kg^{-1} (odds ratio 1.6, 95% confidence interval 1.2–2.2). This excess was not found in male rats and mice exposed below 2 W kg^{-1}, and exposure at higher SARs did not result in a significant change from unity in either males or females. The authors attributed the excess to under-representation of tumours in the sham-exposed groups in two of the three studies considered, resulting in a spurious increase in tumour incidence overall.

4.6 Immunology and Haematology

It has long been held that the most consistent effects of RF fields on immune function and the haematological system are transient, and are associated with exposures that elevate core body temperatures by about 1 °C. However, some studies have suggested that effects may occur in the absence of any heating, and a series of early Soviet studies described pronounced effects on the immune system of rats following chronic, low level exposures. Studies published since the AGNIR review in 2003 are considered below (Table 4.15).

4.6.1 Immune system

Three studies from an Italian group provide no evidence of changes in immune function in rats following exposure to GSM signals for several weeks. Gatta et al (2003) evaluated the effects of daily exposure on spleen lymphocytes. No significant alterations in either T- or B-lymphocytes were found. Nasta et al (2004) reported that exposure had no effects on B-cell peripheral differentiation or on antibody production. Prisco et al (2008) investigated the ability of bone marrow cells to rescue X-irradiated mice from death. Irradiated mice were injected with bone marrow cells from donor mice that had been exposed to 900 MHz fields. All recipient animals survived for 6 weeks, and no differences were observed in the ability of bone marrow precursor cells to reconstitute the immune system and to generate fully functioning mature lymphocytes.

Exposures standards in some countries have been influenced by the results of Soviet studies published in the 1970s and 1980s that indicated effects on the immune response from semi-chronic, low level exposure to continuous wave 2.375 GHz fields, and that injection of blood serum from exposed animals into non-exposed pregnant animals resulted in increased mortality in embryos and decreased fetal body weight*. Two independent studies, but using a common protocol, were conducted in France and Russia to try to replicate these results.

Using modern methods and techniques, Poulletier de Gannes et al (2009b) did not confirm the original results. Rats were exposed for 30 days to 2.45 GHz at 0.16 W kg^{-1}, and killed up to 2 weeks after exposure. No measurable effects on circulating antibody levels in blood serum were found using enzyme-linked immunosorbent assay (ELISA) on a panel of 16 antigens. These antigens included some

* See Vinogradov and Dumansky (1974, 1975) and Shandala and Vinogradov (1982).

that correspond to autoimmune mechanisms and neurodegenerative processes in brain tissues; effects unrelated to the chosen antigens would not be measured. In addition, no teratological effects or postnatal changes in development were seen in fetuses of mothers injected with serum on gestational day 10.

In contrast, Grigoriev et al (2010) provided some evidence in support of the original results, although there were differences in outcome. A complement fixation assay (CFA) was (again) carried out to test the ability of antigen-bound antibodies to bind to complement. An increase in antibodies to brain tissue was seen in both the sham-exposed and exposed animals (but not in the cage controls), with the largest effect occurring in serum taken from animals 14 days after exposure. These results do not appear to be identical to the original, although they do show the same tendency. Results of ELISA reinforced this conclusion. Grigoriev and colleagues also reported that very few pregnant animals receiving serum from exposed animals gave birth to live animals (4 out of 12), which is also supportive of the previous results. However, postnatal mortality was unexpectedly high in all groups, including the cage controls, which suggests that other factors were having a substantial impact, so any conclusions relating to the effects of exposure become very dubious.

Taken together, with the French study providing no support, and the Russian study providing only mild support, it is clear that the results of the original Soviet studies have not been confirmed. Further, the international oversight committee responsible for the conduct of both of these studies has published a critical analysis of Grigoriev et al (2010), and concluded that the overall evidence from both studies provides no convincing support for the original Soviet results (Repacholi et al, 2011b). In a response to this analysis, the lead researcher of the Russian study concluded that the studies overall supported the hypothesis that exposure to non-thermal RF fields causes biological responses (Grigoriev, 2011). It was suggested that differences in the age or weight of the animals could account for the differing responses to exposure observed in the French and Russian studies.

4.6.2 Haematology

Trosic and colleagues have investigated the effects of exposure to 2.45 GHz for 30 days on erythropoiesis in rats: transient effects have been observed, which were attributed to adaptive responses to stress associated with exposure. Busljeta et al (2004) reported increases in erythrocytes counts and haematocrit values in peripheral blood following daily exposures for 1–2 weeks. Trosic et al (2004b) reported a decrease in lymphoblast count in bone marrow after 2 weeks of exposure. Trosic and Busljeta (2006) reported transient increases in polychromatic erythrocytes: these occurred in blood after a few days of exposure, and in bone marrow after a week. In these studies, equilibrium had been re-established by the end of the exposure period.

Effects on circulating blood cells have also been investigated in some studies on tumorigenic effects. No field-dependent changes have been observed in studies using a tumour-prone model chronically exposed to GSM or UMTS signals (Sommer at al, 2004, 2007) or using a DMBA rat mammary tumour model exposed to GSM signals (Hruby et al, 2008). Sporadic differences in a few parameters of the complete blood count and serum chemistry were found in young Sprague-Dawley rats following exposure to combined CDMA and WCDMA signals for a year (Jin et al, 2011).

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

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

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

Study	Model used	Exposure conditions	Results of exposure	Comments
Grigoriev et al, 2010	Antigens in brain, liver, circulating antibodies (IgA, IgG and IgM) in Wistar rats, 7 and 14 days after exposure, by CFA, ELISA, teratology following maternal ip injection of blood serum (1 ml) taken 14 days after exposure on gestational day 10	2.45 GHz, CW, 7 h/day, 5 days/week for 6 weeks at 5 W m^{-2}, 0.16 W kg^{-1}, animals freely moving	Significant difference in brain on day 14 by CFA Significant increase in IgM Significant increase in prenatal mortality, decrease in postnatal weight gain	CFA measured subjectively Provided some support for early Soviet studies
Busljeta et al, 2004	Red cell counts in blood, bone marrow (BM) of male Wistar rats, using automatic cell counter, haemocytometer, 2 h after exposure	2.45 GHz, CW, 2 h/day, for 2 , 8, 15 or 30 days, at 1–2 W kg^{-1}, animals restrained	Anuclear cell count in BM significantly decreased on day 15, erythrocyte count, haemoglobin and haematocrit significantly increased on days 8 and 15	Also incidence of micronucleus (MN) cells in BM significantly increased on day 15
Trosic et al, 2004b	White cell counts in blood, BM of male Wistar rats, using automatic cell counter, haemocytometer	2.45 GHz, 2 h/day, for 2, 8, 15 or 30 days, at 1–2 W kg^{-1}, animals restrained	Significant decrease in lymphoblast counts on days 15 and 30	–
Trosic and Busljeta, 2006	Polychromatic erythrocytes (PCE), in blood, BM of male Wistar rats, using fluorescence microscope	2.45 GHz, 2 h/day, for 2, 8, 15 or 30 days, at 1.25 W kg^{-1}, animals restrained	BM PCE significantly increased on days 8 and 15, blood PCE significantly increased on days 2 and 8	Exposure induced temperature rise of <1°C Also MN incidence increased in BM on day 15, and in blood on day 8

4.6.3 Summary

Given the importance of the immune system, it is perhaps surprising that so few studies have been performed using animals. Results from one group indicate that T- and B-cell compartments are not significantly affected by daily exposure of rats for a few weeks, and that bone marrow cells from exposed animals will reconstitute the immune system of lethally X-irradiated mice and rescue them from death. A well-conducted French study did not replicate the results of some influential early Soviet studies that suggested that RF fields caused an autoimmune response, nor did blood from exposed animals cause teratological or developmental effects when injected into unexposed pregnant animals. Results of a similar study from Russia provided only very limited support for the original studies. Transient changes have been reported on the haemopoietic system of rats exposed to RF fields, which are suggestive of a stress response.

In summary, there is no compelling evidence from recent studies to suggest that exposure to low level RF fields has an adverse effect on the various components of the immune system or on blood forming processes.

4.7 Reproduction and Development

The possibility that RF fields may affect male fertility, pregnancy success or fetal development has continued to be investigated in animal models. AGNIR (2003) concluded that there was no convincing evidence from rodent studies that exposure to RF fields at levels associated with mobile communications posed any risk to the fetus or on male fertility, although it is clear that long-lasting exposures that cause hyperthermia can lead to transient infertility in males and result in adverse developmental consequences in the fetus.

4.7.1 Testicular function

Responding to concerns surrounding mobile phone usage by men, there has been a revival in studies investigating the effects of exposure to RF fields on testicular function in animals (Table 4.16). Unfortunately, many of these data are of very limited use for health risk assessment, because many of the studies used a commercial mobile phone as the source of exposure and, especially with unrestrained animals, the exposures would have been very variable and detailed dosimetry would be highly complex. Further, some studies also used the phone in standby mode, when its emissions would be very small compared with those from a phone in use (see Chapter 2).

Ozguner et al (2005) examined the testes of rats for signs of histological change following exposure to continuous wave 900 MHz fields for 4 weeks. No effects were seen on spermatogenesis, but the diameter of the seminiferous tubules and the mean height of the germinal epithelium were decreased. A significant decrease was also reported in circulating levels of testosterone. Ribeiro et al (2007) reported that subchronic exposure to a mobile phone signal caused no deleterious effect on testicular function in rats. However, the exposure was produced by a mobile phone and the animals were free to move within their home cage, making any determination of the SAR very difficult.

Text continues on page 182

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

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

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

TABLE 4.16 *Continued*

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

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

Changes in sperm motility were reported by Yan et al (2007) in rats following subchronic exposure to PCS signals from a mobile phone. Curiously, the heads of the animals were preferentially exposed, so the SAR in the testes would be far smaller than the 1–2 W kg^{-1} quoted: the basis of this estimation is also unclear, and the mode of operation of the phone was not revealed. In addition, increased numbers of dead sperm were seen in the exposed animals with the sperm clumped together, often to form umbrella-shaped masses, and the expression of two cell surface adhesion proteins was significantly increased. Nevertheless, these data are largely uninterpretable due to uncertainties associated with the exposure.

Using a carousel exposure system, Daşdağ et al (2008) found that repeated daily, head-only exposure to GSM signals did not affect levels of apoptosis in the testes of rats. However, the decision to expose the head preferentially seems curious, given the target organ. A companion study that used a mobile phone as an exposure source, reported that daily, whole-body exposure for 1 month was without significant effect on levels of an anti-apoptotic protein in the testes (Yilmaz et al, 2008).

Mailankot et al (2009) found that exposure to GSM signals from a mobile phone for 1 hour per day for a month significantly reduced sperm motility in rats. However, the phone was placed in a small wooden box inside the home cage to eliminate heating effects (supposedly from the battery) and these cages contained three freely moving animals, as well as a supply of water. No estimates of the SAR or other measures of power output of the phone were provided. Again, nothing of value can be deduced from this study due to the complete lack of dosimetry.

Salama and colleagues have reported highly significant changes in testicular function, including profound decreases in sperm count and motility (Salama et al, 2009, 2010a) and changes in male sexual behaviour (Salama et al, 2010b) following repeated, daily exposures of rabbits to GSM signals. However, a mobile phone in standby mode was used as the exposure source, which indicates that the time-averaged exposures would have been very low, far below the value of 0.43 W kg^{-1} quoted by the authors. Any field-dependent effect becomes highly implausible under these conditions, and it is not surprising that these exposures caused no increase in rectal temperature or in levels of circulating hormones. The effects on testicular function are presented in two papers, and although they clearly represent the same dataset, the exposures are ascribed to different frequencies (900 or 800 MHz) and to different group sizes (11 or 8) in each. In a published letter, Lerchl and Bornkessel (2010) have criticised these results, and consider the effects on sperm counts and motility to be biologically incomprehensible*.

Otitoloju et al (2010) exposed groups of five mice to the fields from GSM mobile phone base stations for 6 months and examined the effects on sperm morphology. A number of major abnormalities were reported to be field-intensity dependent. In this study, animals were housed in cages close to a base station, either in a residential area with two base stations (mean electric field strength of 625 mV m^{-1}), an office block with one base station (490 mV m^{-1}) or a control location with no base station within 300 m (59 mV m^{-1}). The percentage of sperm head abnormalities increased from 2% in the control location, to 40% in the office location and 46% in the residential area. Very few details were provided in this

* *Note added in proof:* Salama et al (2010a) was retracted by the authors in March 2012 for a number of reasons, including uncertainty about the accuracy of the data presented.

preliminary study, and it is not possible to exclude differential influences from other environmental or biological factors at each of the testing locations*.

Using a reverberation chamber to expose the rats, Lee et al (2010) reported that daily exposure to CDMA signals for 3 months had no significant effect on direct and other measures of spermatogenesis. These measures included sperm counts and histological evaluation of the testes, as well as apoptosis measured using the TUNEL assay. There was also no change in the expression of key proteins related to apoptosis.

Sources and therapies using millimetre and sub-millimetre waves are increasing, and a few studies have begun exploring the effects of these fields on male fertility. Subbotina et al (2006) investigated the effects of repeated, daily exposure to (unspecified) extremely high frequency fields on spermatogenesis in rats. The percentage of sperm with morphological abnormalities was reported to increase progressively from about day 7 of exposure, and degenerative changes were noted after about 50 days, but the lack of experimental details and paucity of data make these results uninterpretable.

Two studies from the same laboratory report similar, but not identical effects with repeated exposure of rats to 10 or 50 GHz. Using 10 GHz fields, Kumar et al (2011) reported increases in apoptosis and in reactive oxygen species content in sperm, and reductions in the percentage of sperm in mitosis. Using 50 GHz fields, Kesari and Behari (2010) reported changes in the activities of antioxidant enzymes in sperm as well as increases in apoptosis and effects on the spermatogenesis cycle. The activities of glutathione peroxidise and superoxide dismutase both decreased, while the activity of catalase increased. In both studies, the changes were attributed to a field-induced increase in reactive oxygen species.

4.7.2 Pregnancy outcome and development

Animal studies on hyperthermia (summarised by Edwards et al, 2003) have shown that, depending on the extent to which temperature is elevated above normal and the duration of this elevation, heat either will have no perceptible effect or will kill pre-implantation stage embryos. Surviving embryos treated during pre-implantation go through gestation to form offspring having normal birth weight without an increased incidence of anomalies. Hyperthermia during organogenesis induces various developmental defects which can be related to the amount by which maternal body temperature was elevated. Mild hyperthermia may induce behavioural changes in the offspring of pregnant animals, and deficits in the performance of learned tasks have been seen in mice and guinea pigs exposed to heat during corticogenesis and also in guinea pigs exposed during glial cell proliferation.

AGNIR (2003) noted that comparable results have been found following exposure to RF fields that produces similar increases in maternal temperature, and that there is no consistent evidence of adverse effects in the absence of hyperthermia. While uncertainties remain about the effects of RF-field-induced hyperthermia, recent studies investigating effects on pregnancy and embryo-fetal development have tended to use low level exposure, typical of those from mobile phone handsets (Table 4.17). Animal studies have also shown that hyperthermia combined with endotoxins, arsenic, vitamin A, alcohol or

* A study by Magras and Xenos (1997) describing the effects of environmental RF field exposures on female fertility in mice was criticised by the IEGMP (2000) for a similar lack of experimental controls.

Text continues on page 188

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

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

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

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

TABLE 4.17 *Continued*

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

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

aspirin is more effective in causing developmental defects than when administered alone. This suggests that there is a need to consider combined effects of exposure to RF fields and chemical agents, but no recent studies have investigated this possibility.

A number of well-conducted teratology studies indicate that prenatal exposure to a variety of signals associated with mobile telecommunications does not result in any consistent detrimental effects. Lee et al (2009) reported no significant effects on mouse fetuses following daily, acute exposure to CDMA signals or CDMA and WCDMA signals throughout pregnancy, even using whole-body SARs as high as 4 W kg^{-1}. This appears to be the first animal study to have explored the effects of simultaneous exposure to two different signals. In a follow-up study, Jin et al (2011) reported that exposure of young rats to these signals for a year had no adverse impact on health: no significant changes were seen except for some altered parameters of the complete blood count and serum chemistry (see Table 4.11, page 165).

Ogawa et al (2009) examined the effects of head-only exposure to a CDMA signal during pregnancy. Mothers were exposed for 90 minutes each day during early differentiation and organogenesis, and mothers and fetuses were examined on gestational day 20 for implantation and fetal losses, internal abnormalities and external malformations. No significant changes were seen in either the mothers or fetuses.

Sommer et al (2009) examined the effects of lifetime exposure to UMTS signals over four generations of mice. No significant changes were seen on testicular function or female fertility, rates of malformations and abnormalities or on early development of offspring. Exposure was associated with a reduced food intake, possibly due to a decrease in metabolism caused by the absorption of RF energy. This effect was independent of exposure level and occurred in all four generations of mice.

A lack of teratological effects was reported by Takahashi et al (2010) following whole-body exposure of pregnant rats to a 2.14 GHz field associated with downlink signals from base stations with the WCDMA system in Japan. Animals were exposed for 20 hours per day from day 7 of gestation to weaning. Offspring were assessed for growth, physical and functional development, behaviour in an open field arena and spatial learning in a water maze. In addition, the fertility and reproductive ability of the offspring when adult was assessed. The few significant effects reported were discounted as being transient or inconsistent. However, in the probe trial in a water maze task, the exposed males spent a small, but significant increase of time in the target quadrant compared with the sham-exposed animals, suggesting a modest improvement in learning had occurred.

Sambucci et al (2010) examined the early and late effects of acute, daily exposure to a Wi-Fi signal during pregnancy, with particular emphasis on the immune system. Pregnant mice were exposed from day 5 of gestation for 2 hours each day. No effects on pregnancy outcome were seen, and there were no consistent effects on immune parameters including B-cell compartment and antibody production in offspring at 5 or 26 weeks of age (see Figure 4.7). Sporadic differences were noted, but these were attributed to the effects of confinement stress during exposure, or to sex- or age-related changes.

No significant effects on the circadian rhythms for triglycerides, total cholesterol or glucose levels in plasma were reported in rats by Contalbrigo et al (2009) following long-term exposure to 1800 MHz GSM signals beginning on gestational day 12. However, no details of the exposure system were provided and other details were lacking, so no conclusions can be drawn.

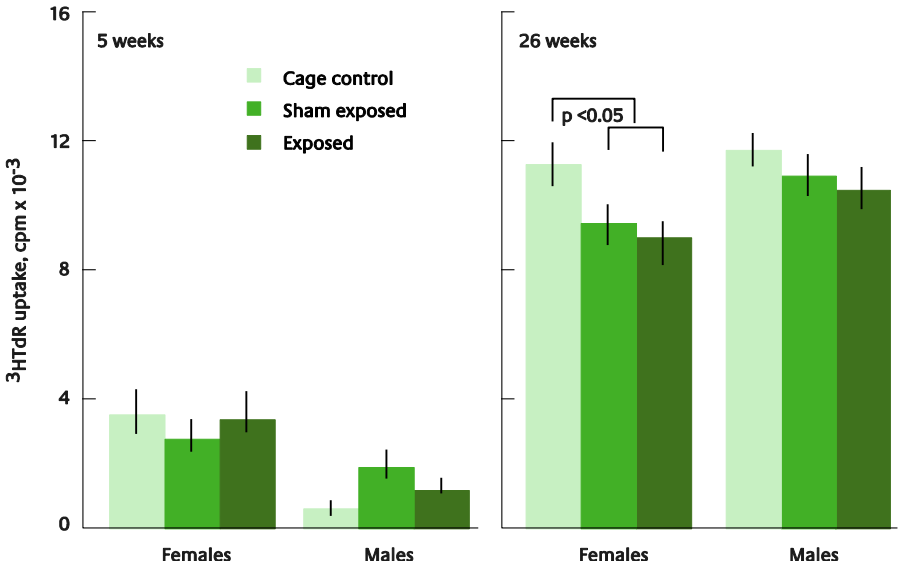

FIGURE 4.7 Early and late effects of prenatal exposure to pulsed 2.45 GHz Wi-Fi signals at 4 W kg^{-1} on B-cell proliferation. Spleen cells from 5 and 26 week old male and female mice born to cage control, sham-exposed and microwave-exposed pregnant mice were stimulated with lipopolysaccharide for 48 hours. Cell proliferation was measured by tritiated thymidine (^{3}HTdR) uptake and is expressed as counts per minute (cpm). Values represent means ± SEM. Redrawn with permission from Sambucci et al (2010)

The effects of early postnatal exposure to 1800 MHz GSM signals in the developing brain were investigated by Watilliaux et al (2011). Young rats were exposed for a single 2-hour period on postnatal day 2, 15 or 35. No evidence of early neural cell damage was seen, as measured by expression of HSPs or for markers for glial development or activation. There was also no significant effect on the proteins involved in astroglial modulation of glutamate neurotransmission.

In contrast to the above studies, Gul et al (2009) reported that the number of offspring per litter and the number of ovarian follicles in the females (examined at weaning) were significantly reduced following daily exposure throughout pregnancy to a mobile phone mainly in standby mode. The phones were placed beneath the home cages and the time-averaged SAR, especially in the fetuses, must have very low, but there was a complete lack of dosimetry.

Fragopoulou et al (2010b) reported transient delays in ossification of cranial bones and thoracic ribs in neonatal mice following exposure to GSM signals from a mobile phone during gestation. These changes were no longer observed when offspring were 35 days old.

Further, some studies have described a variety of subtle effects in newborns following prenatal exposures. Pyrpasopoulou et al (2004) investigated changes in gene and protein expression in the neonatal kidney following exposure to a very low intensity pulsed 9.4 GHz signal during early gestation. Although no malformations in the kidney were seen, significant differences in a bone morphogenetic protein and two receptor subunits were reported that depended on the time of exposure, broadly reflecting

embryogenesis and early organogenesis. It was concluded that exposure had delayed the development of the kidney. The signal used was considered to be equivalent for a rat to a GSM signal for a man on the basis of relative penetration into tissues.

In two studies from the same laboratory, prenatal exposure has been reported to affect the major cell types of the hippocampus in young rats. Odaci et al (2008) reported that daily, acute exposure to a continuous wave 900 MHz signal during gestation resulted in significant losses in the number of granule cells in the dentate gyrus of young rats, and Bas et al (2009b) reported significant losses in pyramidal cell numbers in area CA1.

Rağbetli et al (2009, 2010) reported that repeated exposure of pregnant mice throughout gestation to the RF fields from a mobile phone, mainly in standby mode, resulted in significant decreases in Purkinje cells in the cerebellum of offspring, but no effects on pyramidal cell numbers in the hippocampus.

Guler et al (2010) measured levels of oxidative DNA damage and lipid peroxidation in the brain following acute exposure of New Zealand white rabbits to GSM signals for 7 days during mid-gestation. While significant increases were seen in the brains of the mothers (in both the exposed and sham-exposed groups), no significant differences were observed in the brains of offspring. Exposure was not associated with any change in weight of either the mothers or offspring. Although the field used (14 V m^{-1}) was below the reference value for public exposures (58 V m^{-1}), no dosimetry was performed and the whole-body or localised SAR values are not known. In a companion study, Tomruk et al (2010) reported a similar lack of effects in liver tissues, although changes were again seen in the mothers, which were unrelated to their exposure status.

Using an exposure system based on a microwave oven, Orendáčová and colleagues have investigated the effects of pulsed 2.45 GHz fields on neurogenesis in the subventricular zone of the forebrain. The subventricular zone is a region of sustained neurogenesis, and cells migrate via the rostral migratory stream to the olfactory bulb where they differentiate. Orendáčová et al (2009) reported that, compared with unexposed animals, short-term exposure of very young rats over 2 days resulted in a transient increase in proliferating cells in the rostral migratory stream, whereas longer exposure over 3 days resulted in a lasting reduction in proliferation and also produced a severe loss of body weight. Both exposure regimes produced negligible effects in elderly rats. More recently, Orendáčová et al (2010) reported that acute exposure of very young rats or early adult animals resulted in an increase in expression of Fos protein in the subventricular zone. In addition, exposure of the very young animals resulted in an increase in nitric oxide activity in the rostral migratory stream, whereas exposure of the older animals resulted in a decrease in activity. These results were considered to be consistent with the effects of other stressors on neurogenesis in animals, such as exposure to noise or maternal deprivation. The absence of sham-exposed control groups and the paucity of information about the exposure system and signal used in these studies means that the confounding effects of heat, or auditory or other effects, cannot be ruled out. The dramatic loss of weight in one group of animals following exposure is also in contrast to the overall results from a number of well-performed teratological studies.

Gagnon et al (2003) investigated the effects of exposure of mice to a broadband field (0–25 MHz) from late in gestation until weaning. A variety of changes were reported including greater numbers of offspring with various lesions in the thymus and adrenals, and the time to run a corridor was increased. The

mothers themselves displayed less efficient grooming, with more disorganised nests; they also had changes in white blood cell counts that were consistent with stress responses. These changes were observed in both exposed and sham-exposed mothers. Overall, due to the unusual nature of the field and lack of details about the exposure, very little of value can be deduced from this study.

Gathiram et al (2004) reported that exposure to a commercial wideband signal (100 MHz – 3 GHz) had no effect on reproductive ability in rats. Exposure of either the males or the females in a breeding pair, or exposure of both males and females in a pair, had no effect on latency to produce a litter, litter size or sex ratio of offspring. The uniqueness of the signal and the lack of dosimetry mean that it is not possible to draw any conclusions from these results.

4.7.3 Summary

A substantial number of studies have investigated the effects of RF fields on testicular function, principally in rats, and most report large, obvious effects. However, these results are largely uninterpretable due to inadequate dosimetry or other shortcomings in the studies, and thus are unsuitable for the purposes of health risk assessment. One well-conducted study reported no effect on testicular function in rats exposed to 848 MHz CDMA signals.

Hyperthermia is known to be teratogenic in animals and RF-field-induced hyperthermia will induce similar developmental abnormalities. Six well-conducted studies using rodents exposed to a variety of signals associated with mobile telecommunications systems indicate an absence of any consistent teratological effect following prenatal exposures that did not induce maternal hyperthermia. While most of these studies reported at least one significant difference between treatment groups, there was no consistency with regard to the particular endpoints either within or between studies. One study, however, did report that prenatal and early postnatal exposure was associated with an improved performance of a spatial memory task, which is comparable to the results of a study investigating effects in immature rats. Other studies have reported a variety of outcomes, but these suffer various methodological shortcomings, and none offers robust evidence of RF-field-related changes.

4.8 Overall Summary

Studies with animals have proved highly useful for investigating whether exposure to the RF fields associated with mobile phones can cause health effects. Many new studies have been published since the previous review by AGNIR in 2003 and these have employed a wide range of biological models, exposure levels and signal modulations. There is no clear evidence of harmful effects with exposures below guideline values, although some studies have reported subtle biological changes, often following single, acute exposures. It is noteworthy that several large-scale studies investigating the initiation and development of cancer have all been robustly negative, and a similar lack of effect has been seen regarding auditory function.

Studies investigating effects on the brain and nervous system in adults have not produced consistent evidence of weak-field effects. In particular, recent studies do not indicate that exposures are associated

with consistent changes in gene expression or in altered permeability of the blood-brain barrier. In addition, two recent studies have been unable to confirm previously reported deficits in behaviour in spatial mazes. However, effects on a wide range of behavioural endpoints remain largely unexplored, including specific effects on immature or juvenile animals. The results of a well-performed study reporting behavioural changes following repeated exposure of young animals are particularly intriguing because they suggest improvements in learning may occur, but this requires further examination and independent replication before conclusions can be drawn. In addition, the results of a study using a transgenic animal model of Alzheimer's disease are of great interest: improvements in the performance of a cognitive task were reported following long-term exposure of transgenic mice, as well as enhancements in performance of normal, non-transgenic animals. Whether RF fields may provide protection against behavioural deficits in Alzheimer's patients, however, remains highly speculative at this stage.

There is no evidence that daily, repeated exposure to the fields associated with mobile phones has any detrimental effect on hearing, either through changes to the inner ear or on the central auditory pathways.

Regarding carcinogenesis, there is very little experimental evidence to suggest that exposure to any RF field increases the risk of any cancer. Although some studies have reported increased risks, a substantial number of large, well-performed studies show that long-term exposure does not promote the development of any specific kind of cancer, even in tumour-prone models, nor does exposure appear to affect the progression of various tumours induced by genotoxic agents or chemical carcinogens. Further studies exploring the effects of new signals or exposures associated with emerging technologies are necessary to ensure a comprehensive health risk assessment, and independent replication of results remains essential. Whether an RF field itself may cause genotoxic effects is slightly less clear. While some early studies suggested that exposure may cause DNA strand breaks and cytogenetic changes, later, well-conducted studies have generally not confirmed these results, and it has been suggested that differences in methodology may go some way to explain these different outcomes. Nevertheless, the balance of evidence strongly favours RF fields not being genotoxic.

Two studies from the same laboratory suggest that some effects of 2.45 GHz microwaves may be blocked by simultaneous exposure to temporally incoherent magnetic fields. In one, behavioural deficits were reduced, while genotoxic changes were reduced in the other. The effects of microwaves alone on both outcomes, however, remain highly controversial and they have not always been observed by independent laboratories. Thus it would seem to be premature to conclude that magnetic fields can reliably prevent either biological effect, but they are interesting and intriguing observations that deserve further study.

Studies investigating effects on immunology and haematology have provided no consistent evidence that RF fields may cause adverse outcomes. In particular, a well-conducted study did not confirm earlier studies suggesting that exposure to RF fields may cause adverse effects, including autoimmune responses in the brain.

Despite many studies investigating effects on male fertility, there is no convincing evidence that low level exposure results in any adverse outcomes on testicular function. A lack of consistent field-dependent effects has also been reported on adverse birth outcome and development in rodents following prenatal or early postnatal exposure to a variety of signals associated with mobile phones and wireless communications.

Taken together, the results of the more recent studies support and reinforce the conclusions previously reached by AGNIR (2003).

Whether children are at an increased risk from exposure to mobile phone signals remains unclear. Studies with immature and juvenile animals allow effects on development to be investigated using a wider variety of signals and exposure conditions than would be possible with human volunteers. As yet, few animal studies have been undertaken, and the available evidence does not suggest that immature animals are more sensitive than adults. For example, several studies indicate that exposure is not associated with neural cell damage in the developing brain, with changes in the permeability of the blood-brain barrier, or on cochlear function following repeated exposures. One study has shown that exposure to a Wi-Fi signal does not cause effects on the developing immune system, and two studies suggest that spontaneous tumour rates in normal or tumour-prone animals are not increased by exposure to mobile phone signals. In contrast to these negative results, a possible co-carcinogenic effect has been reported in a pilot study using UMTS signals, and two behavioural studies indicate that exposure of young animals to RF fields may cause improvements in performance in the water maze.

Thus, while the results of many laboratory studies strongly indicate the absence of any consistent biological changes as a result of exposure to low level RF fields (although a number of studies report effects due to some experimental manipulations, such as caused by immobilisation stress or in cage control animals), some caution needs to be exercised since it is impossible to dismiss all possibilities. There is also very little consistency between different studies in the signals (carrier frequencies and modulation), power densities, and durations and schedules of exposure that have been used, and this wide diversity of exposure parameters hinders direct comparison between experiments. Whether manipulations of any of these parameters may increase the likelihood of effects cannot be answered with any certainty at present, due in part to the lack of an appropriate biological model with which to investigate these possibilities, and the lack of experimental evidence for non-thermal interaction mechanisms. In addition, little can be said about whether specific drugs, chemicals or other agents (which may or may not cause an effect in their own right) may modulate the effects of RF fields. Finally, the extent to which the present results can be extrapolated to future technologies remains unclear.

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5 Neurocognitive Effects in Humans

Since the last AGNIR review in 2003, several studies have been carried out on the acute, short-term effects of exposure to RF fields, such as those emitted by mobile phones and base stations. This chapter reviews provocation studies with volunteers investigating the effects of RF fields on objective measures of cognitive performance and brain function. A short section at the end reviews neurocognitive studies with observational designs, ie those not based on provocation.

5.1 Provocation Studies

Provocation studies are the most robust method for investigating the acute effects of RF fields. Provocation studies typically comprise two or more experimental conditions: one condition involving a genuine RF field exposure and another involving sham exposure. Additional conditions may include different levels or types of RF field exposure. The methodology for provocation studies follows the general principles of experimental design. Ideally, neither participant nor experimenter is informed of which condition involves genuine RF field exposure. In addition, the conditions should be counterbalanced, so that equal numbers of participants experience each order of exposure conditions. Finally, where participants are allocated to different experimental groups, the allocation should be done at random.

Provocation studies offer a powerful, well-controlled method for investigating the possible effects of RF field exposure on cognitive performance and nervous system function. However, they cannot generally reveal the mechanisms by which RF fields affect the nervous system. The RF field exposures in the studies reviewed here are below the ICNIRP guideline levels for known effects of RF fields (see Appendix B). These guidelines are based on limiting the heating of any biological tissue to less than 1°C.

This chapter reviews provocation studies of the acute effects of RF fields from mobile phone and base station signals, published since the previous AGNIR review (AGNIR, 2003). The studies are grouped as follows: studies of human performance, electroencephalogram (EEG) studies, other neurophysiological studies, and auditory and vestibular studies.

5.1.1 Cognitive and performance studies

Early studies reported significant effects of mobile phone signals on reaction times and other human performance measures. The previous AGNIR review in 2003 noted that many of these early effects were not replicated in better-controlled, double-blind studies. Since then, additional studies of human cognitive performance have been published.

Many recent studies have attempted to replicate previously reported effects of RF fields on reaction times and working memory performance. Russo et al (2006) exposed 168 healthy volunteers to sham and

GSM-like signals for around 45 minutes using a head-mounted system producing an exposure with a 10 g averaged SAR of 1.4 W kg^{-1}. A double-blind randomised crossover design was used. Half the participants received pulse-modulated GSM signals in the active session, while half received continuous wave only. Half had the phone placed over the left ear, and half over the right ear. Participants performed a vigilance task, a reaction time task, and a mental arithmetic task during exposure. No significant effects of exposure were found. Cinel et al (2007) reported the minimum time separation at which participants could report the order between an auditory tone presented in one ear and another tone presented in the other ear (auditory order threshold). The data were collected as part of the same study as that of Russo et al (2006). No significant effects of exposure were found. Cinel et al (2008), again working with the same study population, presented data from further cognitive tasks designed to involve working memory (two versions of a three-back task and a vigilance task). Each task included low and high cognitive load conditions, to explore previous suggestions that effects of RF field exposure might emerge only with higher cognitive loads. No significant effects of exposure were found in any task or load condition.

Haarala et al (2007) tested 36 healthy volunteers in three double-blind and counterbalanced exposure conditions: pulse-modulated GSM, continuous wave only and sham exposure. The peak SAR was given as 1.18 W kg^{-1} in the active conditions. Both hemispheres were exposed in each session in counterbalanced order. Nine cognitive tasks, covering reaction time, working memory (*n*-back) and vigilance, were performed during exposure. No significant effects of exposure condition on any of the cognitive tasks were found.

While most published cognitive studies focused on GSM signals, the possible effects of other signals have also been studied. Unterlechner et al (2008) tested 40 healthy participants under sham, high power and low power UMTS signals. The 10 g averaged SAR was 0.37 W kg^{-1} in the high power condition, and 0.037 W kg^{-1} in the low power condition. A double-blind randomised crossover design was used. During each exposure, participants performed four cognitive tasks drawn from an established battery testing perception, attention and vigilance. Twelve measures from these tasks were compared across the three exposure conditions. No significant effects of exposure were found on any task.

Sauter et al (2011) compared the effects of sham, and GSM- and 3G/UMTS-type, signals on cognitive function in 30 young male volunteers. Neither participants nor experimenters were aware of the exposure condition. The different exposures were delivered on separate days, for a total of 7 hours 15 minutes per day. A customised antenna system was used to deliver RF signal exposures similar to those during mobile phone use. Power was varied to achieve exposures that approached but did not exceed a 10 g averaged SAR of 2 W kg^{-1}. Tests of divided and selective attention, and of working memory, were performed during exposures. There were no significant or consistent effects of exposure on any of the cognitive tasks. Delays in reaction time observed during the morning session of UMTS exposure were followed by shortening of reaction times in the afternoon session, so that no overall effects were found after statistical correction for the number of tests. The authors concluded that prolonged exposure to GSM- and UMTS-phone-like signals did not produce acute cognitive effects on attention or working memory.

Riddervold et al (2010) investigated the possible effects of signals from TETRA phones on cognitive performance in a double-blind randomised crossover design. The peak SAR value averaged over 10 g was 2 W kg^{-1}. The participants were 53 emergency service workers, who volunteered for the study. The main

outcome measure was the 'Trail-making Test B', which involves a combination of perceptual, executive and motor function. Measures of simple and choice reaction time were also collected, in addition to a questionnaire relating to subjective symptoms (see Chapter 6). No significant differences were found between exposure and sham exposure for any of the cognitive tests.

Eltiti et al (2009) reported the effects of GSM base station signals, 3G/UMTS base station signals and sham exposure on cognitive function in 114 healthy volunteers and 44 people reporting sensitivity to electromagnetic fields. A double-blind randomised crossover design was used. Digit substitution, digit span and mental arithmetic tasks were tested. No effects of exposure were found for any of the cognitive tests. Blood pressure, heart rate and skin conductance, and subjective well-being were also measured during the cognitive tasks, and were reported for a subgroup of 44 participants who served as matched controls for the group of 44 people reporting sensitivity. No effects of exposure on any physiological variable were found in either group, after statistical correction for the number of tests performed.

5.1.1.1 Studies in children

The possibility that the developing brain might be particularly susceptible to RF field exposure makes studies of acute effects in children particularly important. At the time of the previous AGNIR review in 2003, very few studies had investigated the effects of RF field exposures on cognitive function in children. A number of studies have appeared since, and these are reviewed here.

Haarala et al (2004) exposed 32 children aged 10–14 years to sham or GSM-like signals in a double-blind, randomised crossover design. The peak SAR was estimated at 2.07 W kg^{-1}. Participants performed a range of vigilance, reaction-time and working memory tasks while exposed. No significant effects of exposure were found.

Preece et al (2005) tested 18 children aged 10–12 years in a double-blind, counterbalanced crossover design with three exposure conditions: no RF, full power GSM and low power GSM. The peak SAR was estimated at 0.28 W kg^{-1}. During each condition, participants performed a cognitive testing battery including tests of vigilance, reaction time and working memory. The battery comprised 16 separate tasks, and gave 22 dependent variables. The effects of exposure on each variable were tested with one-way analysis of variance. Only one variable showed a significant exposure effect: simple reaction time was lowest in full power conditions, higher in low power and highest in sham conditions. However, Preece et al applied a Bonferroni correction to adjust for the 22 different analyses performed, and then concluded that the result was not significant. The authors concluded that acute mobile phone exposure did not affect cognitive function in children. However, the Bonferroni correction is not designed to adjust for multiple endpoints, and may be overly conservative in this case. Therefore, caution is needed in interpreting the effect of exposure on simple reaction time, particularly since the effect replicates those observed in earlier studies of adults (Preece et al, 1999; Koivisto et al, 2000).

5.1.1.2 Base station signals

Exposures to RF fields from base station signals are typically small relative to exposures from phones. Perhaps for this reason, few cognitive studies have focused on base station signals. However, reports that UMTS base station signals might influence well-being and cognitive performance (Zwamborn, 2003;

reviewed in AGNIR, 2003) have led to some further studies. Several of these studies focused on the symptoms produced by exposure to base station signals. These are discussed in Chapter 6 on subjective symptoms. Only effects on performance and brain function in healthy volunteers are discussed here.

Riddervold et al (2008) investigated the effects of UMTS base station signals on cognitive function. They exposed 40 adult volunteers and 40 adolescents (aged 15–16 years) for 45 minutes to sham, a full UMTS signal, a modulated UMTS signal lacking some UMTS control features, and UMTS continuous wave only. A double-blind, randomised crossover design was used. Several cognitive tests from an established neuropsychological test battery, and a questionnaire focusing on symptoms and well-being, were administered in each exposure condition. The Trail-making Test B was selected as a primary outcome measure. No significant effects of exposure were found on this measure, or on any of the other cognitive tasks. The authors concluded the UMTS base station signals did not affect cognitive functions.

5.1.2 Electroencephalogram and event-related potential studies

In many studies, electrodes are placed on the scalp of healthy volunteers, and the electrical activity of the brain, or electroencephalogram (EEG), is recorded. Several different measures may be calculated from the original EEG recording. These measures are compared between an exposed and a non-exposed control condition.

EEG studies can be broadly divided according to the type of activity measured, as follows.

a **Resting EEG** This refers to the ongoing background activity of the brain, and is generally measured by calculating the power in each of a range of frequency bands, such as the delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–50 Hz) bands.

b **Sleep EEG** EEG is recorded continuously during sleep. The characteristic patterns of brain oscillatory activity in each frequency band are measured. Results are often reported for each phase of sleep.

c **Event-related potential (ERP)** This refers to the specific electrical activity associated with the neural response to a stimulus, or performance of a particular cognitive task. ERPs appear as a series of voltage changes, often called ERP components, at scalp electrodes, distinct from background EEG activity. The latency and amplitude of each ERP component can be measured.

EEG is a common and convenient measure of brain function. However, wide variations exist between individuals in EEG and ERP patterns. For this reason, crossover, or 'within-subject' designs are generally used, with each participant's EEG being compared between two different conditions.

Some studies reviewed previously (AGNIR, 2003) had reported increases in EEG power due to RF field exposure (Borbély et al, 1999; Krause et al, 2000; Huber et al, 2002), while others reported no effects (Hietanen, 2000). More recent research has continued to report a mixed set of results. Research methods in the field have generally improved, with more studies using within-subject designs, double-blinding, careful control of exposures, detailed reporting of dosimetry, and awareness of the statistical problems of multiple comparisons.

5.1.2.1 Resting EEG studies

Curcio et al (2005) exposed 20 volunteers to the RF field from a GSM mobile phone for 45 minutes. The phone was run at an average power of 0.25 W. The SAR in a phantom head was measured as 0.5 W kg^{-1}. Each participant completed three sessions: a baseline session in which participants wore the phone-mounting helmet but without the phone, a session in which the mobile phone was present and emitting an RF field *(RF on)*, and a session in which the mobile phone was present but not emitting *(RF off)*. Session order was randomised. For half the participants, the EEG was recorded for the last 7 minutes of the 45-minute exposure session. For the remaining participants, the EEG was recorded immediately *after* the exposure session.

The study found a small, but significant increase in alpha band power (8–10 Hz) in the *RF on* condition relative to the *RF off* and baseline conditions. These effects were found at several electrodes, not only those closest to the phone antenna. For one electrode, over the parietal cortex, the effects were statistically greater when the EEG was recorded during exposure compared to after exposure. For other electrodes, there was no significant difference between recordings made during and after exposure.

This study provides some evidence that RF fields from mobile phones may increase the alpha-band EEG power of the human brain. The finding of effects that can outlast RF field exposure is particularly important, since such effects cannot be explained by direct interference of the phone signals with the EEG recording equipment. However, some aspects of the study suggest caution. The sample size was relatively small. Although the study was reported to be double-blind, the procedures for ensuring the blinding of the researchers were not described. The statistical analysis treated each EEG frequency as an independent observation, which is questionable. It is unclear whether alternative analyses of the data would reach similar conclusions. Finally, it remains unclear whether such small changes in EEG power have implications for health.

Krause and colleagues have performed several studies on the effects of RF fields from a mobile phone on auditory memory performance and EEG activity. Krause et al (2004) tested 24 healthy participants in an auditory memory task. The participants were either exposed to RF fields from a GSM phone, or not exposed, in a double-blind, counterbalanced order design. EEG activity during the memory task did not differ between conditions. RF field exposure caused a significant increase in errors on the task. The authors noted that their results did not replicate their own previous positive finding of effects of RF fields on EEG in a single-blind design.

Krause et al (2006) carried out a very similar double-blind study with 15 children aged 10–14 years. The peak SAR was estimated at 1.98 W kg^{-1}. RF field exposure produced a 5–10% increase in the EEG power in the theta band (4–8 Hz), during the periods of encoding auditory stimuli, and recognising whether a probe word had been presented previously or not. The increase was statistically significant using tests designed to compensate for the interdependence of the different EEG frequencies. The effects were quite widely distributed over the brain, although they were more prominent for left temporal electrodes than for right temporal electrodes. The phone was held adjacent to the left ear. Importantly, debriefing after the test showed that the children were unaware whether the signal was on or off, ruling out any effects of knowledge or strategy. This study provides evidence for an effect of mobile phone signals on

children's brain activity. However, the sample size was small. Moreover, as the authors themselves noted, the mechanism of the mobile phone signal's interaction with the brain remains unclear.

Krause et al (2007) carried out an extension of their 2004 study, in which 36 participants performed a visual memory task and a further 36 performed an auditory memory task. Each subject was tested under six exposure conditions, obtained by exposing the left and right sides of the head to a pulse-modulated GSM-like signal, a 902 MHz continuous wave signal lacking the modulations of the full GSM signal, and a sham consisting of no signal at all. The measured peak SAR in a phantom head for this exposure was 1.18 W kg^{-1}. The authors carried out several statistical comparisons. Most importantly, the GSM-like signal increased EEG power in the 8–12 Hz band relative to continuous wave only during the encoding phase of the auditory task. In the recognition phase, however, a significant relation was found in the opposite direction, with GSM-like signals producing decreased 8–12 Hz band power. In the visual task, GSM-like signals produced decreased 8–12 Hz band power relative to continuous wave only. The authors themselves noted the inconsistency of the results between different phases of the task, and between their own and other studies. Rather than interpreting their results as an effect of RF field exposure on the human brain, they suggested that these effects could have arisen due to chance. In particular, the effects on the EEG were reported to be unsystematic, since they varied with numerous other factors in each experiment.

Regel et al (2007a) exposed 24 healthy volunteers to pulsed GSM-like RF fields, continuous wave only, or sham exposure for 30 minutes. SARs averaged over 10 g were given as 1 W kg^{-1}. The resting EEG was recorded before, immediately after exposure, and again 30 and 60 minutes later. The resting EEG power in the alpha band was significantly enhanced, relative to baseline, 30 minutes after exposure to pulsed RF, compared with the other conditions. It is unclear whether any attempt was made to correct statistically for the number of EEG frequency bands measured. No effects were seen immediately after exposure, and no effects were found in EEG recordings made with the eyes open. These results suggest a specific effect of pulse-modulated RF field exposure on alpha-band EEG.

Three cognitive tasks were also performed *during* exposure: simple reaction time, choice reaction time, and an *n*-back working memory task. The more difficult conditions in the working memory task led to significantly slower performance in the pulsed exposure condition. However, this was accompanied by improved accuracy, so may reflect a change in speed/accuracy trade-off, rather than a fundamental effect of exposure on information-processing ability. The authors did not report the full set of statistical comparisons between each pair of conditions, but it appears that the changed performance was confined to pulsed exposure.

Kleinlogel et al (2008) tested 15 healthy volunteers in a double-blind crossover design. Customised signal generator and amplifier equipment was used to expose participants to a signal resembling the GSM test signal, to UMTS (3G) low power, to UMTS high power and to sham exposure, in separate sessions. The peak SARs for the three exposure conditions were 1, 0.1 and 1 W kg^{-1}, respectively. In the first study, the resting state EEG was measured in the standard EEG frequency bands, and well-being was assessed. No significant effects of exposure were found. In the second study, visual and auditory ERPs were measured, and a continuous performance task was used to assess cognitive function. The authors looked for differences between the four exposure conditions using non-parametric tests. Among 43 tests reported,

only two were significant. Although the authors did not formally attempt to adjust for multiple comparisons, they treated the overall pattern of results as negative. They concluded that their results did not suggest effects of mobile phone signals on adult human neurocognitive function. A strength of this pair of studies is the large number of measurements taken from each individual. However, its negative conclusion should be interpreted with caution, given the small size of the sample.

De Tommaso et al (2009) measured the contingent negative variation (CNV) in 10 healthy volunteers. The CNV is an ERP that occurs after a warning signal and in preparation for a second stimulus to which the participant responds. Measures were made in a phone-off condition, exposure to a normal GSM signal, and a second sham exposure condition in which the power was diverted to an internal load, rather than the antenna. The peak SAR was estimated at 0.5 W kg^{-1} in the normal GSM condition, and negligible in the diverted-sham condition. A double-blind, randomised crossover design was used. The results showed that CNV amplitude was significantly reduced in full GSM exposure and diverted-sham conditions, relative to power-off. Diverted-sham and full GSM conditions did not differ. Similar differences between exposure conditions were found for the habituation of the CNV across trials. Caution is needed in interpreting these results, given the small size of the sample. In addition, this study does not offer strong evidence for an effect of mobile phone signals on the human brain, since the results were comparable for the full GSM condition that emitted the RF signal and the diverted-sham condition that did not.

Kwon et al (2009) studied perceptual processing in 17 healthy volunteers by measuring the auditory mismatch negativity (MMN). MMN is a frontal negative-going ERP that occurs when an infrequent, deviant sound occurs embedded in a sequence of other sounds. It reflects the ability of the auditory brain regions to process different features of sounds, such as intensity, frequency and duration. A mobile phone antenna driven by a signal generator and amplifier exposed the left ear to a GSM signal, producing a peak SAR of 1.28 W kg^{-1}. Each participant was tested with the signal on and off (sham condition), and the phone was also placed over either the left or right ear, in counterbalanced order. No significant differences between sham exposure and either ipsilateral (use on the same side of the head) or contralateral exposure were found.

The same group performed a very similar study in 17 healthy children (aged 11–12 years) (Kwon et al, 2010). A larger number of ERP measures was analysed than in the same authors' study with adults. Because six separate analyses were performed, a Bonferroni correction was applied. No significant effects were found after this statistical correction. However, this is not the scenario for which Bonferroni techniques were conceived, and the correction may be overly conservative in this case. Further large-scale studies in children would therefore be valuable.

Hamblin et al (2006) measured visual and auditory ERPs, and a range of cognitive behavioural measures in 120 participants. The tasks and measures were selected to include those thought sensitive to RF field exposure in previous studies. Each participant performed in two sessions. Each session began with baseline measures in a sham condition where the participant wore a helmet-mounted phone, but was not exposed to RF fields. These measures were then repeated in an experimental condition with a different phone. In one session, the experimental phone was set to sham, while in the other it was set to expose the participant to a GSM-like signal producing a 10 g averaged SAR of 0.11 W kg^{-1}. Sessions were counterbalanced and double-blind. A control experiment showed that a new group of participants could

not detect the RF field exposure. For most analyses in the main experiment, specific predictions were made from pilot data, and no corrections for multiple testing were performed. Nevertheless, no significant effects of exposure on any ERP or cognitive measures were found. The authors noted that they thus failed to replicate their own earlier results, as obtained in a small-sample, single-blind pilot study (Hamblin et al, 2004).

Stefanics et al (2008) measured ERPs and EEG changes in 36 healthy volunteers, in two sessions of 20 minutes each, using an auditory oddball paradigm. A 3G/UMTS signal or sham stimulation was applied in each session, using a double-blind design, from a modified mobile phone. The peak SAR averaged over 1 g was measured as 1.75 W kg^{-1}, using a phantom head. No significant differences between exposure conditions in any ERPs or event-related EEG power in the gamma band were found.

Papageorgiou et al (2006) measured the P50 ERP in 19 healthy volunteers, while exposed to an unmodulated, continuous 900 MHz field emitted from an antenna 20 cm away, and while the signal was switched off. The field strength at the head position was given as 3 V m^{-1}, but no SAR values or other dosimetry were provided. The participants appear to have been blind as to the exposure condition, but it is not stated whether the experimenters were blind or not. The P50 ERP was recorded in response to an auditory tone that served as an instruction to recall numbers in a working memory task. RF field exposure increased the amplitude of the P50 ERP component for low frequency tones, but decreased the P50 for high frequency tones. Other studies by the same group, which appear to have included the EEGs from the same participants and recording sessions, showed RF-field-related changes in EEG power (Papageorgiou et al, 2004), in spectral coherence of EEG bands (Hountala et al, 2008), and in later P600 ERPs in the working memory task (Maganioti et al, 2010). However, these last three studies all involved interactions between the RF field exposure and gender, and these interactions had different forms across the three studies. While this body of studies is interesting, the small sample size and the re-analysis of the dataset for different measures raise questions about the generality of results. The effects of RF field exposure were always specific either to one gender or to a particular subset of stimuli, without any obvious reason why this should be so. Finally, no SAR value was given for the RF field exposure, and the RF field lacked the pulsing modulations characteristic of mobile phone signals.

Bak et al (2010) measured ERPs to auditory tones in 15 healthy adults. In one condition, participants were exposed to GSM signals from a mobile phone during a voice call carried over a commercial network, while in another condition the phone was switched off. The manufacturer's figures give the SAR value for the phone as 0.81 W kg^{-1}, but the actual exposure in the experiment was not assessed. The participants were said to be blind to the exposure condition, but it is not stated whether the experimenters were also blind. The ERPs were measured before, during and after exposure. P300 amplitudes were significantly decreased during GSM exposure, but not during sham exposure. This effect did not outlast the exposure period. The authors concluded that the RF fields from GSM phones could influence neurocognitive functions. Although interesting, this study raises some concerns because of the small sample size, the apparent lack of double-blinding, and uncertainties about the actual level of RF field exposure. Independent replication in a larger sample with a more precisely controlled exposure would be desirable.

Croft et al (2008) analysed the resting EEG from the same dataset as that of Hamblin et al (2006). The authors aimed to investigate the hypothesis that the RF fields from mobile phones increase alpha-band

EEG power. They found a numerically small, but statistically significant increased alpha-band EEG power during exposure. Additional exploratory analyses were corrected for the intercorrelation of the measures tested. The EEG power increase was more marked on the same side of the head as the phone, compared with the opposite side. However, the most statistically reliable changes were in frontal electrodes, a considerable distance forward from the antenna. Post-exposure measures showed some differences in EEG power between exposure conditions contralateral to the phone, but these were not consistent with those during exposure. The frontal increase found during exposure was not statistically significant after exposure. The authors concluded that the RF fields from mobile phones increased human alpha-band EEG power. However, they pointed out the small size of these changes relative to the variations in EEG power that occur during normal, everyday activity. They also pointed out that there was a lack of evidence regarding whether such small changes could be relevant to health.

Croft et al (2010) used a very similar experimental design to investigate effects of sham, GSM and UMTS exposure from mobile phones in 41 adolescents (aged 13–15 years), 40 young adults (aged 19–40 years), and 20 older adults (aged 55–70 years). Each participant performed each condition in a separate session. The peak SAR averaged over 10 g was estimated as 0.7 W kg^{-1} for the GSM signal and 1.7 W kg^{-1} for the UMTS signal. None of the groups showed better-than-chance performance in detecting whether the phone signals were on or off. There were no significant effects of UMTS exposure. A significant alpha-band power increase was found for the young adult group only during 2G exposure. This increase was not confined to specific electrodes, but was distributed equally across the scalp. There were no significant effects in either the adolescent or older adult group. This study replicates the finding of the same group of increased alpha-band power during GSM exposure in young adults (Croft et al, 2008). However, the interpretation of this study is not straightforward. First, although an age-dependent effect of RF fields on EEG cannot be ruled out, this seems quite unlikely given the relatively close age groups tested in the study. Second, since the SAR values were lower for the GSM than for the UMTS exposure, the finding of an effect for the former but not the latter is surprising. There could be some specific feature of the GSM signal that leads to effects on brain activity, although it is unclear why this should be so. Third, the GSM effect was found for both hemispheres, and was equally present at the different electrode sites recorded. A direct effect of exposure might be expected to be largest closest to the antenna, as reported previously by the same group (Croft et al, 2008). However, remote effects of RF fields, and compensation for local RF field effects by remote areas, cannot be excluded.

Leung et al (2011) reported another analysis of what appears to be the same dataset as that of Croft et al (2010). Performance on an auditory oddball detection task was not affected by RF field exposure, but the auditory N1 component of the ERP was increased during GSM exposure. In an *n*-back working memory task, accuracy was reduced during UMTS exposure, but *post-hoc* analysis suggested this effect was largely due to the adolescent group. Electrophysiological data showed a delay in event-related changes in alpha-band EEG power during both GSM and UMTS exposures, when the age groups were combined. This study provides evidence that RF fields can have modest effects on human EEG. However, it remains unclear why these effects are age specific. Moreover, since some of the EEG effects were not associated with changes in task performance, their implications for cognitive function are unclear.

Hinrikus et al (2008) exposed several groups of participants, varying in number from 13 to 19, to 450 MHz signals. The exposure session alternated between *RF on* (1 minute) and *RF off* (1 minute) (the 'reference'

period), repeated 10 times. The groups differed in the modulation frequency of the signal: 7, 14, 21, 40, 70, 217 and 1000 Hz modulations were tested. Each subject completed both an exposure session and a sham session, in randomised order. The power was switched off during sham exposure. Both modulation frequency and exposure were stated to be double-blinded. During exposure, the spatial peak SAR averaged over 1 g was calculated as 0.303 W kg^{-1}, based on measured field power densities of 0.16 mW cm^{-2} and calculations following IEEE Standard 1528. EEG power was measured in the standard frequency bands.

Statistical results for the group overall were not reported, making it difficult to draw any conclusions about the generality of the results. Instead, the authors reported the number of participants who showed significant changes in EEG power between sham and exposure conditions. Some participants showed significant EEG power increases in each group, except for those exposed to 1000 Hz modulated signals. The most common effect (four participants, 31% of the group) was an increase in lower beta-band EEG power during exposure modulated at 14 Hz. Of those, three also showed increases during exposure modulated at 21 Hz.

These results are interesting, but need to be treated with caution. First, it is unclear if there was a statistically significant effect of exposure on the group as a whole. Second, it is unclear why some individuals were affected while others were not. Although the authors discussed their results in the context of sensitivity to electromagnetic fields, it is unclear if there was any relationship between the self-reported sensitive status of the individuals participating in the study and their susceptibility to EEG modulations. However, this paper does provide independent evidence for EEG changes induced by RF field exposures. As for the other studies reviewed here, RF field exposure generally *increased* EEG power. EEG power decreases were rarer.

Vecchio et al (2007) investigated the coherence of EEG patterns between the two cerebral hemispheres during 45 minutes of exposure from a GSM phone or sham exposure in 10 healthy volunteers, using a double-blind crossover design. No SAR data were given, but the average power of the phone was stated as 0.25 W. GSM exposure decreased the interhemispheric coupling in frontal brain regions in the alpha-band EEG (8–12 Hz), but increased the same coupling in temporal brain areas.

Vecchio et al (2010) tested a group of 16 elderly participants in an identical study. They also tested five younger participants, and pooled their data with those they had published previously (Vecchio et al, 2007). A maximum SAR of 0.5 W kg^{-1} was given for the exposures, although it is unclear if this was averaged over 10 g of tissue or not. The elderly participants showed a significant increase, relative to the younger group, in frontal interhemispheric coupling during GSM exposure, compared to sham exposure. Control analyses showed that this result was not just an artefact of the EEG power in the two groups. These results are interesting, and deserve replication in a larger sample. However, the reversal of the effect with age makes it unlikely that they reflect a direct effect of mobile phone signals on brain activity.

5.1.2.2 Sleep EEG studies

Several studies have investigated the effects of mobile phone signals on sleep behaviour and sleep EEG. The relatively long period available for both exposure and measurement means that sleep is likely to be a sensitive indicator of any biological effects of mobile phone signals. Some early studies reviewed

previously (AGNIR, 2003) suggested that RF field exposure increased alpha-band EEG during sleep (Borbély et al, 1999; Huber et al, 2000, 2002), recalling the alpha-band changes seen in some awake EEG studies reviewed above.

Regel et al (2007b) exposed 15 healthy volunteers to either no RF field exposure or a GSM-like signal giving a 10 g averaged SAR of 0.2 or 5 W kg^{-1} for 30 minutes immediately before sleep, in a double-blind crossover design. An effect on non-REM sleep EEG activity in the 13.6 Hz (fast spindle) range was found, with 5 W kg^{-1} exposure causing an increase of approximately 13% in EEG power relative to sham exposure. It is unclear whether any statistical adjustment was made for comparison of multiple frequency bands. This effect was sustained across three separate periods of sleep monitored throughout the night. No effects on the organisation of the various phases of sleep were found. These results are interesting for a number of reasons. First, the delay between exposure and EEG recording suggests that RF fields may have effects on the brain that outlast exposure. Second, the delay in the effect would seem to rule out explanations based on thermal effects. Third, the EEG changes occurred in frequency bands similar to those noted in studies of waking EEG. However, some caution is required in interpreting this study. The number of participants was relatively small. Further, although the authors spoke of a dose-dependent effect of RF field exposure, the significant effects were confined to contrasts between sham and 5 W kg^{-1} exposures. This exceeds the ICNIRP guidelines for public exposure (2 W kg^{-1}), although it is below those for occupational exposure (10 W kg^{-1}).

The authors also reported the results of cognitive tests performed during the pre-sleep exposure period. The tests were identical to those of their earlier study (Regel et al, 2007a). In general, increasing RF field exposure produced slower, but more accurate performance. While some individual results were significant, the overall pattern may reflect participants changing their trade-off between speed and accuracy across the different conditions, rather than any fundamental change in cognitive capacity. The authors also noted some inconsistencies with their own previous results (Regel et al, 2007a).

Fritzer et al (2007) exposed 10 healthy volunteers to GSM-like RF fields, and a further 10 volunteers were sham exposed, using antennas situated approximately 30 cm from the head, producing an estimated 1 g averaged SAR of 1 W kg^{-1}. This apparatus exposes a much larger volume of brain tissue than exposure from a phone. Exposure took place for approximately 8 hours on six successive nights of an eight-night sleep experiment. Participants performed a range of cognitive tasks. The EEG was recorded on an initial, unexposed baseline night, and on three further exposed nights. The EEG was inspected to estimate the classic sleep 'architecture' variables, such as the frequency, latency and duration of different sleep stages. No statistically reliable differences between exposure conditions were found on either the sleep measures or any of nine cognitive measures. The authors suggested that RF field exposures resembling those from mobile phones do not influence the organisation of sleep. Caution is need in interpreting these null results, however, given the relatively small sample size and the between-participants design. In addition, no measures of EEG amplitude or power were taken in this study.

Hung et al (2007) exposed 10 healthy volunteers to talk, listen and standby modes of a GSM phone operating at 12.5% of maximum power, and to sham stimulation, in a single-blind, randomised crossover design. The 10 g averaged peak SARs of the three exposure conditions were 0.133, 0.015 and below 0.001 mW kg^{-1}, respectively. These exposures were chosen as being typical of actual exposure scenarios

for mobile phone users, although they are much lower than those in other provocation studies. In addition, the authors noted that the pulse modulation of the GSM signal differs between the talk and listen modes, so any differences between these conditions could be due either to differences in level of exposure or to the different spectral composition of the signals. In each condition, 30 minutes of exposure was followed by an afternoon sleep opportunity, during which the EEG was measured. Sleep onset time was significantly higher in the talk-mode condition than in the listen or sham conditions. In addition, EEG spectral power in the low delta band (1–4 Hz) over frontal electrodes rose in the period after sleep onset in the listen, standby and sham modes, but not in the talk mode. This study is interesting in reporting significant post-exposure effects of mobile phone signals on sleep, but some caution is necessary in interpreting the results. First, the sample size was small. Second, the effect was clearly not dependent on the level of RF field exposure. Although RF field exposure was lower in the standby mode than in the other exposure conditions, sleep onset time was later following standby-mode exposure than following listen-mode exposure, yet did not differ from talk-mode exposure. Third, the EEG analysis was restricted to a single frequency band, without apparent attempt to correct for multiple comparisons across either time or frequency. Interestingly, the condition with the highest RF field exposure (talk mode) produced a suppression of EEG power, in contrast to the increase seen in some other studies (Curcio et al, 2005; Croft et al, 2008).

Loughran et al (2005) exposed 50 healthy participants to sham exposure or to a GSM signal having a peak SAR of 0.29 W kg^{-1} for 30 minutes prior to overnight sleep. A double-blind, randomised crossover design was used. REM sleep onset occurred significantly earlier following RF field exposure than following sham exposure. Spectral analysis showed that RF field exposure significantly enhanced EEG power around 11.5 Hz during the first period of non-REM sleep. No correction for multiple comparisons was performed, since the frequencies of interest were predicted from previous research. The authors did not comment on whether they examined later phases of sleep. Overall, the results of this study seem consistent with those in other sleep and resting EEG studies. The sample size, however, is larger than in most other sleep studies.

Lowden et al (2010) exposed 48 volunteers to 3 hours of a 900 MHz GSM signal, or sham stimulation, prior to sleep. A repeated-measures design was used, with counterbalanced order of exposure. EEG measures were recorded throughout sleep, and subjective reports of sleepiness/wakefulness were obtained. Both experimenters and participants were blind as to the exposure condition. The GSM signal used a customised antenna, but aimed to imitate the key features of a mobile phone exposure scenario. Periods of discontinuous transmission (DTX) and non-DTX were alternated to mimic a typical call. The 10 g averaged peak spatial SAR for the overall exposure was estimated at 1.4 W kg^{-1}. Relative to sham exposure, the GSM exposure delayed onset of slow-wave sleep and reduced its duration. Stage 2 sleep was also prolonged. There were no effects on self-reported sleepiness. EEG recordings showed increases in alpha-band power during the earlier periods of stage 2 sleep following RF field exposure, compared to sham exposure. This large, well-controlled study adds to the body of evidence that mobile phone exposure leads to increased alpha-band EEG power during subsequent sleep.

Two further studies reported details of sleep behaviour based on EEG sleep recording methods, although the underlying EEG data were not reported in detail. Danker-Hopfe et al (2011) exposed 30 male volunteers to GSM, 3G/UMTS phone-like signals, or sham exposure during an 8-hour period of sleep. Each

exposure condition was repeated three times in random order. The exposure system was similar to one used previously (Sauter et al, 2011): a customised antenna system was used to deliver RF field exposures similar to those during mobile phone use. The power was varied to achieve exposures that approached, but did not exceed, a 10 g averaged SAR of 2 W kg^{-1}. Several sleep behaviour variables were measured from polysomnographic recordings, including the EEG. These variables were compared between exposure conditions. REM sleep duration was significantly increased by GSM exposure. However, after statistical adjustment for the number of tests performed, the authors concluded that this effect could have been due to chance. 3G/UMTS exposure produced only three significant differences from sham exposure on the different variables tested. None survived correction for multiple comparisons, and they were attributed to chance. The authors concluded that the macrostructure of sleep was not affected by exposure to these phone-like signals, and that RF field exposure could not explain the disturbed sleep that some people attribute to mobile phone signals.

Danker-Hopfe et al (2010) installed a base station transmitting 900 and 1800 MHz GSM band signals in rural locations in Germany where no mobile phone service was present. The sleep of 397 participants was recorded using an in-home somnographic monitor over several nights, during which the base station was either *on* or *off*. Neither participants nor experimenters were aware of the exposure condition. Sleep behaviour and subjective assessments of sleep quality were assessed. No significant differences in objective markers of sleep behaviour, or in subjective reports of sleep quality, were found.

5.1.3 Other neurophysiological studies

Inomata-Terada et al (2007) used magnetic stimulation at various brain and spinal locations to elicit motor-evoked potentials, allowing the cortical component of neural excitability to be isolated. These measures were made before and after 30 minutes of active or sham exposure in 10 healthy participants in a double-blind, within-participants experiment. Because the phone was held by the subjects themselves, the exact exposure is hard to estimate, but a 10 g averaged SAR value of 0.54 W kg^{-1} was estimated. The phone used the 800 MHz band and the Japanese TDMA mobile phone standard. No significant effects of exposure on any measures of cortical excitability were found. Two multiple sclerosis patients known to have highly sensitive cortical motor tracts were also tested, and again no significant effects were found. The authors concluded that mobile phone use did not have immediate effects on cortical excitability.

Ferreri et al (2006) measured the response of the motor cortex to transcranial magnetic stimulation (TMS) in 15 volunteers before, immediately after, and 1 hour after, a 45-minute exposure to 900 MHz GSM signals from a mobile phone. The results were compared with those from a further session in which the phone was switched off. Both participants and experimenters were blind regarding the exposure conditions. Standard TMS protocols were used to measure inhibitory and excitatory circuits in the motor cortex in both the exposed and unexposed hemisphere. The SAR, measured in a phantom head, was given as 0.5 W kg^{-1}. Exposure to the GSM signal significantly increased the motor cortical response to the excitatory TMS protocol in the exposed hemisphere immediately after exposure. The effect had reduced, and was no longer statistically significant, 1 hour after the end of exposure. There were no changes in the unexposed hemisphere. These findings suggest that RF fields from mobile phones have a transient effect

on the brain, changing the operation of glutamatergic circuits in the motor cortex. The fact that these changes were specific to the hemisphere exposed and the period of exposure is consistent with a biological effect of RF fields. However, the details of the exposures themselves are unclear. In particular, the phone antenna appeared to have been some distance posterior to the motor cortex, which is thought to house the neural circuits responsible for the TMS effects that were measured. The exposure of the motor cortex itself is unclear. Therefore, these interesting findings should be replicated in a larger sample, with a better characterisation of the level of exposure of the neural circuits actually probed by the TMS technique. For the moment, there is a clear discrepancy between the results obtained by Ferreri et al (2006) and those of Inomata-Terada et al (2007) using broadly similar experimental designs.

Huber et al (2005) measured regional cerebral blood flow (rCBF) changes due to RF fields using positron emission tomography (PET) brain scanning. Twelve healthy volunteers were exposed to a pulsed GSM-phone-like signal, an unmodulated base-station-like signal or a sham exposure. The 10 g averaged peak SAR was given as 1 W kg^{-1} for both the RF field exposures. Exposure lasted 30 minutes and brain scanning commenced approximately 10 minutes after the end of exposure. Participants were asked to count silently during the scans. A double-blind, randomised crossover design was used. The rCBF data were corrected for multiple comparisons across the whole brain. Frontal rCBF in the exposed hemisphere was significantly elevated following the phone-like signal, relative both to sham exposure and to the base-station-like signal. Interestingly, the rCBF peak was several centimetres anterior to the area of peak SAR, suggesting that the effects were not thermal in origin. The rCBF after exposure to the base-station-like signal did not differ from that after sham exposure, suggesting that the pulsed character of the phone-like signal could be responsible for the effects. This finding replicates and extends previous reports of altered rCBF and EEG following pulse-modulated exposure (Huber et al, 2002).

Aalto et al (2006) exposed 12 healthy participants to either sham or GSM-like RF fields with a 10 g averaged SAR estimated at 1.51 W kg^{-1}. Measures of rCBF were collected *during* exposure. A double-blind, randomised crossover design was used. A random effects analysis showed a decreased rCBF in the exposure condition, relative to sham, near the region of peak SAR in the inferior temporal lobe. This analysis was statistically adjusted for the number of comparisons made within a small, 3 cm^2, region under the antenna. A second analysis showed increased rCBF in the exposed condition, in several foci in the frontal lobes, on the same side of the head as the phone, corrected for multiple comparisons across the entire brain. However, this second analysis treated the participants as a fixed rather than a random effect, and cannot therefore be generalised to the population as a whole.

Curcio et al (2009) used functional near-infrared spectroscopy to measure haemodynamic changes in the brain's frontal lobes of 11 volunteers before and after 40 minutes of GSM or sham exposure. The peak SAR was estimated at 0.5 W kg^{-1}. Both participants and experimenters were blind to the exposure condition. Frontal cortex deoxygenation showed a significant and progressive increase with time of exposure to GSM, but not with sham exposure. Interestingly, these changes were found both in the brain hemisphere stimulated directly by the signal and also in the other hemisphere. This small study requires further confirmation in a larger sample. The presence of changes in the unexposed hemisphere suggests that these effects may reflect factors other than changes in brain metabolism caused by the GSM signal. However, a remote effect of exposure, or compensation by one hemisphere for exposure-induced changes in the other, cannot be excluded.

Mizuno et al (2009) measured rCBF in nine healthy participants before, during and after 30 minutes of exposure to either sham or a UMTS phone signal from a microstrip patch antenna giving a 10 g averaged peak SAR of 4.4 W kg^{-1}. A single-blind, randomised crossover design was used. No differences between conditions were found after appropriate statistical correction for multiple comparisons over the whole brain.

Volkow et al (2011) used 18FDG (fluorine-18-labelled fluorodeoxyglucose or ^{18}F-FDG) PET to measure brain glucose metabolism in 47 volunteers. In one session, participants were exposed for 30 minutes to a signal from a commercial mobile phone receiving a call, while in another session the phone was off. The actual SAR during exposure was not quantified, but the manufacturer's rating of maximum SAR for the phone was 0.901 W kg^{-1}. Participants sat quietly at rest during the exposure. Injection of 18FDG was before each session so that the maximum uptake occurred during the exposure period. PET scanning after the exposure measured the level and location of 18FDG uptake in the brain. The authors modelled the electric field emitted by the antenna, and restricted their brain analysis to the region around the antenna where the field would have exceeded half its maximum value in the absence of the head. Within this search volume, they identified clusters of voxels showing a linear relation between 18FDG uptake and electric field strength. Increased glucose metabolism, as measured by 18FDG uptake, was found in the orbitofrontal and temporal pole regions, suggesting an effect of RF fields from mobile phones on brain metabolism.

These results are interesting because of the relatively large sample size, and the linear dose-response relation between glucose metabolism and electric field strength within the search volume. However, some methodological difficulties with the study suggest that independent replication is required before further conclusions can be drawn. First, the actual level of RF field exposure is not clear. If the phone was connected to a network, as appears to have been the case, the precise power output of the phone will have depended on the level of network coverage at the test site, and the signal level could have varied with the amount of network traffic. Moreover, the calculated electric field values were based on free-space analysis of the RF field, and did not take into account the electrical properties of the tissue exposed. Thus, the true exposure level in the relevant brain areas is not known. Second, there was no formal assessment of the participants' ability to detect whether the phone was *on* or *off*. In particular, the phone body is likely to have become warm in the *on* condition, but not in the *off* condition, providing a potential cue to participants. Further, the experimenters were apparently not blinded to the exposure condition. Therefore, it is possible that participants knew when the phone was on, and that this knowledge influenced their brain activity. Third, the statistical treatment of the PET data raises some questions. The choice of a restricted search volume requires some justification, since the probability of finding a significant difference with neuroimaging data depends on the severity of correction for testing across multiple voxels in the brain. Moreover, it is surprising that the authors found no decreases in metabolic activity, given the combination of a local increase near the antenna, and no difference in overall activity across the whole brain. A double-blind replication of this study, with better control of exposure, might provide more convincing evidence for effects of RF fields on brain metabolism.

Kwon et al (2011) performed an 18FDG PET study in 13 adult volunteers. The volunteers wore a helmet with an inactive phone mounted next to the left ear and an active phone mounted next to the right ear. The active phone had its battery and internal components removed and the RF signal was fed to it by

cable. The antenna of the active phone was powered by hardware in a different room and driven by software producing a GSM-like signal. Measurements in a phantom estimated the 10 g averaged SAR as 1.0 W kg^{-1}. Participants were exposed for 33 minutes in two separate counterbalanced sessions, to either real or sham exposure. An 18FDG bolus was injected at the time of exposure, and imaged using PET after exposure. Both participants and experimenters were blind as to the exposure condition. During exposure, participants performed a visual match-to-sample task, and had temperature measures taken from five probes distributed over the facial skin. Cognitive performance did not differ significantly between exposure conditions. Real exposure produced a higher increase in temperature than sham exposure, and more so on the right side of the head adjacent to the active phone. However, the authors judged the mean temperature increase of 0.36°C too small to have any effect on brain function. Analysis of PET images showed a decrease in whole-brain 18FDG uptake in the exposed condition, relative to the sham condition, suggesting that RF fields reduce brain metabolism. The decreases survived correction for multiple comparisons across the whole brain. The decrease was maximal in the right temporal lobe regions that were highly exposed to the RF field from the antenna. This study was small, but included good quality features of dosimetry, experimental design and statistical analysis. Interestingly, the exposure-related decrease in brain metabolism in this study stands in direct contradiction to the exposure-related increase reported by Volkow et al (2010). Further research on the effects of RF fields on brain metabolism is therefore required to reach a firm conclusion. In addition, it remains unclear whether changes in brain metabolism of the size found in these experiments are relevant to health or not.

Kwon et al (2011) also used H2O15 (oxygen-15 water) PET to monitor rCBF while 15 young adult volunteers were exposed to RF fields from one of three mobile phones placed over the left ear, right ear or forehead, or were sham exposed. Exposure was given through one phone only at a time. The experiment was double-blind. Modified mobile phones were used, and were externally driven, producing an estimated 10 g SAR of up to 245 mW kg^{-1} averaged over the whole brain tissue. The rCBF data were gathered during 5-minute periods of exposure, during which participants performed a working memory task. Temperature monitoring showed small, but significant increases in ear canal temperature during exposure, but these were judged to be so small as to be physiologically unimportant (0.06°C), and unlikely to account for rCBF differences. No significant rCBF differences were found between exposure and sham conditions, even when the analysis was restricted to areas immediate adjacent to the phone where significant effects of exposure were reported previously (Aalto et al, 2006). This study did not replicate significant effects of RF fields on rCBF reported in earlier studies.

Carrubba et al (2010) delivered either sham exposure or a pulsed RF field designed to emulate the 217 Hz pulsing of a GSM mobile phone signal. They investigated whether EEG recordings showed an ERP in response to RF fields, ie brain activity directly caused by the pulse. Conventional evoked potential analysis showed no difference between sham exposure and phone-like pulses. An alternative analysis based on 'non-linear recurrence' showed significant differences between exposure and sham conditions in 18 out of 20 participants. However, it is unclear whether the results of the group as a whole provided consistent evidence for an ERP. In addition, the location on the scalp where the effects were found was variable. Finally, the authors did not mention whether the participants and experimenters were blind as to the control condition. Although interesting, these results require replication with more complete analysis, and using standard analysis techniques, before any clear conclusions can be drawn.

Wallace et al (2010) measured the effects of TETRA base station signals on heart rate, skin conductance, blood pressure and subjective well-being in 132 healthy volunteers, in a double-blind, randomised crossover design study. In addition, 48 participants reporting sensitivity to RF fields were also tested: their subjective symptoms are discussed in Chapter 6. No significant effects of exposure were found in either group.

5.1.4 Auditory and vestibular studies

Several studies have investigated the possible effects of mobile phone signals on the auditory and vestibular systems. This interest is motivated by the close proximity of the hearing and vestibular organs of the inner ear to the normal position of the phone antenna, and by the high physiological sensitivity of the inner ear's receptor structures. The results of these studies have been largely negative. There is a well-known microwave hearing effect, which results from RF-field-induced thermoacoustic tissue expansion. This effect has been further investigated in recent years (Elder and Chou, 2003; Lin and Wang, 2007; Silny, 2007; Yitzhak et al, 2009), but there has been no evidence of any related adverse health effect.

Pau et al (2005) found acute exposure of 13 volunteers to continuous or pulsed 900 MHz fields had no effect on nystagmus, which can be used as a marker of vestibular function. The SAR was estimated at 1.9 W kg^{-1}, but the dosimetry was incompletely described.

Uloziene et al (2005) measured hearing levels and otoacoustic emissions in 30 volunteers before and after 10 minutes of GSM or sham exposure. Half of the participants experienced 900 MHz GSM signals, and the other half 1800 MHz. A synthesised speech stimulus was presented at the same time, to simulate normal phone use. No significant differences from sham exposure were found. Paglialonga et al (2007) measured the detailed time-frequency profile of otoacoustic emissions in 29 volunteers before and after 10 minutes of either sham exposure or exposure to a 900 or 1800 MHz GSM signal having peak SARs at the cochlea of 0.41 or 0.19 W kg^{-1}, respectively. No significant effects of exposure were found. Other studies using otoacoustic emissions to evaluate auditory function have also found no effects related to acute RF field exposure (Monnery et al, 2004; Janssen et al, 2005; Parazzini et al, 2005).

Bamiou et al (2008) exposed 21 healthy volunteers and nine individuals reporting sensitivity to mobile phone signals. Each participant was exposed in three separate 30-minute sessions to pulsed RF fields from a head-mounted exposure system, to continuous fields and to a sham control condition. The mean SAR was given as 1.3 W kg^{-1}. Otoacoustic emissions and vestibulo-ocular reflexes were assessed before and immediately after each exposure. No significant effects of exposure were found.

Stefanics et al (2007) found no effects on the auditory brainstem responses (ERPs) in healthy volunteers exposed for 10 minutes to a GSM signal giving a peak SAR of 0.41 W kg^{-1}. This study used a between-participants design (with 15 subjects exposed to RF signals and 15 sham exposed), so differences between individuals could be confounded with any possible effect of RF field exposure.

Kwon et al (2010a,b) measured auditory brainstem responses in a group of 17 healthy volunteers *during exposure* to a GSM signal giving a peak 1 g averaged SAR estimated at 1.2 W kg^{-1}. Results were compared to a baseline condition without a phone, and to a condition where the phone was present but emitted no

RF signal. No significant effects of exposure were found. Several further studies (Arai et al, 2003; Bak et al, 2003; Oysu et al, 2005; Sievert et al, 2005) provided no evidence that auditory brainstem responses were affected by acute exposure to RF fields.

In GUARD, a European multicentre study (Parazzini et al, 2007a,b), 169 healthy young volunteers were exposed to either a sham or genuine 10-minute RF field from a GSM-type signal emitted by a phone driven using customised software, and using a double-blind design. Multiple measurements of auditory function (including otoacoustic emissions and evoked potentials) immediately before and after exposure demonstrated no effects. A similar study in 20 healthy young men (Mora et al, 2006) detected no auditory impairment following 15–30 minutes of RF field exposure at 900 and 1800 MHz.

In another European multicentre study (EMFnEAR), Parazzini et al (2009) exposed 134 healthy volunteers to a UMTS mobile phone signal or to a sham-exposure condition for 20 minutes. The SAR at the cochlea was given as 69 mW kg^{-1}. No effects of exposure were found on measures of hearing threshold, otoacoustic emissions or auditory ERPs. Hearing thresholds at high frequencies were increased after exposure, but the increase was not statistically significant after correcting for multiple comparisons.

Parazzini et al (2010) used a patch antenna designed to produce much higher exposures than those used by the same group previously (Parazzini et al, 2009). With this system, they estimated that the SAR at the cochlea, averaged over 1 g, was 1.75 W kg^{-1}. A total of 73 participants were exposed for 20 minutes to UMTS signals, or were sham exposed, using a double-blind crossover design, and the same measures as in the 2009 study. No significant effects of UMTS exposure were found. In particular, the authors found no evidence for a change in hearing threshold, suggesting that their previous result (Parazzini et al, 2009) may have been a false positive. Several similar studies concentrating on otoacoustic emissions as an indicator of auditory function have also found no effects related to acute RF field exposure (Monnery et al, 2004; Janssen et al, 2005; Parazzini et al, 2005).

Finally, a meta-analysis of recent studies covering both auditory and vestibular function (Balbani and Montovani, 2008) has also concluded there is no evidence of an effect on human hearing function as a result of short-term RF field exposure.

Most of these studies have used careful experimental designs, including double-blinding, and carefully controlled exposures. Many followed the protocol defined by the European GUARD and EMFnEAR projects, ensuring a consistent experimental approach and allowing integration of results from several studies. The results of these studies suggest that mobile phone signals do not have acute effects on the auditory system.

One retrospective study investigating the effects of chronic RF field exposure demonstrated a significant selective impairment of sensorineural auditory function at 4 and 8 kHz (Oktay et al, 2004). In this study, 28 male participants living close to or working at radio and TV broadcasting stations for a period of at least 10 years were compared with a control group. The exposure group was shown to suffer a high frequency hearing impairment. Although age- and sex-matched control participants were used in the study, it is not clear how well matched the two groups were for other environmental factors likely to impair hearing function. A follow-up study in three groups of men with varying histories of exposure to RF fields from mobile phones demonstrated impairment at 500 Hz and 4 kHz in the right ear and at 4 kHz

in the left ear of the men in the group with the highest exposure history compared with controls. There were only 20 participants in each group and, again, the exclusion of other environmental factors that influence hearing function is not convincing. It is also unclear whether the impairment is related to RF field exposure or direct acoustic exposure from mobile phones (Oktay and Daşdağ, 2006).

Hutter et al (2010) conducted a hospital-based case–control study of mobile phone use and acute and chronic tinnitus at the Ear-Nose-Throat Department of the Medical University of Vienna, Austria. Patients aged 16–80 years were recruited consecutively as they visited the clinic from November 2003 to November 2004. Exclusion criteria were diseases of the middle ear, post-middle-ear surgery status, retrocochlear disease, severe psychiatric and systemic diseases, and medication with drugs that can influence tinnitus. Patients were also excluded if they had an underlying disease (eg hypertension or noise-induced hearing loss). Controls were outpatients at the same clinic (eg phoniatric patients without speech disorders and without myognathic problems, or patients with acute laryngitis, about to have a tonsillectomy, or with acute pharyngitis), matched to cases on age, sex and ethnic group. Patients with any otolaryngologic disease other than those mentioned were ineligible as controls (M Kundi, personal communication).

Participation rates in this study were very high, only four cases and seven controls refused. In total, 100 cases and 100 controls were interviewed. About half of the cases had chronic tinnitus (ie that had lasted more than 3 months). Mobile phone use was assessed using a paper version of the Interphone study questionnaire (see Chapter 8). Exposure was only assessed up to the date of first occurrence of tinnitus and the corresponding date for controls. Unexposed was defined as 'never use' of a mobile phone (for intensity of use) and never use or use for <1 year for duration of use. This means that very little mobile phone use would count as exposed, contrary to the Interphone study where unexposed was defined as 'never regular use' (see Chapter 8). Categorisation of the exposure was made according to the median level among controls. In some, but not all, analyses the categorisation was based on the distribution among controls with ipsilateral phone use, as this was regarded by the authors as the main analysis (M Kundi, personal communication). Having ever used a mobile phone was associated with an odds ratio of 1.86 (95% confidence interval 0.74–4.65). The results for ipsilateral and contralateral use were of the same magnitude, although both were lower than the overall result: odds ratios of 1.37 (95% CI 0.73–2.57) for ipsilateral and 1.31 (95% CI 0.65–2.44) for contralateral use, respectively. This pattern was seen for all exposure indices except for years of mobile phone use, where the opposite was seen, ie a higher risk estimate for ipsilateral use than for both contralateral use and overall mobile phone use. A borderline significantly raised odds ratio was observed for over 4 years of ipsilateral use (OR 1.95, 95% CI 1.00–3.80). Generally, risk estimates were unstable, resulting in wide confidence intervals. Retrospective self-reported mobile phone use and reported side of the head where the phone was held prior to disease onset are prone to potential reporting errors, which may differ between cases and controls (recall bias). A limited number of potential confounding factors were controlled for (eg education and urban/rural residence), and did not affect the results, but no information was available on, for example, exposure to loud music in portable players, which might be related to both mobile phone use and to the risk of tinnitus. Overall, it remains possible that other environmental exposures may explain the moderately raised risks observed. The study does not provide strong evidence that mobile phone use affects the risk of tinnitus.

Tinnitus was also studied in a cross-sectional study in Germany and Austria of people who reported being sensitive to electromagnetic fields and of a group of controls (Landgrebe et al, 2009). The aim of the study was to investigate if people reporting sensitivity to RF field exposure suffered more from tinnitus than others, and whether clinical characteristics pointing towards common pathophysiological mechanisms could be identified. Thus, the association between mobile phone use and tinnitus was not the primary aim of this study. Sensitive individuals were recruited through advertisement, and controls were selected among people living in the same vicinity or working at the same workplace. This type of subject recruitment is prone to selection bias, and it is difficult to assess whether the two studied groups constitute representative samples. Furthermore, the cross-sectional design makes it impossible to assess the time sequence of events, ie if mobile phone use preceded tinnitus or development of sensitivity. There is a considerable risk of reversed causality, eg that tinnitus affects the likelihood that a person becomes a mobile phone user. The study found no association between mobile phone use and tinnitus, but given the limitations of the study, no conclusions can be drawn based on these findings.

To summarise, these retrospective studies investigated a possible chronic-exposure-related hearing impairment or tinnitus, but it remains unclear as to how well the studies were controlled for other environmental exposures causing high frequency hearing loss or tinnitus, including direct exposure to sound in the auditory range.

5.2 Observational Neurocognitive Studies not based on Provocation

A number of studies have investigated the possible effects of RF fields on neurocognitive performance not by provocation, but by attempting to relate neurocognitive performance to estimates of exposure in daily life.

Three studies have measured objective cognitive functioning in participants with varying levels of mobile phone use. In one study, Arns et al (2007) compared 100 'heavy' mobile phone users, 100 non-users and 100 'intermediate' users with respect to EEG measures and a battery of neuropsychological tests. Controlling for the different personality characteristics that were identified between the three groups, heavy users were found to perform best on a 'word interference task', similar to the classic Stroop test (Stroop, 1935). Mobile phone use was also associated with EEG slowing, with higher delta and theta power and lower alpha peak frequency.

In a second study, Abramson et al (2009) used self-report measures to assess the total number of voice calls or text messages made or received per week in a sample of 317 Australian adolescents aged 11–14 years. These students were then asked to undergo a range of tests assessing cognitive function. All analyses were adjusted for age, sex, ethnicity, socioeconomic status and handedness. Participants who reported more calls per week had significantly shorter reaction times for simple and associative learning tasks, performed less accurately on working memory tests and associative learning tests, and experienced greater interference during a Stroop test. Participants who reported more text messages per week also demonstrated shorter response times to the simple learning task and less accuracy on working memory and associative learning tasks.

A follow-up of 232 of the adolescents who took part in the study reported by Abramson et al (2009) was conducted by Thomas et al (2010), who repeated the same exposure and outcome measures 10 months later. The researchers first assessed whether changes in cognitive outcome between the baseline and follow-up assessments were predicted by exposure at baseline, in order to test for any latency in the effects of exposure. No consistent associations were observed between the number of voice calls at baseline and changes in accuracy for any measure, although response time on two working memory tasks increased among those participants who reported a large number of calls at baseline. Increased response time to one of these working memory tasks was also associated with a higher number of text messages at baseline. In addition, the researchers assessed whether changes in exposure variables from baseline to follow-up were associated with changes in outcome measures. Changes in exposure followed a pattern of 'regression to the mean', with reported calls and text messages increasing for those students who originally reported low levels and decreasing for those who originally reported high levels. Participants who reported increased voice calls also experienced significant reductions in response time for one working memory task, but fewer reductions in response time for a simple reaction time task.

These three studies do not provide sufficient evidence to conclude that long-term exposure to RF fields can affect cognitive function. Instead, the authors of each study have rightly suggested that alternative mechanisms are more likely to account for the observations. In particular, a training effect has been suggested, with mobile phone use helping participants learn how to focus on tasks despite surrounding distractions. A similar training effect may also encourage users to surrender accuracy for speed in certain tasks, given that the predictive text functions of most mobile phones can normally correct for any minor errors that are made. The finding by Abramson et al (2009) that higher rates of text messaging are also associated with cognitive changes makes such explanations even more plausible. Given that mobile phones are normally held away from the body while texts are sent, it seems unlikely that this effect relates to a bioelectromagnetic mechanism.

Two additional studies have assessed cognitive function in relation to exposure to RF fields from mobile phone base stations. Both are described in more detail in Chapter 6. Abdel-Rassoul et al (2006) used 10 neurobehavioural tests in their study of people living or working near to an Egyptian base station. Participants who lived or worked close to the base station performed significantly worse in one test of attention and one test of short-term memory than those who worked further away. They also performed significantly better in tests of visuomotor speed and attention. In an Austrian study by Hutter et al (2006), the associations between exposure in a participant's bedroom (categorised as <0.1, 0.1–0.5 or >0.5 mW m^{-2}) and performance on 13 measures of cognitive function were assessed. The authors reported a non-significant tendency ($p = 0.06$) for greater perceptual speed among participants in the higher exposure category, adjusting for self-reported concern about base stations, age, sex and mobile phone use. As noted in Chapter 2, however, it is difficult to assess the total RF field exposure that a person receives on the basis of the type of measures used in these studies (proximity to a base station and exposure measured in the bedroom). Identifying whether exposure from mobile phone base stations genuinely contributes to a long-term effect on cognitive performance would require more detailed studies employing personal exposure meters and a prospective design.

5.3 Summary

Studies of cognitive function and human performance do not suggest acute effects of exposure to RF fields from mobile phones and base stations. Several of the studies published since the last AGNIR review are highly powered, sensitive and methodologically rigorous. Methodological improvements in recent studies have generally produced results that do not replicate earlier reports of effects of RF fields on cognition. These recent studies therefore increase the balance of evidence against short-term cognitive effects of RF fields.

Studies of auditory and vestibular function do not provide evidence of an acute effect of RF field exposure on the functions of the inner ear.

Neurophysiological studies of brain function are inconsistent. Many of these studies are of higher quality than those considered in earlier AGNIR reviews (AGNIR, 2001, 2003). Some recent studies are large and methodologically rigorous, while others still suffer from small sample sizes, poor exposure control or poor blinding. Four of six recent studies using vascular and metabolic measures suggest possible effects of RF fields on brain function. However, of the four studies that found an effect of RF fields, only one involved a large sample size, and the exposure system used in that study means that the actual RF field exposures are unclear.

Among several EEG and ERP studies, some found effects of RF field exposure, while others did not. Where EEG effects have been found, the effects are sometimes specific to one age group or one gender, with no obvious reason why this should be so. In some studies, numerous EEG measures were analysed without clear justification for the choice of measures, and without consideration of how multiple measurements might have influenced the chance of a false positive result. Therefore, much of the EEG research to date should be considered exploratory. In contrast, confirmatory studies are lacking. Finally, the mechanism by which RF fields might influence EEG activity remains unknown.

A number of EEG studies have reported increased alpha-band EEG power during and/or after exposure. Such effects have been found both in resting EEG and during sleep. These studies provide the most consistent body of evidence for an effect of RF field exposure on brain function. However, the reliability of these findings still remains unclear, and they do not currently provide convincing evidence for an effect of RF field exposure. Some studies with similar designs have shown no effects; other studies that have reported effects of RF field exposure are inconsistent in the brain regions affected, and have suggested that the effect is restricted to some age groups. Therefore, further confirmatory research, in large representative samples, and in independent laboratories, would be required to make this evidence convincing. Finally, the effects of RF field exposure on the EEG are small in those studies that have found them. For example, many perceptual and cognitive tasks produce EEG changes that are much larger than those recently reported to be associated with RF field exposure. Therefore, it remains unclear whether these RF effects, if they exist, are material to human health or not. Nevertheless, the EEG studies published since 2003 do provide some evidence that RF fields could influence brain function, and this should remain an area of interest.

The effects of RF field exposure on neurocognitive function reviewed here could, in principle, be due to any of several biological mechanisms (apart from statistical chance). These mechanisms could include

mild heating of brain tissue below guideline levels, highly localised heating of specific brain structures, or some unidentified non-thermal mechanism of interaction between RF fields and biological tissue. The current chapter has focused on identifying whether there are any neurocognitive effects of RF fields below guideline levels, irrespective of the mechanism involved.

Existing studies of cognitive and neurophysiological effects in children do not support the hypothesis that they are more susceptible to the effects of RF fields than adults. However, these studies have been few in number, and most have used small sample sizes. There is still insufficient, good quality evidence to draw strong conclusions about potential effects of RF fields in children.

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6 Symptoms in Humans

Among the general population, the adverse effects most commonly attributed to RF field exposures are acute, subjective symptoms such as headache, fatigue and nausea (Oftedal et al, 2000). Within the UK, as elsewhere, a small percentage of the population report being particularly sensitive to RF fields, regularly experiencing symptoms when exposed to mobile phones, base stations or other sources (Irvine, 2005). Questionnaire studies of people who report this sensitivity have found the condition to be very heterogeneous. Sufferers differ in terms of the type of symptoms that they report, the speed with which symptoms develop and the types of electromagnetic field that appear to be problematic (Hillert et al, 2002; Levallois et al, 2002; Röösli et al, 2004). Despite difficulties in defining the condition, it is clear that this apparent sensitivity can be associated with a poor quality of life (Irvine, 2005). Because of this, a substantial body of research has developed assessing whether particular types of electromagnetic fields are responsible for causing symptoms.

Most studies in this area have used an experimental design to test whether single- or double-blind exposures to RF fields trigger higher levels of symptoms than sham exposures. These studies have also frequently tested whether people can consciously detect if an RF field is present. However, although these studies are the best way of testing whether short-term exposures can trigger acute symptoms, it is difficult to use this method to assess whether longer-term exposure can cause symptoms that may take more time to develop. Because of this, observational studies have also been conducted to explore the association between chronic exposure to RF fields and symptoms. This chapter reviews both experimental and observational studies that have assessed the effect of RF field exposure on symptoms. In each case, studies are divided according to whether they assessed the effects of signals that are similar to those produced by mobile phone handsets or those produced by mobile phone base stations. It should be noted that several of the studies discussed in this chapter have included data relating to neurocognitive outcomes. Those data have been discussed in Chapter 5.

6.1 Experimental Studies

6.1.1 Handset-type signals

With respect to mobile phone handsets, the previous review by AGNIR (2003) described the results of one experiment involving a group of 20 volunteers, all of whom reported being sensitive to mobile phone signals (Hietanen et al, 2002). Participants were exposed under blind conditions to three or four exposures of 30 minutes, of which one was a sham condition involving no exposure to RF fields, while the others involved exposure to either 900 MHz NMT (an analogue mobile phone signal: see Chapter 2 for details), or 900 or 1800 MHz GSM signals. The authors noted that symptoms were more commonly reported in the sham condition than in the exposed conditions. No statistical analysis of this effect was reported, however.

Since 2003, six additional blind or double-blind volunteer studies have tested whether people who report some form of sensitivity to man-made electromagnetic fields experience more symptoms when exposed to an RF field designed to replicate that produced by a handset than when exposed to a sham signal (Rubin et al, 2006; Wilen et al, 2006; Oftedal et al, 2007; Hillert et al, 2008; Nam et al, 2009; Nieto-Hernandez et al, 2011). These studies are summarised in Table 6.1. The studies tested the effects of exposure durations ranging from 30 minutes to 2 hours 45 minutes, with each including between 6 and 69 volunteers who reported being sensitive to electromagnetic fields. All bar one (Oftedal et al, 2007) also included a control group of people who did not report sensitivity to electromagnetic fields. Only two studies reported any significant effect of exposure. In the first of these, an increased level of headache was observed following exposure for 2 hours 45 minutes to a GSM signal in the non-sensitive control group and higher levels of self-reported heating around the ear were observed in both the control and sensitive groups (Hillert et al, 2008). However, this latter finding was observed in only one of the three techniques which the authors used to score heat sensations, raising the possibility that it was a Type 1 (false positive) error. In the second study to have observed a significant effect, 50 minutes of exposure to a continuous wave signal was found to reduce the presence of 'skin itching, tingling, stinging and numbness' amongst participants who believed themselves to be sensitive to TETRA signals (Nieto-Hernandez et al, 2011). This same study did not identify any robust effect on nine other subjective measures or any effect from exposure to a TETRA signal.

In addition to studies that have tested participants who report sensitivity to electromagnetic fields, seven studies have looked solely at 'healthy' volunteers. Cinel et al (2008) tested the effects of GSM and continuous wave handset exposure in three groups of healthy participants, with a combined sample size of 496. Although in one sample an increase in self-reported dizziness was observed, this could not be replicated in the other two groups. No effect was observed on headaches, fatigue, itching or sensations of warmth. Similarly, Kleinlogel et al (2008) observed no effects of exposure to GSM or UMTS handset signals on measures of well-being in a sample of 15 men. In a study published in 2001, Koivisto et al (2001) reported two single-blind experiments, each involving 48 healthy participants, assessing whether 30 or 60 minutes of exposure to a GSM signal caused higher levels of headache, dizziness, fatigue, itching or tingling, skin reddening or skin warming. Exposure to RF fields did not result in worse symptoms than exposure to a sham condition. Curcio et al (2009) exposed 11 women to two 40-minute testing sessions, one involving sham exposure and the other involving GSM exposure. The severities of 10 symptoms were assessed at the end of each session. Only one symptom showed any significant effect, with an increase in headache being observed in the sham condition. Hung et al (2007) tested the effects of GSM exposure on sleep in 10 male volunteers. Each was exposed for 30 minutes to a 900 MHz GSM mobile phone operating in 'talk,' 'listen', 'stand-by' and sham modes. No effect of exposure was found for subjectively rated sleepiness. Similarly, Curcio et al (2005) identified no effect of 45 minutes of exposure to a 902.4 MHz GSM signal on subjective sleepiness in a sample of 20 healthy participants. Riddervold et al (2010) investigated the effects of 45 minutes of exposure to a TETRA handset signal on 11 self-reported symptoms among 53 male volunteers. Once again, RF field exposure had no greater effect than sham exposure.

Finally, one single-blind experiment has assessed the effect of exposure for 30 minutes to a 900 MHz GSM signal compared with sham exposure in a group of 15 people with atopic dermatitis and a group of 15 healthy participants (Johansson et al, 2008). Although symptoms were assessed in this study, the authors noted that 'the number of symptoms was not sufficient for a statistical evaluation of the relation between experienced symptoms and exposure condition'.

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

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

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

6.1.2 Base-station-type signals

With respect to studies on the potential effects of base station signals, the 2003 AGNIR report described the findings of one experimental study which identified a significant effect of exposure to a UMTS base station signal on symptom reporting among a group of participants who described themselves as being sensitive to GSM signals (Zwamborn et al, 2003). This same study also identified that exposure to 900 MHz GSM signals and UMTS signals resulted in altered reporting of some symptoms among the non-sensitive control participants. Since then, five more double-blind experimental studies have assessed the effect of short-term exposure to base-station-type signals on participants who report sensitivity to various forms of electromagnetic fields (Regel et al, 2006; Eltiti et al, 2007a; Augner et al, 2008; Furubayashi et al, 2009; Wallace et al, 2010). These are outlined in Table 6.2. The exposures tested in these studies have included TETRA, 900 or 1800 MHz GSM, UMTS and WCDMA signals, with all exposures lasting less than 1 hour. The original results reported by Zwamborn et al have not been replicated by these studies. While in two cases, apparently significant effects of exposure were observed on self-reported symptoms, in both cases the significance of effects could be removed by adjusting for the number of endpoints that were tested or for the order in which the exposures were presented (Eltiti et al, 2007a; Augner et al, 2008).

Two additional studies have examined the effect of short-term exposure to base-station-type signals on symptoms in the non-sensitive participants. In one study, Fritzer et al (2007) randomly assigned 20 volunteers to be exposed to either a 900 MHz GSM base station signal or a sham condition for six consecutive nights while in a sleep laboratory: this study did not use a conventional crossover design. No effects of exposure were found in terms of self-reported sleep quality or well-being. In the other study, a group of 40 children (aged 15–16 years) and 40 adults (aged 25–40 years) were asked to record the presence of headaches or concentration difficulties during double-blind exposure to sham and UMTS signals (Riddervold et al, 2008). All exposures lasted for 45 minutes. For adults, there was a marginally significant difference between the two conditions in terms of concentration difficulties ($p = 0.048$). When results for the adult and child groups were combined, an effect for headache was also observed ($p = 0.027$). However, the authors noted that the baseline scores for these variables were different between the conditions, making it difficult to draw firm conclusions from their findings.

All of the studies discussed so far have tested the effects of relatively short-term exposure to RF fields. Because most people who report adverse effects from RF field exposure in their day-to-day life describe a rapid onset to their symptoms (Röösli et al, 2004), this length of testing is valid in most cases. However, some people report that lengthier exposures to RF fields, lasting hours or days, are required before symptoms begin to develop. In this context, two German studies are of interest. In the first study, real or sham electric conductive netting was erected over the beds of 43 volunteers who reported sensitivity to RF fields from local base stations. Netting was present for a total of six nights for each participant: three nights with genuine protective netting and three nights with the inactive, placebo netting (Leitgeb et al, 2008). Although some changes in sleep EEG recordings were observed, only three participants reported any subjective improvements in the quality of their sleep as a result of the real netting. In each case, the research team subsequently identified 'suspicious' changes in the

electromagnetic field levels recorded within the netting during the evenings, suggesting that the participants had broken the study blinding by checking whether the netting was effectively blocking RF fields or not. In the second, much larger, study, 397 participants drawn from 10 rural villages in which no mobile phone service was available slept for 10 nights in their own homes while exposed to real or sham GSM base station signals transmitted by a mobile phone base station which was brought into the village by the research team (Danker-Hopfe et al, 2010). This base station produced 900 and 1800 MHz GSM signals in a test mode, ensuring that no signal would be registered by any nearby mobile phones. For each participant, objective sleep parameters were recorded using an ambulatory EEG device, while subjective measures of sleep quality were recorded using questionnaires. No effects of exposure on any sleep parameter were identified.

6.1.3 Detection of RF fields

As mentioned in Section 6.1.1, the previous review by AGNIR (2003) described one study that assessed the ability of 20 volunteers who reported sensitivity to mobile phone signals to discriminate consciously between a sham condition and an active condition involving either 900 MHz NMT, or 900 or 1800 MHz GSM signals (Hietanen et al, 2002). None was able to discriminate reliably between the conditions. Since then, several other studies have tested whether people who are apparently sensitive to electromagnetic fields are able to detect the presence of an RF field. The results of these studies are given in Table 6.3, which includes three additional studies that were available at the time of the previous AGNIR report, but which were not included then because they were not readily available in the English-language peer-reviewed literature. None of the studies listed in the table found evidence to suggest that people who report sensitivity to electromagnetic fields are capable of detecting RF field exposure at better-than-chance levels. Many of the studies in the table also tested the ability of healthy control participants to discriminate active from sham exposures, while several additional studies described in detail in Chapter 5 included only healthy control participants and also examined this outcome (Haarala et al, 2005; Loughran et al, 2005; Aalto et al, 2006; Krause et al, 2006; Riddervold et al, 2008, 2010; Croft et al, 2010). Again, none of these studies has found evidence to support the existence of this ability.

It is possible, however, that some individuals are better at detecting RF fields than others. Some provocation studies have therefore repeatedly tested individual participants in the hope of finding one or more people who are reliably able to do this. In the largest study of this type, Kwon et al (2008) investigated whether 84 participants could correctly detect when a mobile phone signal (902 MHz GMS, pulsed at 217 Hz) was present. Each participant performed 600 detection trials. While overall performance was no better than chance, two individual participants performed extraordinarily well, getting 94% and 97% of the discrimination tasks correct. However, both individuals came from the study's control participant group, rather than its sensitive group, and neither was able to replicate their performance when tested again a month later. While other provocation studies have occasionally identified individuals who correctly identify all exposures that they undergo, given the large number of participants who have been tested in this way across the literature, a small number would be expected to show these results by chance alone. Taken together, the literature does not support the hypothesis that some people are able to detect RF fields.

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

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

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

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

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

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

TABLE 6.3 *Continued*

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

6.1.4 Summary

A large body of experimental evidence now exists concerning the impact of RF fields on self-reported symptoms. The controlled conditions and use of blinding in these studies makes this a robust body of work, although the small sample sizes in some of the studies means that rare effects of RF field exposure may have been missed. This is particularly true for studies that have assessed people who report sensitivity to electromagnetic fields, where recruitment of participants is understandably difficult. Nonetheless, when taken together the experimental evidence suggests that short-term exposure to RF fields below guideline levels (see Appendix B) does not cause acute symptoms, either in the general public or in people who report being sensitive to electromagnetic fields. Similarly, these studies have found no replicable evidence that healthy individuals or people who report sensitivity are able to detect the presence of RF fields.

6.2 Observational Studies

6.2.1 Handsets

While the effects of short-term exposures to RF fields are best tested using an experimental design, the impact of longer exposures can often only be assessed using observational studies. The previous review by AGNIR (2003) described three such observational studies that assessed whether use of a mobile phone was associated with increased reporting of symptoms (Chia et al, 2000; Sandstrom et al, 2001; Santini et al, 2001). All three used cross-sectional data and based their analyses on self-reported exposures. Each found that increased use of mobile phones was associated with an increased tendency to report symptoms.

Since then, other cross-sectional studies have replicated this association. Many of these have also relied upon self-reported exposure. For example, Balik et al (2005) questioned 695 residents of a town in Turkey with respect to their use of mobile phones and the occurrence of six eye-related symptoms. These participants were described as being 'randomly selected from different ages, educations, earning, locations and occupations', although no other description of the recruitment strategy or response rate was given. Amongst the sample, mobile phone users were significantly more likely to report blurred vision (reported by 52.7% of non-users versus 72.6% of users), secretion from the eyes (2.1% vs 6.2%), inflammation in the eyes (13.0% vs 20.3%) and lacrimation (11.6% vs 20.0%) than non-users. Within the user group, increasing numbers of years of use were associated with an increased probability of blurred vision or lacrimation. A second paper by this group, but using the same sample of respondents, described increased rates of headache (63.0% vs 78.9%), 'extreme irritation' (23.3% vs 35.5%), forgetfulness (12.3% vs 20.2%), carelessness (23.3% vs 39.1%), slowed reflexes (3.4% vs 13.3%) and clicking sounds in the ears (12.3% vs 20.2%) among mobile phone users, with increased length of mobile phone ownership correlating with increased rates of headache, dizziness, extreme irritation, carelessness, decreased reflexes and clicking sounds (Balikci et al, 2005).

Using a similar study design, Khan (2008) distributed a questionnaire to medical students at a university within Saudi Arabia, achieving an 86.6% response rate. Among the 286 respondents, significant associations were found between higher self-reported use of mobile phones and higher rates of self-reported

headache, concentration impairment, memory impairment, fatigue, sleeplessness, hearing problems, skin disease and warmth around the ear.

Not all studies using self-reported measures of mobile phone use have observed a link with symptoms, however. In a second study of Saudi Arabian medical students, Meo and Al-Drees (2005) collected data from 873 people. No indication of response rate was given. In contrast to the results of Khan (2008) and Balik et al (2005), no statistically significant association was observed between the length of time a student reported spending on a mobile phone each day and their reports of impaired hearing, ear ache and/or warmth on the ear, or of decreased and/or blurred vision.

Particular caution is required in interpreting these studies, however, as none attempted to control for potential confounder variables. Numerous non-RF-field-related variables exist which might explain why people who have higher levels of mobile phone use can also experience higher levels of symptoms. These range from sociodemographic variables that are associated with both mobile phone use and symptom presence (see, for example, Thomas et al, 2010a), to differences in levels of stress or personality traits among mobile phones users (see, for example, Butt and Phillips, 2008), to lifestyle differences (see, for example, Sanchez-Martinez and Otero, 2009). To assess adequately any relationship between mobile phone use and symptoms, studies must take the possible influence of such confounders into consideration.

For example, in a convenience sample of 132 people in Germany, Herr et al (2005) initially observed an association between decreases in self-reported sleep quality, sleep latency, sleep duration and global sleep quality and increases in self-reported daily duration of mobile phone use. However, after adjusting for potential confounders such as gender, age, the presence of chronic, medically unexplained symptoms, daily working hours and self-reported levels of stress, this association was no longer apparent.

Similarly, Mortazavi et al (2007) distributed a questionnaire to 690 Iranian university students, with 518 (75.1%) replies. No significant differences between mobile phone users and non-users were observed for 10 different symptoms. A significant association was found between cordless phone use and difficulties with concentration or attention. However, the authors reported that correcting for gender removed this effect.

In a random sample of 6121 members of the Finnish population (representing a 41% response rate), Korpinen and Pääkkönen (2009) assessed the association between self-reported use of different technological devices, including mobile phones, and self-reported sleep disorder, depression, exhaustion at work, substance abuse, anxiety and/or fear. Symptoms were assessed in relation to 'the past 12 months'. The primary analyses assessed the main effects of mobile phone use and the two-way interactions between mobile phone use and age, gender, use of a desktop computer and use of a portable computer or minicomputer. Only one of these 30 terms suggested any significant effect, with a significant interaction being observed between gender and mobile phone use for the depression outcome.

Al-Khamees (2007) distributed a questionnaire to 4000 people in Kuwait, described as 'college and school students and their families, employees in selected ministries and companies, and attendees at selected gatherings'. This questionnaire assessed patterns of mobile phone use, and the presence of 31 symptoms or medical conditions. A total of 3274 fully completed questionnaires were returned. Although full statistics for the binary logistic regressions that were used to analyse the data were not reported, the

author noted that they revealed significant associations between varying types of self-reported mobile phone use and burning sensations on the ear, dizziness, difficulties in concentrating, sleep disturbances, breathing problems, learning difficulties, unstable walking, pain in the temporal area, heart disturbances, noises in the ear, pain in the back of the head, ear pain and ear numbness. These regressions included age, gender and employment status as covariates.

Two other studies have assessed the association between mobile phone use and symptoms in children. In the first study, Soderqvist et al (2008) sent postal questionnaires to 2000 adolescents (aged 15–19 years) randomly selected from Sweden's population registry, of whom 1269 (63.5%) replied. The percentage of respondents who reported using a mobile phone for 2 minutes or more a day increased from 55.6% in 15 year olds to 82.2% in 19 year olds. Similarly, the percentage who reported using a DECT phone for 5 minutes or more a day increased from 56.4% of 15 year olds to 74.7% of 18 year olds and 70.6% of 19 year olds. Twenty-three self-reported symptoms were measured along with sleep quality and perceptions about general health. Adjusting for the potential confounding effects of age and sex, using a mobile phone for 2 minutes or more a day was significantly associated with reporting insufficient sleep (odds ratio 1.9, 95% confidence interval 1.3–2.6), asthmatic symptoms (OR 1.8, 95% CI 1.1–3.0), headache (OR 1.5, 95% CI 1.1–2.0) and concentration difficulties (OR 1.4, 95% CI 1.1–1.9), while using a DECT phone for 5 minutes or more a day was significantly associated with insufficient sleep (OR 1.9, 95% CI 1.4–2.7), asthmatic symptoms (OR 1.9, 95% CI 1.1–3.3), headache (OR 1.5, 95% CI 1.2–2.1), concentration difficulties (OR 1.4, 95% CI 1.03–1.9), hay fever (OR 1.5, 95% CI 1.01–2.2), stress (OR 1.4, 95% CI 1.03–1.8) and tiredness (OR 1.3, 95% CI 1.01–1.8). Nonetheless, the authors cautioned that these results should be seen only as 'explorative', as the large number of associations that were tested raised the probability of apparently significant findings occurring by chance alone.

In the second observational study of mobile phone use among children, Heinrich and colleagues recruited a sample of 1484 Bavarian children aged 8–12 years and 1508 adolescents aged 13–18 years, as part of a larger study described in more detail in Section 6.2.2 (Heinrich et al, 2010). Each participant completed a 24-hour diary relating to symptom experience and mobile phone use. Adjusting for sex, age, level of education, town and level of worry about the environment, self-reported use of a mobile phone by 13–18 year olds for more than 5 minutes during the morning was found to be associated with a significantly increased rate of headaches (OR 1.6, 95% CI 1.1–2.3), irritation (OR 1.6, 95% CI 1.1–2.4) and fatigue (OR 1.8, 95% CI 1.2–2.6) at noon. No association was found for self-reported use in the afternoon and symptoms recorded in the evening. Nor was any association observed for the 8–12 year old group. Moreover, RF field exposure as measured by personal exposure meters worn during the same 24-hour period showed only a limited number of marginally significant associations with symptoms, which appeared to reflect chance findings resulting from multiple testing rather than any genuine effect. In a separate analysis of a subset of 1025 of the adolescents (Milde-Busch et al, 2010), no significant association was observed between self-reported duration of mobile phone use each day and experiencing a headache at least once per month, after adjusting for sex, age, family composition and socioeconomic status.

While some, though by no means all, of the studies reviewed above appear to suggest an association between mobile phone use and symptoms, almost all of the studies share a fundamental methodological problem which makes it difficult to draw any firm conclusions from them: these studies relied upon the

participants' own descriptions of their mobile phone usage as the exposure variable for their analysis and on self-description of symptoms while knowing exposure status. Unfortunately, a person's ability to recall how much they have used their mobile phone is likely to be unreliable over any reasonably lengthy period of time (Vrijheid et al, 2006). Even in situations where recall is likely to be more accurate, self-reported use remains a poor way of assessing how much exposure to RF fields an individual has experienced, a suggestion supported by the study of Bavarian children and adolescents which identified substantial mismatch between exposure metrics derived from the 24-hour diaries completed by participants on the day of assessment and exposure metrics based on data from the personal exposure meters worn by the participants during the same 24-hour period (Heinrich et al, 2010).

Rather than reflecting the influence of some bioelectromagnetic mechanism, it therefore seems likely that alternative explanations may account for the associations that have been identified in this literature. Several possible explanations exist.

First, it is possible that people who suffer from symptoms may overestimate their previous mobile phone use, resulting in a false association being discovered. This is particularly likely to occur in contexts where a potential link between mobile phone use and health effects is made salient to participants – for example, if the participants are not kept blind as to aims of the study or if local media reporting has often focused on the potential health effects of mobile phones (see, for example, Mortazavi et al, 2007).

Second, it is possible that it is the perception a person may have of being exposed to mobile phone signals, rather than the actual exposure itself, which accounts for the link between mobile phone use and symptoms. Numerous studies have observed that the belief that exposure to an electromagnetic field is taking place can be sufficient to trigger the onset of symptoms in a person, regardless of whether the exposure genuinely exists or not. This effect was observed in many of the experimental studies described earlier (see also Rubin et al, 2010). It has also been demonstrated in several experiments that have deliberately deceived people into thinking that they are being exposed to an electromagnetic field (Schweiger and Parducci, 1981; Landgrebe et al, 2008; Szemersky et al, 2010). This phenomenon, which has been recognised in the wider medical literature for well over a hundred years (Mackenzie, 1886), is referred to as a 'nocebo' effect (Barsky et al, 2002) and can itself be the result of several psychological and neurobiological mechanisms (Tracey, 2010).

Third, other non-bioelectromagnetic mechanisms might also result in mobile phone use causing more symptoms. Qualitative research by Thomée et al (2010) with a group of young adults (20–28 years old) explored some of these other potential links. The participants suggested a range of factors related to mobile phones that might cause symptoms, including the stress associated with being permanently contactable, frequent interruptions of work and other activities, difficulties separating work from leisure, feeling overwhelmed by calls or text messages, and worries about cost. Sleep disturbance as a result of being contacted at night or feeling compelled to check for messages during the night was also a dominant theme among participants' responses. A study by Punamaki et al (2007) has assessed this sleep disturbance effect in more detail. All 12, 14, 16 and 18 year olds born in Finland on a given set of dates were eligible for this study and were sent a postal questionnaire measuring, among other things, mobile phone use, sleeping habits, waking time tiredness, and measures of perceived health. In total, 7292 people (70%) returned the questionnaire. Using a mediation analysis, the authors demonstrated

that any association between mobile phone use (modelled as a latent variable loaded on by mobile phone ownership, duration of mobile phone use and intensity of mobile phone use) and poor health (characterised by health complaints, musculoskeletal pain and poor health status) could largely be explained by the mediating effects of poor sleeping habits and subsequent tiredness during the day.

Finally, the potential for selection bias among many of the studies reviewed also makes it unwise to place undue weight on this literature. People who are concerned about the health impacts of mobile phone technologies are more likely to take part in this type of study than people who are not concerned (Thomas et al, 2008b). Given that concern itself correlates with both higher perceived exposure (see, for example, Blettner et al, 2009) and increased symptom reporting (see, for example, Hutter et al, 2006), this selection bias again increases the potential for spurious associations being identified.

6.2.2 Base stations

The previous review by AGNIR (2003) described a single study that tested the association between chronic exposure to mobile phone base station signals and the presence of symptoms (Santini et al, 2002). This questionnaire-based survey identified significantly higher rates of various symptoms among people living within 300 m of a base station compared with those living further away. In this study, exposure was measured by asking participants to estimate the distance between their home and the nearest base station. As with studies assessing self-reported exposure to mobile phone handsets, the use of self-reported distance to a mobile phone base station can cause difficulties in interpreting a study's findings. In the case of base stations, a particular problem is that participants who experience symptoms may believe that they live closer to a base station than respondents without symptoms, even when no actual difference between the two groups exists (see, for example, Eltiti et al, 2007b). Even when objectively measured, distance from a base station is, in any case, an unreliable way of assessing the level of exposure to RF fields within a residence (see Chapter 2).

Other studies have examined whether objectively measured proximity to a specific base station is associated with increased symptom reporting. Navarro et al (2003) used a self-completion questionnaire to assess how far residents of a Spanish town lived from two local GSM base stations described as being 'on a hill at the edge of the town'. These questionnaires were 'always introduced to respondents as part of a study to evaluate the impact on the area of the [base station]'. A subsequent report by this team (Oberfeld et al, 2004) noted that 144 questionnaires were distributed in 'frequently used locations' such as hairdressers or pharmacies, of which 101 were completed and used in the analyses (Navarro et al, 2003). Participant ages ranged from 14 to 81 years. The questionnaire data were supplemented with electric field measurements carried out in the bedrooms of respondents. In the analyses described by Navarro et al, participants were grouped according to whether they lived within 150 m of the base station (54 participants) or whether they lived more than 250 m away (47 participants). Electric field measurements confirmed that the average power density in participants' bedrooms was higher in the closer group. This group also reported significantly greater levels for nine out of the sixteen symptoms that were measured. Significant correlations were also discovered between the recorded power density and the severity of almost all recorded symptoms. In a subsequent analysis of the data for 94 of these participants, described by Oberfeld et al (2004), exposure in the bedroom was categorised as low

(0.02–0.04 V m^{-1}), intermediate (0.05–0.22 V m^{-1}) or high (0.25–1.29 V m^{-1}). Controlling for sex, age and self-reported distance to the masts, seven symptoms were significantly more common among participants with intermediate exposure compared with low exposure, and all but two symptoms were significantly more common in the high exposure group. However, although self-reported distance to the mast was included in this model as a proxy for concern about the health effects of the mast, the failure of this study to control for concern more directly is a major weakness. Selection bias is also problematic, particularly given that the aims of the study were emphasised to participants prior to their participation.

In a similar study by Abdel-Rassoul et al (2006), 85 people who were considered to be exposed to an Egyptian base station because they either lived in the building on which it was sited (37 people) or else worked in a building 10 m opposite (48 people) were compared with a control group of 80 employees from a different building 2 km away and who were matched on age, sex, occupation, education level and mobile phone use. Again, procedures for selecting exposed and unexposed participants were not explicitly stated, although no participants were informed about the true purpose of the study. Higher levels of self-reported symptoms were recorded in the exposed group for headache (OR 2.8, 95% CI 1.1–7.4), memory changes (OR 7.5, 95% CI 2.3–27.0), tremors (8% in exposed group, 0% in unexposed), dizziness (OR 4.4, 95% CI 1.3–16.5), depressive symptoms (OR 2.8, 95% CI 1.0–7.9) and sleep disturbance (OR 2.8, 95% CI 1.1–7.4). However, no attempt was made to control for confounding variables such as concern or anxiety about the presence of the base station, despite this having been described by the authors as the first base station to have been constructed in the local region. Other, unmeasured, differences between the two locations, such as traffic noise, pollution or social factors within the buildings, might also have contributed to this effect.

In response to local concern, Preece et al (2007) assessed the health status of residents of three villages in Cyprus, two of which were located near to a large military antenna array and one of which was located further away and served as the unexposed or control village. Spot measurements within each village revealed that the average broadband outdoor field strength from all sources in the villages near to the array were 0.57 and 0.46 V m^{-1}, while readings from the control village were less than 0.01 V m^{-1}. All households within each village were sent a health questionnaire, with response rates of between 77% and 92% being achieved. Amongst other things, the questionnaire recorded the presence of four self-reported symptoms (migraine, headache, dizziness and depression) and included standard measures of health-related functioning along eight dimensions. Adjusting where relevant for educational status, age, sex, smoking status, mobile phone usage and for a variable relating to the perceived health risk arising from 22 different hazards, living within the exposed villages was found to be a significant risk factor for the presence of the four symptoms, with odds ratios ranging from 1.8 (95% CI 1.1–2.8) to 5.6 (95% CI 3.7–8.6). Univariate analyses also suggested that the levels of health-related functioning were lower among residents of the exposed villages. As the authors noted, however, the health of residents from the exposed villages may also have been affected by the clear visibility of the controversial antenna array and by the repeated, sudden presence of loud aircraft noise from a nearby military airstrip, as well as by any confounding differences in health-related exposures and behaviours between the villages. Separating the effects of RF fields from the effects of these other environmental exposures was not possible.

Local concern also resulted in a series of studies by Abelin and colleagues in the area surrounding a short-wave radio transmitter that operated in Schwazenburg, Switzerland, at frequencies of 3–30 MHz from 1939 to 1998 (Abelin et al, 2005). Local residents were categorised into four groups, based on their distance to the mast. Two surveys were conducted, in 1992 (404 participants) and 1996 (399 participants), to assess a range of symptoms and potential covariates. These both suggested a similar pattern of results, with distance from the transmitter directly affecting difficulty of maintaining sleep and indirectly affecting other symptoms through the mediating effect of disrupted sleep. Believing the transmitter to have a negative effect on health did not fully account for these associations. Two 'shut-down' studies were also conducted as part of this work. The first, in 1993, identified a decrease in awakenings during the night among 65 participants after the transmitter's operation was interrupted. In the second study, the permanent shut-down of the transmitter in 1998 was found to be associated with improved sleep quality among a sample of 54 residents who completed sleep diaries for 1 week before and 1 week after the shut-down. This was particularly true for those who were most exposed to the transmitter. While this detailed series of studies had several strengths, the authors noted that blinding the participants to their exposure status was not possible, making it difficult to separate the effects of exposure from the effects of knowledge about the exposure.

In addition to studies that have assessed the impact of specific individual base stations, several have assessed whether symptoms might be associated with exposure to any base station. For example, using postcode data with a UK sample population, Eltiti et al (2007b) identified no difference in self-reported symptom severity between people living near to any mast and those living further away. In a much larger study, Blettner et al (2009) asked a sample of 51,444 people in Germany to record the presence and severity of 38 symptoms. These potential participants were selected from a larger, commercially owned database of individuals willing to take part in market research surveys, such that the eventual sample was representative of the German population in terms of sex, age, income and region of residence. A total of 30,047 people (58.4%) provided useable data. Comparison of the addresses for survey respondents with the known locations of all mobile phone base stations in Germany enabled the sample to be divided into those living within 500 m of a base station and those living further away. A slightly higher level of total symptom severity was identified in those participants living closer to a mast. This effect persisted even after adjusting for the self-reported level of worry that participants had regarding the health effects of mobile phone base stations. However, in a second stage of this study (Berg-Beckhoff et al, 2009), a sub-sample of 1500 of these participants allowed RF field measurements to be made inside their homes, using personal exposure meters that were placed in various positions on their beds. Three downlink frequencies were analysed (900 and 1800 MHz GSM and UMTS), with participants categorised as 'exposed' if the mean total field was above 0.1 V m^{-1}. Participants also completed five more self-report scales relating to symptoms, sleep quality and general well-being. Regression analyses identified no differences in any of these five scales between those categorised as exposed and those categorised as unexposed. The same pattern of results held true when the total exposure, which also included exposures from TV and radio broadcast towers, cordless phone base stations and Wi-Fi, was measured.

Another study involving spot measurements of RF fields in participants' bedrooms was that conducted by Hutter et al (2006). The researchers first identified five base stations in an urban region of Austria and five in a rural region. These had been operating, usually at only the 900 MHz band, for at least 2 years,

had provoked no protests by the local community and were not near to another base station. Local residents were then randomly selected to take part in the study. Slightly fewer than 60% of those contacted in the urban region, and 68% in the rural region, elected to take part. The 336 participants completed questionnaires relating to their level of concern about the adverse health effects of base stations, the severity of fourteen symptoms, and eight measures of subjective sleep quality. The researchers measured high frequency electromagnetic fields in the bedroom, with homes categorised according to whether the maximum exposure from the local base station of the power densities across all mobile phone frequencies was ≤0.1, 0.1–0.5 or >0.5 mW m^{-2}. Some concern about base stations was recorded by 35% of urban respondents and 39% of rural respondents. A highly significant effect of concern was found for overall sleep quality, with more concerned participants reporting worse sleep. Controlling for age, sex, regular mobile phone use and concern, participants whose bedrooms fell into the high exposure category were more likely to report headaches, with a relative risk of 3.1 (95% CI 1.2–7.7), cold hands or feet (RR 2.6, 95% CI 1.2–5.7), or difficulty concentrating (RR 2.6, 95% CI 1.1–6.1) compared with those whose bedrooms had the lowest exposure.

All of the base station studies discussed so far have based their exposure assessments on the distance between a participant's home and the nearest mast, or on RF field measurements obtained within a participant's bedroom. In practice, however, most of the exposure to RF fields that an individual receives over the course of a day is likely to come from other sources: from their mobile phone, for example, or from sources encountered while travelling (Frei et al, 2009b). Accurate assessment of the impact of RF fields on self-reported symptoms requires that these other exposures are taken into consideration. The relatively recent development of personal exposure meters that can be worn by a participant over an extended period of time has allowed newer studies to assess the impact of total exposures more accurately.

In the largest of these studies, Thomas et al (2010b) used personal exposure meters with samples of 8–12 year old children and 13–17 year old adolescents in order to assess the association between overall exposure to the RF fields from 900 and 1800 MHz GSM, UMTS, DECT and 2400 MHz WLAN frequencies, and mental health symptoms and behaviours. Mental health was assessed using five self-report and parental-report scales, encompassing emotional symptoms, conduct problems, hyperactivity, peer-relationship problems and prosocial behaviour. Exposure was assessed over a single 24-hour period for each participant. In total, 1484 children and 1508 adolescents were included in the analyses, out of 5870 eligible children and adolescents who were originally randomly selected from the registration offices of four Bavarian cities. Adolescents whose exposure was in the highest quartile for the sample exhibited more behavioural problems than other adolescents (OR 2.2, 95% CI 1.1–4.5). Greater conduct problems were seen in both children (OR 2.9, 95% CI 1.4–5.9) and adolescents (OR 3.7, 95% CI 1.6–8.4) who were in the top quartile for exposure. These associations were adjusted for possible confounders such as age, sex, education level, environmental worry, self-reported mobile and cordless phone use, and self-reported distance from home to the nearest phone mast. Given that removing self-reported exposure variables from the analyses did not affect the results, it seems unlikely that these results reflect the fact that behavioural problems may simply cause children to use their mobile phones more. However, behavioural problems might be associated with a greater tendency to frequent areas where there are higher levels of RF fields (such as shopping malls, trains or buses) and to avoid areas with low levels of RF fields (such as

schools) (Frei et al, 2009a). This leaves open the possibility that the association observed in this study reflected reverse causality. As the authors noted, a prospective cohort study using a better measure of mental health status at several time-points would be useful in clarifying the exact relationship between exposure to RF fields and behavioural disorders in children. A more in-depth analysis of the association between the personal exposure meter data and symptoms has been conducted for the 8–12 year old sample within this dataset, without identifying any significant associations (Kuhnlein et al, 2009), while a separate analysis of the association of self-reported mobile phone use and headache in a subset of this sample has been reported earlier (see Section 6.2.1; Milde-Busch et al, 2010).

In a separate study, Thomas et al (2008a) used a design similar to that used in the Bavarian children and adolescents study (Thomas et al, 2010b) to assess the association between exposure to RF fields over 24 hours measured using personal exposure meters and the presence of chronic symptoms (occurring at least twice per month for the last 6 months) or acute symptoms of at least 'moderate' intensity. Participants were randomly selected from the registration offices of four Bavarian towns. For the 329 adults who participated (40% response rate), no statistically significant association was observed between the presence of chronic symptoms and overall levels of exposure, between exposure during the morning and acute symptoms recorded at midday, or between exposure during the afternoon and acute symptoms measured in the evening. These analyses were adjusted for age and sex.

Mohler et al (2010) assessed the exposure status of 1212 residents of Switzerland using a questionnaire that assessed variables previously demonstrated in a study using personal exposure meters (Frei et al, 2009a) to be associated with higher levels of exposure (eg owning a mobile phone, having wireless LAN in the house, house construction or hours per week spent on public transport). Data on mobile phone use in the past 6 months were also obtained for a subset of mobile phone owners from their network operator, while geo-coding allowed the researchers to model the exposure received from fixed-site transmitters located near to each participant's home. No significant association was found between any exposure surrogate and self-reported daytime sleepiness or self-reported sleep disturbances. Although 20.9% of the sample reported either being sensitive to electromagnetic fields or that they experienced adverse health effects as a result of exposure to RF fields, the results for this subgroup showed the same absence of any effect.

The personal exposure meter studies described above offer a more accurate assessment of the total exposure to RF fields than those using distance from a participant's home to a base station or spot measurements within a participant's home. These studies have their own complexities, however. Given that the exposure measured by a personal exposure meter is dependent on a participant's behaviour, the problem of reverse causality arises. If the presence of symptoms causes an individual to alter their behaviour and visit areas that tend to have higher or lower areas of RF fields, this may result in spurious associations being observed or in genuine associations being obscured. A similar phenomenon may occur if people who believe that their health has been affected by RF fields deliberately try to avoid such exposures. The physical presence of a personal exposure meter, acting as a reminder about potential exposure, may also cause participants to alter their behaviour or may prompt them to recall more symptoms than would otherwise be the case. Again, this effect would serve to reduce the ability of a study to detect a genuine association. These problems are exacerbated by the cross-sectional nature of the studies that have been conducted to date, with studies that have directly assessed exposure only

having done so for a maximum of 24 hours. Longitudinal studies with longer measurement periods might allow for a better assessment of the causal link between exposure to RF fields and the onset of symptoms, as well as providing a better understanding of the impact of long-term exposures. Finally, low statistical power is an issue for this literature. The personal exposure meter studies that have been conducted so far might not have been capable of detecting subtle effects of exposure.

6.2.3 Summary

Although numerous observational studies have attempted to assess the association between exposure to RF fields and symptoms, many of these have suffered from important methodological deficits. In particular, the common reliance upon self-report exposure measures or limited spot measurements within a single place in the home, together with the frequent failure to account for potentially important confounders, makes it impossible to draw any firm conclusions from many of the studies. More recent studies using personal exposure meters offer a more promising way to assess the relationship. These raise the possibility of an association between RF field exposure and behavioural problems among children, but here too the cross-sectional nature of the research presents difficulties in interpreting causality. Additional research that expands and improves upon this model would be worthwhile.

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7 Other (Non-cancer) Studies in Humans

There are several established and well-understood thermally related effects of acute exposure to RF fields. These include the microwave hearing effect resulting from RF-field-induced thermoacoustic tissue expansion (see Section 5.1.4). The known adverse effects include tissue heating, injury and damage resulting from accidental exposure to RF field levels well above the current guidelines. There have been several reviews of these exposures and effects (Ryan et al, 2000; Hocking, 2001).

The previous AGNIR review in 2003 concluded that there was no definite evidence of any effects (such as increased incidence of cataract) on the lens of the eye, as a result of RF field exposure within the current guideline levels (AGNIR, 2003). Also there was no evidence of any consistent haematological changes in individuals exposed to low level fields. There has been no substantial change in the literature on these topics since 2003.

There have been appreciable advances in three areas covered below. These are studies of reproductive function, child development and cardiovascular function (heart rate, rhythm or blood pressure).

7.1 Reproduction

7.1.1 Male sexual function and fertility

The previous AGNIR review concluded that the evidence on RF fields and male sexual function was extremely limited; only five studies were available at the time. Three of these studies suggested a reduced sperm count, but were based on very small numbers, and one had questionable quality. Since then, two new studies of sperm quality have been published (Fejes et al, 2005; Agarwal et al, 2008). In addition, one study on male subfertility has been reported in two publications (Baste et al, 2008; Møllerløkken and Moen, 2008).

A cross-sectional study from the USA included 361 men attending an infertility clinic from September 2004 to October 2005 (Agarwal et al, 2008). The mean age of the patients was 31.81 years. Men using tobacco or alcohol, as well as those with a history of orchitis, varicocele or a chronic disease, were excluded. Information about the patients' mobile phone use was recorded, and the participants were divided into four groups: no mobile phone use (40 participants), less than 2 hours per day (107 participants), 2–4 hours per day (100 participants) and >4 hours per day (114 participants). Eight sperm parameters were evaluated: volume, liquefaction time, pH, viscosity, sperm count, motility, viability and percentage normal morphology. A decrease in sperm count, motility, viability and normal morphology was seen with an increase in daily mobile phone use. The report is not entirely clear, and results are therefore difficult to

interpret. Participant selection or source of information concerning mobile phone use was not described and the effect of age was not taken into consideration. The reported numbers of hours of mobile phone use per day for many of the subjects seem to be unrealistically high.

A Hungarian cross-sectional study included consecutive men of fertile ages appearing at a fertility clinic during the period from 1 November 2002 to 31 March 2004 (Fejes et al, 2005). After exclusion of 240 men who had other, potentially subfertility-causing factors (organic testicular alterations, trauma, chronic disease or smoking or alcohol use), 371 men were included in the study. The sperm count and motile sperm ratio were assessed. After 3 weeks, a new sample was taken, and the 'the better findings were analyzed'. Exposure was defined as duration of possession of a mobile phone (in months), duration of mobile phone use in minutes per day, and hours per day that the mobile phone was kept on standby closer than 50 cm to the patient. Pearson correlation coefficients were calculated. The means of outcome variables were also compared between selected exposure groups: less than 15 minutes of mobile phone use per day compared with more than 60 minutes per day, and standby within 50 cm less than 1 hour per day compared with more than 20 hours per day. Results for intermediate exposure groups were not shown. It is unclear how the cut-off points for these groups were selected. A weak positive correlation was found between the proportion of sperm with slow motility and duration of mobile phone possession ($r = 0.12$), and a negative correlation was found between duration of mobile phone possession and proportion of sperm with high motility ($r = -0.12$). Other semen quality indices did not show an association with duration of possession. Sperm motility was also associated with daily call time, but not with duration of standby closer than 50 cm. A severe limitation of the study is that the effect of age was not controlled for. Another limitation of the statistical analysis is the use of the Pearson correlation coefficient as the effect measure. It assumes a normal distribution, which was not reported in the paper, and correlations may be strongly influenced by a few extreme observations. The very weak correlation coefficients, even if statistically significant, can easily be explained by confounding, eg from age, or erroneous assumptions about the distribution of the examined variables. The results do not provide strong evidence for an effect of mobile phone use on sperm quality.

In a cross-sectional study of current (2497) and former (15,259) male military employees in the Royal Norwegian Navy (Baste et al, 2008), exposure and outcome information was collected through a mailed questionnaire, with a response rate of 62% among current and 63% among former employees, in total 10,497 respondents. The questionnaire included questions on exposure to RF fields: work closer than 10 m from high frequency aerials, work closer than 3 m from communications equipment and work closer than 5 m from radar. Infertility was defined as an affirmative answer to the question: 'Have you and your partner ever tried to become pregnant without success for more than one year?'. In total, 22% reported working in the proximity of high frequency aerials to a high or very high degree, 19% near communications equipment and 21% near radar. About 25% of respondents had never worked close to such equipment. There was a trend in risk of subfertility by degree of work close to high frequency aerials. Working close to radar and communications equipment gave similar results, but the actual results were not reported. There were no associations between the exposures and whether participants had biological children, or with the number of children. The ratio of boys to girls among offspring to fathers who had worked within 10 m from high frequency aerials, or within 3 m from communications equipment, were significantly lower than among offspring to unexposed fathers. Control of confounding was restricted to

smoking, alcohol consumption, organic solvents, welding and exposure to lead. Age-specific analyses were presented, where age was categorised in 10-year categories, but adjustment for age within categories does not appear to have been made. It is not clear whether other working conditions differed between exposed and unexposed groups, eg time spent away from home. The self-reported exposure was not validated. In another publication (Møllerløkken and Moen, 2008), results for participants currently employed in the navy were reported for work categories assumed to have higher exposure to RF fields; the findings largely overlap those reported by Baste el al, with self-reported subfertility being more common in work with telecommunications equipment or radar (15–18% versus 9% among unexposed).

7.1.2 Female sexual function and fertility

At the time of the previous AGNIR review, only one epidemiological study on female fertility of reasonable quality was available. Results from this study were, however, inconclusive. No further studies have been published.

7.1.3 Spontaneous abortion

Three epidemiological studies on the risk of spontaneous abortion among physiotherapists who used microwave diathermy were reviewed in the previous AGNIR report on RF fields. One study suggested a small elevation in risk, whereas no associations were seen in the other two studies. As potential recall bias might be a problem in studies with self-reported exposure information, the single positive study was not assessed as being a cause of concern.

Spontaneous abortion was studied in the cross-sectional military antenna study from Cyprus described in Chapter 6 (Preece et al, 2007). Information on spontaneous abortions was collected through questionnaires. The proportion of women reporting miscarriages in the exposed villages was compared with that in the unexposed village, and no significant differences were found. No control of potential confounding factors was made, and the quality of the self-reported information was not assessed. Exposure levels are likely to be lower than those found in occupational settings. Considering these limitations, no conclusions can be drawn from this study.

7.1.4 Birth outcome and congenital malformations

The previous AGNIR review identified several studies that reported an increased risk of congenital malformations following maternal RF field exposure, primarily among physiotherapists. It was noted, however, that the results were not consistent with regard to type of malformation, and might at least in part have been influenced by recall bias. There were no indications of increased risk of birth defects associated with paternal RF field exposure. Other birth outcomes were not associated with either maternal or paternal RF field exposure.

Since then, a Norwegian cohort study has investigated the association between paternal occupational exposure to RF fields and adverse pregnancy outcomes (Mjoen et al, 2006). All children born between 1976 and 1995 were identified from the medical birth registry. From the registry, information about birth defects, preterm delivery, low birth weight, male proportion and perinatal mortality was also collected.

Information about paternal occupation was obtained from census data; births during 1976–1985 were linked to the 1980 census, and births during 1986–1995 to the 1990 census. Assessment of occupational RF field exposure was made by an expert group, into 'probably exposed', 'possibly exposed', and 'probably not exposed' categories. Births records were excluded if the father's identify or occupation was missing, or if the occupation could not be categorised. In total, 541,593 births (49%) were included in the study, of which 5% were categorised as probably exposed and 26% as possibly exposed. Analyses were adjusted for year and place of birth, and level of education. A large number of analyses were performed: 24 specific types of birth defects, as well as birth defects combined and analyses of other types of pregnancy outcomes. In addition, analyses were repeated for specific occupations. A few significantly increased risk estimates were reported, as well as a few significantly decreased risks. For example, among children whose father was probably exposed to RF fields an odds ratio (OR) of 1.08 (95% CI 1.03–1.15) was observed for preterm delivery, and 0.63 (95% CI 0.41–0.97) for total cleft lip. No effect was found on the sex ratio in offspring. Exposure assessment in the study was very crude, with the possibility of misclassification both because of a mismatch in time between conception and census (±5 years), and from the use of occupational titles. In addition, control of confounding was very limited. Overall, the study does not provide consistent evidence that paternal RF field exposure affects pregnancy outcome but, given the crude exposure assessment, the study cannot rule out the possibility of a small effect.

7.1.5 Child development

Three studies have assessed the association between prenatal exposure to mobile phones and subsequent developmental progress of the child. Vrijheid et al (2010) recruited 657 women (60% response rate) attending a primary health-care centre for their first-trimester ultrasound scan. Questionnaires administered in the first and third trimesters were used to measure a range of potential confounding variables relating to health, education and social class. The third trimester questionnaire also asked whether the woman used a mobile phone and how many calls she made or received each day. The child's development was then assessed when they reached 14 months old (range 12–17 months) using standardised tests of mental and psychomotor performance. Univariate analysis showed that maternal mobile phone use was not associated with the child's sex, birth weight, prematurity, weeks of breastfeeding, nursery attendance or cord blood mercury concentration. The main analyses were adjusted for the child's age and sex, the mother's socioeconomic status, education, IQ and smoking status, whether anyone smoked in the home and which member of the research team performed the developmental checks. Amongst all participants there was a significant tendency for children whose mothers had the highest mobile use during pregnancy (five calls or more a day) to score lower on psychomotor performance than children whose mothers did not use a mobile phone at all. However, a subsequent test found no evidence of a dose-response effect when the small group of mothers who did not use a mobile at all were excluded. This suggested that some residual confounding associated with not using a mobile phone may have influenced the results. No effect of maternal mobile phone use was found for the mental development scores.

Drawing their participants from the Danish National Birth Cohort, Divan et al (2008) sent a questionnaire to all mothers of children who turned 7 years of age between 1997 and 1999. The questionnaire was completed by 13,159 women. This questionnaire assessed, among other things, the mother's self-report

about whether she had used a mobile phone during pregnancy. As proxy measures for the strength of any prenatal exposure, mothers were also asked how many times a day they had spoken on their mobile phone, what proportion of the time they had used hands-free equipment, what proportion of the time they had left the phone on and where they had kept the phone when not in use. Mothers were also asked to report on their child's current use of a mobile phone. The same questionnaire included 25 questions about their child's behaviour, which were summed to give scores relating to the existence of overall behavioural problems and specific problems regarding emotions, conduct, hyperactivity or peer interaction. The primary analyses tested the association between prenatal exposure only, postnatal exposure only (ie the child's use of a mobile phone) or both types of exposure combined on the child's reported behaviour (categorised as normal, borderline or abnormal). Analyses were adjusted for sex of the child, age of the mother, smoking during pregnancy, whether the mother had psychiatric problems and socio-occupational level. Postnatal exposure was unrelated to any outcome. Prenatal exposure was associated with the existence of hyperactivity (OR 1.29, 95% CI 1.08–1.53), conduct problems (OR 1.21, 95% CI 1.05–1.40) and peer problems (1.27, 95% CI 1.06–1.52). Having both prenatal and postnatal exposure marginally strengthened these associations and also made the association for emotional problems statistically significant (OR 1.25, 95% CI 1.07–1.47). No associations were found for measures relating to the possible strength of prenatal exposure.

Because of concerns that residual or unmeasured confounding might have contributed to their initial results, Divan and colleagues subsequently repeated their analyses using data from the Danish National Birth Cohort relating to a new set of 28,745 children of 7 years of age, born between 1998 and 2001, but including a much wider set of potential confounder variables (Divan et al, 2010). Inclusion of new data from children born in 1998 and 1999 also allowed them to compare their new results directly with those from the original 1997 to 1999 dataset. Overall, and initially adjusting only for those covariates that were present in their original analyses, the new dataset showed a similar pattern of results to the original dataset, with prenatal and combined prenatal and postnatal exposure being associated with overall behavioural problems. Repeating the analyses but splitting the data according to the child's year of birth showed that the association with combined exposure became weaker over time, from 1998 (OR 3.4, 95% CI 1.5–7.9) to 2001 (OR 1.4, 95% CI 1.1–1.8). However, the association for prenatal exposure remained relatively consistent (for 1998, OR 1.5, 95% CI 0.6–3.8, and for 2001, OR 1.3, 95% CI 1.1–1.7). Including additional covariates for the new data did not substantially affect the associations that were identified. These additional covariates included the mother's and father's history of psychiatric, cognitive or behavioural problems as a child, the family's social-occupational status, gestational age, mother's prenatal stress and whether the child was breastfed up to 6 months of age. Other potential covariates such as the reported number of hours the mother spent with the child at 6 and 18 months and whether the child was in nursery by 18 months of age were tested but did not add to the model.

Despite the greater control for confounding in this second study, these results are only suggestive of an effect, rather than being conclusive evidence of one. In particular, the reliance in both Danish studies upon the participants' recall for prenatal exposure and for some covariates such as the number of hours spent with the child presents problems in interpretation. This is particularly true given the large time intervals involved. Prospective studies would provide a more robust test of this association. In addition,

there remains a risk that other, unmeasured, characteristics that differentiate heavy and light mobile phone users might have contributed to the findings (see, for example, Lambe et al, 2006).

7.1.6 Summary

The evidence on the effect of RF fields on sperm quality is still weak and the addition of the two new studies does not allow reliable evaluation of the presence or absence of a health effect. Some suggestive positive results, although not convincing, give justification for further studies with improved methods. The evidence on effects on male subfertility is very limited, and allows no conclusions.

No new evidence on female sexual function and fertility has been published since the previous AGNIR review, and the only available study so far found inconclusive results. One new study on spontaneous abortion has been published, but with limitations in data quality. The conclusions from the previous AGNIR review are still valid, ie that, overall, the epidemiological evidence cannot rule out the possibility that RF field exposure could have a small effect on the risk of spontaneous abortion.

Some studies have reported an increased risk of congenital malformations in offspring to mothers with occupational RF field exposure, but potential recall bias and lack of consistency regarding the type of malformation prevent conclusions. No new studies on maternal exposure have been published since the previous AGNIR review. Paternal occupational RF field exposure has not been related to malformations in offspring, and one new study of paternal exposure gives no reason to change these conclusions.

The evidence on child development related to prenatal exposure to RF fields is very limited. Suggestive effects on behavioural problems from maternal mobile phone use during pregnancy need re-examination in prospective studies before any conclusion can be drawn.

7.2 Other (Non-cancer) Morbidity

7.2.1 Cardiovascular function

The previous AGNIR review found no evidence of adverse health effects related to the cardiovascular system changes following RF field exposure, although many of the studies available for review were retrospective and evaluated chronic exposure. In a small placebo-controlled, single-blind, but non-randomised study of 12 healthy volunteers, a 35-minute exposure to an RF field at 900 MHz resulted in a small, but significant increase in resting blood pressure (Braune et al, 1998). Several subsequent studies (Muller et al, 2004; Tahvanainen et al, 2004; Kantz et al, 2005; Barker et al, 2007) including one by the original authors (Braune et al, 2002), using larger study populations and more rigorous randomisation methods, did not confirm this effect and also demonstrated no effect on heart rate. In two of these studies no effect of RF field exposure on hormone levels was demonstrated: on catecholamines (Braune et al, 2002; Barker et al, 2007) and cortisol and endothelin (Braune et al, 2002). Measurements of skin conductance, skin temperature (Müller et al, 2004; Kantz et al, 2005) and cutaneous capillary perfusion (Braune et al, 2002) also did not demonstrate any changes following RF field exposure.

A study of healthy volunteers demonstrated a significant increase in cutaneous microperfusion of the external ear during exposure to a GSM RF field (Monfrecola et al, 2004). Sequential perfusion measurements were taken with no mobile phone against the ear, followed by contact with the mobile phone whilst turned off, then turned on, turned on and receiving, and then in reverse order, to a final measurement with no contact. It is unclear how well blinded the participants were to the state of the phone during the study and a wide baseline range of normal perfusion values was recorded. There were significant increases in perfusion as a result of contact (+61%), with the phone turned on (+132%) and when receiving (+158%) which reversed as the phone was progressively turned off and removed from contact with the ear. Vasodilatation in response to heating related to both phone contact and RF field exposure was considered the most likely reason for the observations. There was no evidence of any adverse health effects. Changes in regional cerebral blood flow related to RF field exposure have been demonstrated using both PET and infrared spectroscopy and are discussed in Chapter 5.

7.2.2 Other morbidity

The previous AGNIR report reviewed a retrospective cohort study of hospital admissions and disability compensation in 20,000 US servicemen with high potential for radar exposure, and a similar number with low potential (Robinette et al, 1980), as well as reviewing several other, miscellaneous studies of morbidity, but these did not suggest any effect of RF field exposure.

A Danish cohort study of 420,095 people with a mobile phone subscription during 1982–1995 followed these individuals through 2003 for hospital contacts (Schüz et al, 2009): hospital inpatient episodes were ascertained for 1982–1993, and all hospital contacts for 1994–2003. In comparison with expectations from general population rates, the cohort had weakly increased risks for migraine (1.2, 95% CI 1.1–1.3) and vertigo (1.1, 95% CI 1.1–1.2) and decreased risks for dementia (0.7 for each of Alzheimer's disease, vascular dementia and other dementia, with 95% CIs of 0.6–0.9, 0.5–0.9 and 0.6–0.8, respectively), Parkinson's disease (0.8, 95% CI 0.7–0.9) and epilepsy in men (0.7, 95% CI 0.7–0.7) but not women (1.1, 95% CI 0.9–1.2), and no relations for amyotrophic lateral sclerosis (ALS) or multiple sclerosis. Analyses restricted to 10 or more years of use gave similar results except for vertigo, for which risk was not increased, and Parkinson's disease, for which risk was not decreased.

Although the study had the strengths of large size and unbiased ascertainment of the exposure variable, limitations of the study make interpretation of the results uncertain. The cohort was based on subscriptions for, not use of, a mobile phone, with potential misclassification of use. In addition, the members of the cohort had a higher average income than the general population, and therefore are likely to have had different behaviour (eg with respect to smoking) and income-related disease risks than the general population. The disease outcome assessed depended on hospital referral, which, for migraine and vertigo especially, might only have occurred for a small, potentially selected, proportion of individuals with the condition. Finally, prodromal symptoms of conditions such as dementia or Parkinson's disease might have reduced the likelihood of starting mobile phone use, and hence artefactually reduced the apparent risks of these conditions in mobile phone users.

7.2.3 Summary

Several studies investigating cardiovascular function directly and indirectly have demonstrated no consistent acute effect of RF field exposure. Overall there is no evidence to indicate any adverse effects on the cardiovascular system. There is also no substantial evidence suggesting an effect of RF field exposure on other non-cancer morbidity outcomes. It should be noted that studies investigating effects on cerebral blood flow are discussed in Chapter 5.

7.3 References

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8 Cancer Studies in Humans

8.1 Occupational and Avocational Exposures

The previous AGNIR review (AGNIR, 2003) summarised occupational and avocational studies published up to 2002, which had examined risks in relation to exposures, in some instances, as early as the 1950s. The literature had concentrated particularly on brain tumour and leukaemia risks and, although significantly raised risks had been found in some studies, there was no consistent evidence of raised risks for any cancer site. There were methodological weaknesses in many of the studies, especially in exposure assessment, and AGNIR concluded that although the literature did not indicate that occupational exposure to RF fields affected cancer risk, it also did not give strong evidence against the existence of such a risk.

There have been few subsequent studies, and they do not alter this conclusion (see Table 8.1). Berg et al (2006), in data from a German population-based case–control study, found no significant risk of glioma or meningioma from occupational RF field exposure, based on self-reports of work in occupational activities where such exposure occurred or was likely to have occurred. There was a non-significant increase in risk (standardised incidence ratio, SIR, of 1.39, 95% CI 0.67–2.88) for 10 or more years of high exposure.

A population-based case–control study of non-Hodgkin's lymphoma in Australia (Karipidis et al, 2007) found no significant risk or trend in risk in relation to occupational RF field exposure as assessed by a job-exposure matrix applied to self-reported job history. There was a non-significant risk, based on small numbers, in the highest exposure category (odds ratio, OR, of 3.15, 95% CI 0.63–15.87), where exposure was categorised by multiplying together the estimated degree and duration of exposure.

A retrospective cohort study of Belgian male military personnel compared mortality from 1968–2004 in 4417 men who served in anti-aircraft radar units at some time during 1963–1994, with that in 2932 men who worked in the same geographical area in military units not equipped with radar (Degrave et al, 2009). The radar used had an average radiated power of about 1.5 kW and peak power in pulses of about 500 kW, and also emitted ionising radiation. Exposure levels in typical job locations were modelled to be in the range 10–500 V m^{-1}. There was no significant difference in overall mortality between these groups or trend in mortality with longer service in the radar-equipped units. The only specific cause with raised risk for exposed men was neoplasms (relative risk, RR, of 1.23, 95% CI 1.03–1.47) and within this lymphohaematopoietic neoplasms (RR 7.22, 95% CI 1.09–47.9) and eye, brain and other nervous system neoplasms (RR 2.71, 95% CI 0.42–17.49). Using the most recent year of national mortality statistics, rather than the unexposed group, as the comparison, however, the standardised mortality ratio for cancer was decreased – to 0.76 for the radar group and 0.62 for the non-radar group.

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

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

The risk of death from cancer, in comparison with that in the non-radar group, increased non-significantly with length of service in radar battalions, but was not greater in those who had served before shielding of the microwave generators was introduced, in the late 1970s. It is a weakness of the study that the cause of death was only known from the national death registry for 71% of exposed and 70% of non-exposed subjects; causes of other deaths were from the families of the deceased (sometimes supplemented by cancer registry confirmation), and for about 10% the cause was unknown. The family-reported and unknown causes give appreciable scope for bias.

8.2 Residence near RF Transmitters

The scientific evidence on cancer risks in people living near radio or TV transmitters was reviewed by the Independent Expert Group on Mobile Phones (IEGMP, 2000), and updated by AGNIR in 2003 with one new study. Most studies have focused on childhood leukaemia, although some have included other types of tumours in children, as well as adult cancers. Studies have been performed in the USA, Australia, Great Britain, Germany, Italy, South Korea and Sweden. The studies available at the time of the previous reviews had major methodological limitations. All had used distance between the home and the broadcasting mast as a proxy for the RF field exposure; no attempts were made to estimate the exposure through measurements or modelling. Several studies have demonstrated that distance is a poor estimate of RF field exposure from transmitters (Schüz and Mann, 2000). Furthermore, all studies used an ecological design, which means that they had information about the exposure and potential confounding factors on a population level rather than for each specific individual included in the study. They also lacked information about exposure from other sources, such as mobile phone use or base stations. Most importantly, several of the studies were performed because of an observation of an apparent excess of cancer cases in a certain area. The definitions of the 'exposed' areas were largely driven by these observations. Overall, no conclusions could be drawn from these studies.

Since then, one ecological study of melanoma incidence has been published (Hallberg and Johansson, 2002) (see Table 8.2). The study hypothesised that the increase in melanoma incidence over time was caused by FM broadcasting networks. The data and methods used were poorly described, and exposure assessment included no estimates of distance to transmitters or RF fields, but instead compared melanoma incidence between very large entities such as countries, counties or communities within a country, or incidence changes within an entire country over time. The analyses included no information on potential confounders such as ultraviolet radiation exposure. This study does not provide data that can be used to assess a potential impact of FM RF field exposure on melanoma incidence.

Another study with an ecological approach is the Cyprus cross-sectional military antenna study described earlier (in Chapter 6), where information was collected on overall mortality, and specifically on mortality from cancer, brain tumours and leukaemia (Preece et al, 2007). Mortality information was collected from several sources: self-reported data on mortality among family members during the last 10 years and information from cemeteries and from national records. The expected numbers of deaths were calculated based on national mortality rates. A cross-sectional design is not suitable for studying mortality, and it is highly uncertain whether all deceased people could be identified and if appropriate information about the population size and demography in the three villages included in the study were available for

the 10-year period for which mortality data were collected. The study reported no differences in overall mortality or for specific causes of death between the villages, but considering the limitations in data quality, no conclusions can be drawn from these results.

Considerable improvements in study design and exposure assessment were made in two studies on childhood leukaemia in relation to environmental RF field exposure (Ha et al, 2007, 2008; Merzenich et al, 2008; Schüz et al, 2008).

One study from South Korea (Ha et al, 2007) included 1928 leukaemia and 956 brain tumour cases below the age of 15 years, diagnosed between 1993 and 1999. Hospital-based controls were selected among children visiting a clinic with a respiratory disease, matched to the cases on age and sex. In total, 3082 controls were included. Exposure assessment for each individual child was made through calculations of the RF fields generated by AM radio transmitters near the child's home, estimated as the total RF field from all nearby transmitters, and the peak RF field exposure defined as the highest estimated exposure from any one of the nearby transmitters. Calculations were validated through measurements of the RF fields, and correction coefficients for the calculations were developed based on these measurements. In their original publication, the authors concluded that the total RF field exposure was highly correlated with the peak RF field exposure, and therefore they only performed analyses based on the total RF field. A letter to the editor by Schüz and colleagues identified some improbable results for lymphocytic leukaemia (Schüz et al, 2008), and in their reply the authors presented results for both the total and peak RF field exposure (Ha et al, 2008). For the total RF field exposure, there was no association between childhood leukaemia and estimated RF fields, with an odds ratio of 0.83 (95% CI 0.63–1.08) in the highest exposure quartile (≥916.96 mV m^{-1}) for all leukaemia combined, and no associations were seen for lymphocytic or myelocytic leukaemia separately. For the peak RF field, no increased risk was observed for all leukaemia combined, but for lymphocytic leukaemia the odds ratio in the highest exposure quartile (≥608.35 mV m^{-1}) was 1.40 (95% CI 1.04–1.88). However, for myelocytic leukaemia, a statistically significantly reduced risk was observed (OR 0.63, 95% CI 0.41–0.97). There was a borderline statistically significantly increased odds ratio for all leukaemia combined among children living in homes within 2 km from a transmitter, but also a significantly reduced odds ratio for children living at a distance between 2 and 4 km. There were no associations between RF field exposure and childhood brain tumours.

A study from Germany (Merzenich et al, 2008) included 1959 childhood leukaemia cases diagnosed between 1984 and 2003, and 5848 population-based controls. Individual exposure assessment was made through calculations of the RF field exposure from AM and FM radio and television broadcast transmitters. Calculations were validated through measurements of the RF fields (Schmiedel et al, 2009) and results showed that estimated and measured fields were highly correlated (Spearman rank correlation = 0.80). Exposure levels below the 90th percentile of the exposure distribution were regarded as unexposed, whereas the exposed categories were divided into the ≥90–<95 and ≥95 percentiles. There were no indications of increased risk of childhood leukaemia. An odds ratio of 0.86 (95% CI 0.67–1.11) for all leukaemia combined was observed in the highest exposure category (0.683 V m^{-1}). Stratification of the analyses according to time period revealed no difference in the results before and after the introduction of mobile phones. Restriction of analyses to children aged 0–4 years did not change the results. The distance between the home and the nearest transmitter was not associated with childhood leukaemia; for living within 2 km of a transmitter the odds ratio was 1.04 (95% CI 0.65–1.67).

TABLE 8.2 Epidemiological studies of cancer risk in people living close to RF transmitters

Study	Type of study	Study population	Disease outcome	Exposure definition	Number of subjects	Estimated relative risk (with 95% CI)
Ha et al, 2007	Case–control	Children 0–14 years, diagnosed during 1993–1999 at one of 14 large hospitals Hospital controls (respiratory diseases) matched on age and sex	Leukaemia Brain tumours	Calculations of RF field exposure from AM transmitters close to the child's home	1928 leukaemia cases 956 brain tumours 3082 controls	Highest quartile (916.95 mV m^{-1}): leukaemia 0.83 (0.63–1.08) brain tumours 0.77 (0.54–1.10)
Merzenich et al, 2008	Case–control	Children 0–14 years living within defined geographical areas around AM or FM transmitters throughout Germany Cases identified from the population-based German Childhood Cancer Registry diagnosed from 1 January 1984 to 31 December 2002 Three controls per case matched on transmitter area, time of diagnosis, sex and age	Leukaemia	Calculations of RF field exposure from AM and FM transmitters close to the child's home	1959 leukaemia cases 5848 controls	≥95 percentiles 0.92 (0.71–1.19)

Study	Type of study	Study population	Disease outcome	Exposure definition	Number of subjects	Estimated relative risk (with 95% CI)
Elliott et al, 2010	Case–control	Children 0–4 years, diagnosed during 1999–2001 in Great Britain Birth controls matched on sex and birth date	All cancers Brain and nervous system Leukaemia and non-Hodgkin's lymphomas	Distance between birth home and nearest base station Total power output from base stations within 700 m Modelled exposure from base stations within 1400 m	1397 cases of cancer 251 brain and nervous system 527 leukaemia and non-Hodgkin's lymphoma	Modelled exposure, highest exposure category (≥–17.6965 dBm): all cancers 1.02 (0.88–1.20) brain 0.76 (0.51–1.12) leukaemia 1.03 (0.79–1.34)
Hallberg and Johansson, 2002	Ecological	Norway, Sweden and various other countries throughout the world	Skin melanoma	Type of frequency modulation in a country, number of FM transmitters	Unknown	Not estimated
Preece et al, 2007	Cross-sectional	Three villages in Cyprus: two exposed with 800 and 350 inhabitants, and one unexposed with 1000 inhabitants	Cancer, leukaemia (self-reported)	Exposed villages were situated in the vicinity of military air base antennas, the unexposed village was 15 km from the antennas	Unknown	Not estimated

A study from Great Britain investigated maternal exposure from mobile phone base stations during pregnancy and the risk of cancer in children aged 0–4 years (Elliott et al, 2010). All cases of cancer during the period 1999–2001 were identified – in total, 1926 children. Of these, 1397 (73%) had an identifiable birth address for which exposure data were available. Four controls per case, individually matched on sex and date of birth, were selected randomly from the national register of all births in Great Britain; 5588 controls (90%) had complete addresses. A digitised geographical information system was used to determine the location of birth addresses and base station sites. Exposure was assessed in three different ways: the distance between nearest base station and birth address, the total power output from all base stations within 700 m of the birth address, and a modelled power density for base stations within 1400 m, based on distance, characteristics of the base station and some geographical characteristics. The exposure estimates were validated by measurements of the RF field exposure. The Spearman correlation coefficient between measured fields and modelled power density was 0.66. The corresponding correlation with distance was −0.72, and with total power output was 0.66. Analyses were made for all childhood cancers combined and separately for brain and nervous system tumours, and leukaemia and non-Hodgkin's lymphoma. Risk estimates were adjusted for potential sociodemographic confounders, population density and population mixing. Exposure estimates were categorised as follows: for distance and modelled exposure, three equally sized groups; for total power, subjects with no base stations within 700 m constituted one group (58% of the data); and the others were divided into two equally sized groups. The study found no indications of an association between childhood cancer risk and RF field exposure from base stations for any of the exposure proxies used in the study. The study was large, and the national coverage limited potential selection bias. The main limitation was the lack of information about RF field exposure from other sources, and the inability to take the attenuation of the exposure within the home into consideration. In addition, individual data on potential confounding factors were not available. The three exposure estimates seem to perform equally well in estimating RF field exposure from base stations, which is unexpected, as distance alone is generally regarded as a poor estimate of RF field exposure from transmitters.

Taken together, the available studies provide no evidence for an increased risk of cancer among children exposed to RF fields from radio or television transmitters or from mobile phone base stations. The studies have, however, a limited ability to detect a small increase in risk.

8.3 Mobile Phones

At the time of the previous AGNIR review on RF fields in 2003, five case–control studies had reported on the risk of brain tumour in relation to mobile phone use, three on acoustic neuroma, and one each had reported on salivary gland cancers, uveal melanoma, intratemporal facial nerve tumour and testicular cancer. In addition, two cohort studies had been published: one from Denmark following cancer incidence over several years in >400,000 mobile phone subscribers, and one from the USA following mortality for only 1 year in 286,000 subscribers. These various studies give no convincing evidence of a raised risk of any type of malignancy in relation to mobile phone use, but were only able to examine with any power relatively short lag periods between first exposure and cancer incidence. Since the previous AGNIR report, the case–control literature has grown greatly, and the more substantial of the two cohort studies has been updated, as described below.

8.3.1 Tumours other than brain tumour and acoustic neuroma

8.3.1.1 Salivary gland tumours

At the time of the previous AGNIR review only two studies of salivary gland tumours and mobile phone use were available (Johansen et al, 2001; Auvinen et al, 2002). Since then, three additional case–control studies have been published (Hardell et al, 2004a; Lönn et al, 2006; Sadetzki et al, 2008) (see Table 8.3), and the Danish cohort study has been updated (Schüz et al, 2006b).

The study by Auvinen et al (2002) was described in detail in the previous AGNIR report. Briefly, it is a case–control study nested within the Finnish population. Cases of salivary gland tumours in the age range 20–69 years diagnosed in 1996 were identified through the national Finnish Cancer Registry (34 cases), and five age- and sex-matched controls per case were selected from the population registry. Information about mobile phone subscription histories for cases and controls was obtained from the mobile phone network providers. Information was only available on private subscriptions, thus corporate mobile phone use could not be assessed. In total, three (9%) cases of salivary gland tumours had had an analogue phone subscription, and one (3%) case had had a digital phone subscription. The corresponding numbers for controls were 15 (9%) and three (2%), respectively. Ever-having had a mobile phone subscription was associated with an odds ratio of 1.3 (95% CI 0.4–4.7).

The Danish cohort study of 420,095 mobile phone subscribers (Johansen et al, 2001) has been updated by Schüz et al (2006b) (see Section 8.3.2.2), extending the follow-up with an additional 7 years, to 31 December 2002. A detailed description of the study design is given in the previous AGNIR report. The study included only private subscribers, and incident cases of cancer were identified through record linkage to the national Danish Cancer Registry. In total, 26 cases of salivary gland tumours were identified during the study period, all males. The standardised incidence ratio for men was estimated at 0.86 (95% CI 0.56–1.26), and for women 0.00 (95% CI 0.00–1.02).

A Swedish case–control study assessed the risk of salivary gland tumours in relation to mobile phone use (Hardell et al, 2004a). The cases (407 in total) were identified from regional cancer registries covering the whole of Sweden in 1994–1999 (in some regions to 2000) and included malignant tumours only. At the time of the data collection, 96 cases had died, three were too ill to participate, and for 15 cases the treating physician did not grant permission to contact the case. The participation rate among cases was reported as 91%, but if calculated according to conventional standards it was 66% (including deceased, too ill and physician refusal in the denominator). Four controls per case were selected from controls used in previous brain tumour studies by the same group, covering the period 1994–1996 (Hardell et al, 1999) and 1997–2000 (Hardell et al, 2002). They were matched on age and sex. The participation rate among the previously selected controls was 92%. An additional 357 controls were selected when matching criteria were not fulfilled, and to cover two geographical regions not included in the previous studies. Of these, 303 participated (85%). In total, 267 cases and 1053 controls participated in the study. Information on mobile phone use history was collected through a mailed questionnaire, and all subjects were also contacted by telephone to supplement answers given in the questionnaire. Of the cases, 12% had used analogue phones and 17% digital phones. For controls, the proportions were 11% and 16%, respectively. No increased risks were found for either analogue (OR 0.9, 95% CI 0.6–1.5) or digital phone use (OR 1.0, 95% CI 0.7–1.5). In the analyses by anatomical location, a non-significantly increased risk was

TABLE 8.3 Case–control studies of mobile phone use and risk of tumours other than brain tumours

(a) Salivary gland tumours

Study	Country	Tumour type	Number of cases	Number of controls	Age at diagnosis (years)	Source of controls	Prevalence of ever-use in controls	Odds ratios (95% CI) ever-use
Hardell et al, 2004a	Sweden	Salivary gland	267	1053	21–80	Population register	13% analogue 16% digital 19% cordless 33% ever any of above	0.9 (0.6–1.4) analogue 1.0 (0.7–1.5) digital
Lönn et al, 2006*	Denmark, Sweden	Malignant parotid gland	57	681	20–69	Population register	59%	0.7 (0.4–1.3)
		Benign pleomorphic adenoma	112	321			63%	0.9 (0.5–1.5)
Sadetzki et al, 2008*	Israel	Malignant parotid gland	58	194	≥18	Population register	45%	1.1 (0.5–2.1)
		Benign parotid gland	402	1072			56%	0.9 (0.6–1.1)
Duan et al, 2011	China	Epithelial parotid gland	136	2051	All ages	Hospital	56%	1.1 (0.7–1.8)
Takebayashi et al, 2008*	Japan	Pituitary adenoma	101	161	30–69	Population	65%	0.9 (0.5–1.6)

(b) Other tumours

Study	Country	Tumour type	Number of cases	Number of controls	Age at diagnosis (years)	Source of controls	Prevalence of ever-use in controls		Odds ratios (95% CI) ever-use
Schoemaker and Swerdlow, 2009	England	Pituitary adenoma	291	630	18–59	GP lists	61%		0.9 (0.7–1.3)
Kaufman et al, 2009	Thailand	Leukaemia	180	756	≥18	Hospital	14%		1.5 (1.0–2.4)
Cooke et al, 2010	England	Leukaemia	806	585	18–59	Non-blood relatives of cases	83%		1.1 (0.8–1.5)
Hardell et al, 2005a	Sweden	Non-Hodgkin's lymphoma	910	1016	18–74	Population	Not stated overall, but digital 55%, analogue 17%		Not stated overall, but digital 1.0 (0.8–1.3)†, analogue 0.9 (0.7–1.3)†
Linet et al, 2006	USA	Non-Hodgkin's lymphoma	551	462	20–74	Population without HIV	53%		1.0 (0.7–1.3)
Hardell et al, 2007	Sweden	Testicular cancer	889	870	20–75	Population	Not stated overall, but digital 16%, analogue 20%		Not stated overall, but digital 1.1 (0.8–1.5), analogue 1.0 (0.8–1.3)
							Ever	**Regular**	
Stang et al, 2009	Germany	Uveal melanoma	459	827	20–74	Population	80%	36%	0.7 (0.5–1.0)
				180		Ophthalmological	76%	30%	1.1 (0.6–2.3)
				187		Siblings	83%	35%	1.2 (0.5–2.6)

* Interphone studies: individual country analyses.
† Not stated for NHL overall; the figures presented are for B-cell lymphomas, which were 91% of the total, and therefore presumably close to the results for NHL overall.

found for the submaxillary gland (OR 1.4, 95% CI 0.6–3.5 for any phone use), but not for the parotid (OR 1.0, 95% CI 0.7–1.4) or other locations (OR 1.1, 95% CI 0.5–2.7).

Lönn et al (2006) have reported results on parotid gland tumours from the Swedish and Danish Interphone studies. These are case–control studies covering the whole of Denmark and a large part of Sweden – in total, approximately 6.7 million people. Eligible cases were subjects 20–69 years old diagnosed in 2000–2002 with malignant parotid gland tumours or benign pleomorphic adenoma (the latter only from two geographical regions in Sweden), and were identified through the national cancer registries and from clinics treating these patients. There was no overlap of cases with the study by Hardell and colleagues described above. In total, 71 malignant and 128 benign eligible cases were identified, of whom 60 (85%) and 112 (88%), respectively, participated in the study. Controls were randomly selected from population registries, in Denmark individually matched to cases on age and sex and in Sweden stratified on age, sex and geographical region – in total, 966 controls, of whom 681 (70%) participated. Information on mobile phone use history was collected through personal interviews, according to the Interphone study protocol, and included the year when mobile phone use started, number of phone calls, hours of phone use, preferred side of the head and use of hands-free devices. Regular phone use (defined as at least once per week during 6 months or more) was not associated with parotid gland tumour risk: odds ratio of 0.7 (95% CI 0.4–1.3) for malignant tumours and 0.9 (95% CI 0.5–1.5) for benign tumours. No increased risks of either tumour type were related to duration of use, time since first use, cumulative call time or cumulative number of calls. Odds ratios for ipsilateral mobile phone use (use on the same side as where the tumour was diagnosed) were in some analyses increased, while correspondingly reduced risks were found for the contralateral side. For example, the odds ratio for ipsilateral use that started >10 years prior to diagnosis was 2.6 (95% CI 0.9–7.9) for benign tumours, while the corresponding odds ratio for contralateral use was 0.3 (95% CI 0.0–2.3). If there was a causal association between mobile phone use and risk of parotid gland tumours, an increased tumour risk would be expected on the same side as that on which the mobile phone was most frequently held, because the exposure is highest close to the handset and declines rapidly with distance. Furthermore, the risk of developing a tumour on the opposite side would be expected to be the same as for people who have never used a mobile phone regularly, ie close to unity. Mobile phone use on the opposite side would not be expected to be associated with a reduced risk. Therefore the findings related to ipsilateral use were interpreted as information bias.

Results for benign and malignant parotid gland tumours have also been reported from the Israeli Interphone study (Sadetzki et al, 2008). The study covers all Jewish individuals in Israel of 18 years or older during 2001–2003. Cases of malignant or benign parotid gland tumours were identified through periodic review of pathology/cytology reports from all 22 otolaryngology departments in the country. In total, 531 (87%) cases with confirmed tumours were identified. Of the participating cases, 58 were malignant, and the benign cases were distributed as 264 pleomorphic adenoma, 117 Warthin's tumour and 21 others. Controls were randomly selected from the population registry, individually matched to cases identified for the Interphone study, which also included glioma, meningioma and acoustic neuroma. To make use of a larger set of controls, a post-hoc matching of controls to parotid gland tumour cases on age, sex, interview date and continent of birth was made for this study. Through this procedure, up to seven controls per case was selected. In total, 1929 controls were selected, of whom 1266 (66%)

participated. Information on mobile phone use history was collected through personal interviews according to the Interphone study protocol, in the same way as in the Swedish/Danish study described above. Regular mobile phone use was not associated with parotid gland tumours; the odds ratio for malignant tumours was 1.06 (95% CI 0.54–2.10) and for benign tumours 0.85 (95% CI 0.64–1.12). Overall, the odds ratio was 0.87 (95% CI 0.68–1.13). No increased risks or trends were observed according to time since start of use, duration of use, cumulative number of calls or cumulative call time. However, based on subgroup analyses (regular use, rural areas and particularly ipsilateral use) the authors concluded that their results suggest an association between mobile phone use and parotid gland tumours. For example, the odds ratios for above-median ipsilateral use were 1.6 (95% CI 1.1–2.2) for cumulative number of calls and 1.5 (95% CI 1.1–2.1) for cumulative call time. However, the corresponding results for contralateral use were 0.8 (95% CI 0.5–1.2) and 0.8 (95% CI 0.6–1.3), respectively, indicating recall bias when cases reported the usual side of use prior to diagnosis.

Duan et al (2011) performed a hospital-based case–control study of parotid gland tumours in relation to mobile phone use, in Beijing, China. Cases were recruited retrospectively from the authors' clinic covering the time period from January 1993 to March 2010. Unmatched controls were recruited from other patients treated for other diseases at the same clinic during the same time period. In total, 221 eligible cases and 2643 eligible controls were identified. Only living subjects, who agreed to participate, were included in the study, leaving 136 (62%) cases, and 2051 (78%) controls for analyses. Information on mobile phone use and potential confounders were collected through personal or telephone interviews.

No association was found between regular mobile phone use (at least once per week during at least 6 months) and epithelial parotid gland tumours (OR 1.14, 95% CI 0.72–1.81) or mucoepidermoid carcinoma (OR 1.37, 95% CI 0.63–2.10), after adjustment for potential confounding from sex, age, residential area, marital status, education, income and smoking. No adjustment was made for year of diagnosis. However, in analyses of indices of the amount of use, considerable risk increases were presented for all exposure categories. These increases are incompatible with the overall risk estimate of 1.14 (ie close to unity). For example, for time since first mobile phone use, significantly increased risks were observed in all exposure categories, varying from 1.7 to 5.4. The internal incompatibility of the results presented makes them impossible to interpret. In addition, there is potential for confounding from the date of diagnosis, as mortality is likely to be higher among the cases with malignant tumours, than among controls, and therefore a smaller proportion of cases are likely to have been included from the early part of the study period when mobile phone use was less common.

Overall, the evidence from the few studies available does not support the hypothesis that use of mobile phones increases the risk of parotid gland tumours. The available data cover mobile phone use during up to around 10 years, and therefore conclusions cannot be drawn about an effect of longer periods of use. There are, however, some limitations on the available data, primarily the retrospectively collected information on mobile phone use in the case–control studies, with indications of recall bias being present, and selection bias introduced by selective non-participation among controls who have not used mobile phones, which might have led to apparently reduced odds ratios, perhaps of about 10% (see Section 8.3.2.4) (Vrijheid et al, 2009a,b). These biases are not present in the only cohort study available, where no risk increase was indicated. However, use of subscriptions to estimate exposure is subject to non-differential exposure misclassification as it might not be the person who has the

subscription who is the actual user of the phone. Furthermore, corporate mobile phone users could not be identified in the exposed cohort. This type of bias might have led to a dilution of the risk estimates.

8.3.1.2 Pituitary adenoma

Two case–control studies have examined risk of pituitary tumours in relation to mobile phone use, both based on the Interphone study design.

In Japan (Takebayashi et al, 2008), 101 pituitary adenoma cases diagnosed at ages 30–69 years at 21 hospitals in Tokyo were compared with 161 individually matched population controls selected by random digit dialling of home fixed-line phones, with mobile phone use data collected by face-to-face interviews. Participation rates were 76% for cases and 49% for controls. The odds ratio for regular mobile phone use was 0.90 (95% CI 0.50–1.61), with no trends in risk by cumulative length of use or cumulative call time and no relation to type of phone (analogue/digital). The odds ratio for 2000 or more hours of use was 1.41 (95% CI 0.46–4.37). Brief questions to non-participant controls, where they were willing, did not suggest that they were different in mobile phone use from participant controls.

Schoemaker and Swerdlow (2009), in England, compared reported mobile phone use between 291 population-based cases with pituitary adenoma diagnosed at age 18–59 years and 630 controls ascertained randomly, with frequency matching, from medical general practice (GP) lists in the study area. Participation rates were 63% for cases and 43% for controls. Exposure data were obtained by face-to-face interviews. Tumour risk was not raised in regular phone users (0.9, 95% CI 0.7–1.3), nor were risks related to years since first use, years of use, cumulative number of calls or cumulative hours of use, nor with digital or analogue use analysed separately. The risk for the highest category of the latter analysed (top quartile >596 hours) was 1.1 (95% CI 0.7–1.7).

Pituitary tumours are central in the brain, and hence relatively far from the phone antenna and with relatively low RF field exposure. If a putative effect of RF fields on tumour risk depended on exposure at the tumour location (dose), the risk might therefore be expected to be far lower than for laterally placed tumours, but in the absence of knowledge of a biological mechanism, it is not known whether sensitivity might vary between different tissues.

8.3.1.3 Leukaemia

The skull and mandible contain 13% of the body's active bone marrow (Ellis, 1961). Two case–control studies have reported on leukaemia risk in relation to mobile phone use. In one (Kaufman et al, 2009), 180 cases (87 acute myeloid, 40 acute lymphoblastic, 44 chronic myeloid and 8 chronic lymphocytic leukaemia and 1 unclassified) were recruited from a single hospital, in Bangkok, Thailand, aged 18 years or older at interview. These were compared with 756 matched controls from the same hospital with various non-neoplastic diagnoses, mainly acute infections (33%), trauma (22%) and abdominal emergencies (27%), but also including elective admissions. Exposure data were collected by interview and response rates were stated as 100% for cases and controls. Based on a relatively low prevalence of use (19% of cases and 14% of controls) and generally short periods of use (a median among users of 2 years), there was a borderline significantly raised risk of leukaemia in users (OR 1.5, 95% CI 1.0–2.4) with raised risks for AML, CML and CLL, each based on small numbers. As judged by medians among users, no raised risk was

noted in relation to years of use, cumulative hours of use or hours of use per year. A combination of three arbitrarily defined 'high risk' factors – the proportion of time initiating calls, the proportion of use with the antenna extended and whether metal glasses were ever-worn – gave a significant odds ratio of 1.8 (95% CI 1.1–3.2), but not only were these factors arbitrarily defined, they were also apparently selected from among a larger panel of factors because they were more common in cases than controls in the dataset. There was also a significantly raised risk for GSM phone use (OR 2.1, 95% CI 1.1–4.0), especially exclusive use of GSM phones (OR 3.1, 95% CI 1.4–6.4); the median years of GSM use and lifetime hours of GSM use, however, were similar in cases and controls.

The study does not give any convincing evidence of causation, but with the low prevalence of use, small study size and short durations of use, and potential bias from the control source, it is not informative against an association.

The other case–control study, from the UK, was considerably larger (Cooke et al, 2010). In total, 806 cases with leukaemia other than CLL incident at age 18–59 years during 2003–2007 (or 2003–2009 in some parts of the study area) were compared with 585 controls. Potential cases were all residents of the study area, in southeast England, who developed acute and non-lymphocytic leukaemia during the study period. These subjects were identified by frequent contacts with health care staff in haematology and oncology units, with back-up to ensure geographical completeness from the regional (Thames) cancer registry. Controls were non-blood relatives of the cases, living in the same area and of the same age range as the cases; potential controls were identified by the cases. This control source was used because general population response rates in the UK have been decreasing over time, to a level that is unsatisfactory for case–control studies. This source might have led to overmatching, but this would be expected to give a risk of loss of statistical efficiency, not bias. In total, 50% of people eligible to be cases and 75% of those eligible to be controls were interviewed. The main reasons for non-participation of cases were death or illness (27%), followed by an unwillingness to participate (11%). The study questionnaire, which was administered at interview by study nurses, was similar to that used in the Interphone study.

There was no association between regular mobile phone use and risk of leukaemia (OR 1.06, 95% CI 0.76–1.46) and no evidence of trends or significantly raised risk in analyses of risk in relation to years since first use, lifetime years of use, cumulative number of calls and cumulative hours of use. There was a non-significantly raised risk in relation to first use of a mobile phone ≥15 years ago (OR 1.87, 95% CI 0.96–3.63). There was no significant evidence of an association of risk with analogue or digital phones, considered separately, or for particular subtypes of leukaemia – AML (based on 449 cases), ALL (125 cases) or CML (154 cases). The risk of AML ≥15 years after first use was borderline significantly raised (OR 2.08, 95% CI 0.98–4.39). Adjustment for extent of hands-free use, or for other RF field exposures, did not materially alter the results. Analyses restricted to the highest socioeconomic group, in which response rates were highest, also did not materially alter the results. Overall the study did not suggest mobile phone use causes leukaemia, but left open the possibility after long-term use.

In the cohort study of Danish mobile phone subscribers (Schüz et al, 2006b) described earlier (see Section 8.3.1.1), the risk of leukaemia was not raised in subscribers (SIR 1.00, 95% CI 0.90–1.12, in males and 0.97, 95% CI 0.67–1.36, in females) and there was no trend in leukaemia risk with time since first subscription; the SIR in the longest category, ≥10 years, was 1.08 (95% CI 0.74–1.52).

8.3.1.4 Non-Hodgkin's lymphoma

Hardell et al (2005a) conducted a case–control study in Sweden of the risk of non-Hodgkin's lymphoma (NHL) in relation to mobile phone use. Cases were 910 patients aged 18–74 years identified through clinical sources in four of the seven health regions in Sweden. NHL diagnoses were confirmed by members of a panel of five expert pathologists. In total, 1016 controls were included, chosen randomly within frequency matching from residents of the same regions, using the national population register. Data on mobile phone use were obtained by postal questionnaire, supplemented by telephone interview for some subjects, and for a few subjects solely by telephone. Response rates were stated to be 91% for cases (but were actually clearly lower by conventional criteria) and 92% for controls. The risks of NHL were not presented for NHL overall. For B-cell lymphoma, which was 91% of the total, the risks were not increased in users of analogue (OR 0.9, 95% CI 0.7–1.3), digital (OR 1.0, 95% CI 0.8–1.3) or cordless (OR 1.0, 95% CI 0.8–1.3) phones; no results were presented for mobile phones overall. There were no significant or markedly raised risks in data by cumulative hours of use or years since first use.

In separate analyses for T-cell lymphoma – of which there were only 53 cases – there were several raised risks, based on very small numbers, but the risk was only significant for cordless phones (which have much the lowest RF power output), not digital or analogue phones. There were no significant trends in risk with cumulative hours of use or years since first use for digital or analogue phones, but there was a significant trend with years since first use for cordless phones.

For a selected subset of T-cell lymphoma subtypes (seven subtypes arbitrarily aggregated), numbering only 23 cases, some larger odds ratios were noted based on yet smaller numbers.

The existence of significantly raised risks of T-cell lymphoma only in subset analyses for the type of phones (cordless) with the lowest power output, gives no substantial evidence of an aetiological relationship. This is the more so in the data that were further subsetted by arbitrarily aggregating several T-cell subtypes.

A case–control study in the USA compared mobile phone use, ascertained by face-to-face interviews, between 551 population-based cases with NHL diagnosed at age 20–74 years and who did not have HIV infection, and 462 population controls without HIV, chosen, for those aged under 65 years, by random digit dialling and, for those aged 65 years or older, from Medicare files (Linet et al, 2006). The response rates were 61% for cases and 47% for controls. The risk of NHL was not raised for ever-users of mobile phones (OR, 1.0, 95% CI 0.7–1.3) and there were no significant relations of risk to minutes of use per week, years of use, cumulative hours of use or year of first use. Analyses by histological subtype did not suggest type-specific associations. In the longest use category, over 8 years, the odds ratio was 1.6 (95% CI 0.7–3.8): 2.4 (95% CI 0.8–7.0) in males and 0.6 (95% CI 0.1–2.8) in females.

8.3.1.5 Testicular cancer

In a case–control study in Sweden, 889 population-based cases with germ-cell testicular cancer (542 seminoma and 346 non-seminoma) were compared with 870 controls randomly selected, within matching constraints, from the national population register (Hardell et al, 2007). Data on mobile phone use were collected by postal questionnaire supplemented by telephone enquiry for an unspecified subset. The response rates were reported as 91% for cases and 89% for controls, although the calculation, for cases at least, did not follow conventional methods (see pages 282 and 286–9 for why reported response

rates for this research group have been doubted). The risks were not presented for users as opposed to non-users overall, but odds ratios for 1–127, 128–547 and > 547 hours of cumulative use of mobile or cordless phones were 1.1 (95% CI 0.9–1.5), 1.1 (95% CI 0.8–1.4) and 0.8 (95% CI 0.6–1.0), respectively. There was no indication of a raised risk in relation to analogue or digital phones separately, or in relation to duration since first use (the risk in the >10 year category was 1.5, 95% CI 0.6–3.7, for analogue phones, the only phone type with this length of use) or to keeping the phone in a trouser pocket or on a waist belt, or for analyses of seminoma and non-seminoma separately.

The risk of testicular cancer was not raised in the Danish cohort of mobile phone subscribers, described above (SIR 1.05, 95% CI 0.96–1.15) (Schüz et al, 2006b).

8.3.1.6 Uveal melanoma

In a second study to test the apparently positive findings in the case–control study of uveal melanoma they had published in 2001, Stang et al (2009) compared mobile phone use between 455 cases aged 20–74 years recruited at a German referral centre hospital and 827 population-based controls selected from census data, matched with cases on region of residence, and also compared 133 almost entirely overlapping cases with 180 controls with benign eye diseases and 187 almost entirely overlapping cases with 187 sibling controls. Data on mobile phone use were gained by telephone interviews (it is not stated whether the inteviews were via fixed-line phones or mobiles also). The response rates were 94% for cases, and 57%, 52% and 57% for the three control sets. The risk of melanoma for regular users as opposed to never-users of mobile phones was not raised compared with the population controls (OR 0.7, 95% CI 0.5–1.0) nor with the other two control sets (OR 1.1, 95% CI 0.6–2.3, and 1.2, 95% CI 0.5–2.6), nor were there relations to years of use, cumulative number of calls, cumulative hours of use or duration since first use. A short questionnaire to non-respondent potential population controls who were willing to answer it showed them to have lower phone use than participating controls. There is also potential for bias in the use of hospital-based cases from a large geographical area, who may have been selected for whether they attended the study hospital rather than another hospital, and the population-based controls, who will not have had this selection.

In the Danish cohort of mobile phone subscribers, described above, the risk of eye malignancy was not raised (SIR 0.94, 95% CI 0.66–1.29, in males and 1.10, 95% CI 0.40–2.39, in females) (Schüz et al, 2006b).

8.3.1.7 Summary

The case–control studies on risks of salivary gland tumours, pituitary adenoma, leukaemia, non-Hodgkin's lymphoma, testicular cancer and uveal melanoma give no substantial or consistent indication that the risk of any of these tumours is affected by mobile phone use. This view is reinforced by the lack of raised risks in the Danish cohort study of mobile phone subscribers.

8.3.2 Brain tumour and acoustic neuroma

8.3.2.1 Case–control, including case–case, studies

Hardell studies

The previous AGNIR report reviewed two studies of mobile phone use and brain tumour risk from Sweden conducted by Hardell and colleagues (Hardell et al, 1999, 2002). Since then this group has published analyses from the existing material as well as a third, new, case–control study (see Table 8.4).

Hardell et al, 2004, 2005, re-analysis of 2002 study

The second case–control study of mobile phone use and brain tumour risk conducted by Hardell and colleagues was reviewed in the previous AGNIR report. Since then, several re-analyses of these data have been performed. One publication stratified analyses on age at diagnosis (Hardell et al, 2004b), and found the highest odds ratios in the youngest age group (20–29 years). The odds ratio for use of an analogue phone with over 5 years' latency was 8.17 (95% CI 0.94–71) and for cordless phones 4.3 (95% CI 1.22–15) for all brain tumours combined. As is evident from the wide confidence intervals, the numbers of subjects in these analyses were very small. Furthermore, such large risk increases, if real, should have resulted in a considerable increase in brain tumour incidence among young people, which has not been reported (Vrijheid et al, 2009a).

Another publication stratified data on population density (Hardell et al, 2005b). The rationale for this is that mobile phone base stations are more densely situated in urban areas, which leads to lower average output power levels compared with rural areas where mobile phone base stations are fewer and the average distance to a base station is therefore longer (Lönn et al, 2004b). Thus, exposure during a mobile phone call is hypothesised to be higher in rural than in urban areas. The re-analysis of the case–control data found risk estimates that were highest in rural areas for use of a digital mobile phone at least 5 years prior to diagnosis, but the results were based on very small numbers. In addition, the risk estimates for cordless phones were also higher in rural areas, which would not be expected as the cordless phone base station is placed inside the home and exposure levels are therefore independent of population density.

Hardell et al, 2005, 2006

As well as re-analysing their 2002 study, this research group has performed one new case–control study, published in two separate papers, one on benign and the other on malignant brain tumours (Hardell et al, 2005c, 2006c). Analyses were not made of all brain tumours combined, as in the previous studies by this group. Incident cases of brain tumours aged 20–80 years diagnosed between 1 July 2000 and 31 December 2003 were identified through the regional cancer registers covering the geographical regions of Uppsala/Örebro and Linköping in Sweden. The participation rate was reported to be 88% for malignant and 89% for benign tumours. As in the previous studies, participation rates were unconventionally calculated, eg the denominator did not include deceased cases, cases for whom the treating physician did not give permission for contact, or cases who for medical reasons did not want to participate. Enough information is, however, given in the papers to recalculate the participation rate for all brain tumours combined. During the specified study period, 1097 eligible primary brain tumours were identified, and the overall participation rate can be calculated to be 67%. The participation rate is, however, likely to be lower for malignant brain tumours than for benign conditions because of the poorer prognosis

Text continues on page 286

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

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

TABLE 8.4 *Continued*

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

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

* But 801 in most tables.

(91% of deceased cases had a malignant tumour), and is probably below 60% for malignant tumours. One control per finally-included case was randomly selected from the population registry matched to cases on age in 5-year age groups – in total, 820 controls, of whom 692 participated (84%). The matching was ignored in the analyses; all controls were used in the analyses of all types of tumours.

For all malignant tumours combined, an odds ratio of 2.6 (95% CI 1.5–4.3) was found for any use of an analogue mobile phone at least 1 year prior to diagnosis. The corresponding result for digital phones was 1.9 (95% CI 1.3–2.7) and for cordless phones 2.1 (95% CI 1.4–3.0). For phone use starting 1–5 years prior to diagnosis a risk estimate for malignant tumours of 1.6 (95% CI 1.1–2.4) was found for digital phone use and 1.8 (95% CI 1.2–2.8) for cordless phones. No cases and three controls had used an analogue phone with such short latency. With a latency period of >10 years the risk estimates were 3.5 (95% CI 2.0–6.4), 3.6 (95% CI 1.7–7.5) and 2.9 (95% CI 1.6–5.2) for analogue, digital and cordless phones, respectively. The risk estimates were stronger for high grade astrocytoma. Overall results for benign tumours were very similar to those of malignant tumours, although results for specific histological types differed considerably. For acoustic neuroma, the risk estimates were notably stronger: use of an analogue phone for at least 1 year was associated with an odds ratio of 4.2 (95% CI 1.8–10), for digital phones 2.0 (95% CI 1.05–3.8) and for cordless phones 1.5 (95% CI 0.8–2.9). The results for different latency periods were for analogue phone use starting 1–5 years prior to diagnosis 9.9 (95% CI 1.4–69), for 5–10 years 5.1 (95% CI 1.9–14) and for >10 years 2.9 (95% CI 0.9–8.0). Few cases had started to use a digital or cordless phone >10 years prior to diagnosis. The risk estimates for shorter latency periods were generally raised but not significantly; only for digital phone use starting >5–10 years prior to diagnosis was a significantly raised risk found, 2.7 (95% CI 1.3–5.7). For meningioma, an increased odds ratio was found for use of analogue phones with >10 years' latency (OR 2.1, 95% CI 1.1–4.3).

Analyses were also made of duration of phone use, categorised into two groups according to the median number of hours of use among controls. Generally, risk estimates were higher for the highest usage category. For example, use of an analogue phone for over 80 hours in total was associated with an odds ratio of 4.0 (95% CI 2.2–7.3) for malignant tumours, 2.2 (95% CI 1.1–4.3) for meningioma and 6.0 (95% CI 2.2–17) for acoustic neuroma.

The results for different anatomical locations of the tumour did not differ greatly for malignant tumours; the risk estimates were slightly higher for frontal lobe tumours than for tumours in the temporal lobe or at other locations. For benign tumours, odds ratios were higher for temporal lobe tumours, probably driven by the results for acoustic neuroma, which were unconventionally defined as occurring in the temporal lobe. Laterality of phone use in relation to laterality of the tumour also did not affect results to a great extent, eg for malignant tumours increased risks were found for both ipsilateral and contralateral phone use in all analyses, except for digital phone use where the odds ratio for contralateral use was not statistically significantly raised.

Compared with previous studies by the same group, the reported risk estimates in this study appear to be considerably higher; this is also the case for categories of use for which sufficient data were available in the earlier studies, eg for short- or intermediate-term mobile phone use. Comparison of the results is, however, not straightforward as the main results in the two previous studies combined all types of brain tumours into one group, and specific diagnostic types were analysed separately only to a limited extent.

Furthermore, categorisation of the time since first mobile phone use differed between the studies. Inconsistent results between the new and earlier studies are, for example, for malignant brain tumours with a latency period of 1–5 years, the odds ratio for digital phone use was 1.6 (95% CI 1.1–2.4) in the new study compared with 1.08 (95% CI 0.81–1.43) in the study covering the observation period 1997–2000 (the latter result was for a latency period of 1–6 years). Both risk estimates were based on 100 exposed cases. The earliest study, with an observation period between 1994 and 1996, reported an odds ratio of 0.98 (95% CI 0.63–1.50) for mobile phone use of >1 year for malignant tumours, based on 53 exposed cases. For a 5-year latency period, no raised risk estimates were observed for all brain tumours combined in the first two studies, whereas in the new study significantly increased risks were reported for both malignant and benign tumours. A similar pattern is seen for cumulative hours of use: the first two studies found no consistent dose-response patterns when categorising cumulative hours of use according to the median number of hours among controls, whereas the new study reported dose-response patterns for both malignant and benign tumours. The median cumulative hours of use among controls for analogue phones was 224 hours in the first study, 85 hours in the second and 80 hours in the third. The corresponding numbers of hours for digital phones were 88, 55 and 64 hours. The higher amount of use in the first study, despite the very early observation period, may be explained by the requirement of a minimum cumulative exposure time of 8 hours to be considered as a user in that study, and no requirements at all on the amount of use in the two later studies. Given the absence of a minimum amount of use required to be regarded as a mobile phone user, the low prevalence of mobile phone use in the latest study is surprising and troubling; only 51% of controls were mobile phone users (and 56% of cases). A report from the Swedish Post and Telecom Agency (PTS) found that 87% of a random sample of the Swedish population in the age range 16–75 years were mobile phone users in 2002, and 90% in 2003, ie considerably higher.

Hardell et al pooled analyses, 2006, 2007, 2009

Hardell and colleagues have published several papers, with mostly overlapping analyses, where data from their two latest brain tumour studies were pooled (Hardell et al, 2006a,b,d; Mild et al, 2007; Hardell and Carlberg, 2009). The two original studies (Hardell et al, 2002, 2005c, 2006c) used the same study design to enable pooling, but no homogeneity tests were presented in the pooled analyses and it is therefore impossible to assess whether results in the two studies differ more than would have been expected by chance alone. As described above, the results appear to differ between the two studies, although differences in presented analyses, eg chosen cut-points and grouping of disease endpoints, make it difficult to assess if the differences are statistically significant. Some of the implausible results in the individual studies disappear in the pooled analyses; the apparent protective effect for malignant brain tumours associated with contralateral mobile phone use in the 2002 study (OR 0.62, 95% CI 0.35–1.11 for analogue phone use) was offset by the increased risk for both ipsilateral and contralateral phone use in the latest study (OR 2.6, 95% CI 1.3–5.4, for contralateral analogue phone use and 3.2, 95% CI 1.6–6.2, for ipsilateral use). The difference between the results in the two studies for contralateral phone use is statistically significant. In the pooled analysis malignant brain tumours were associated with an odds ratio of 1.1 (95% CI 0.8–1.6) for contralateral analogue phone use and of 2.1 (95% CI 1.5–2.9) for ipsilateral use. The statistically significant increased risk for malignant brain tumours after a very short latency period in the latest study was lowered by the lack of association in the 2002 study. In the pooled analysis the

odds ratio for <5 years since first digital mobile phone use was 1.2 (95% CI 0.96–1.5). For malignant brain tumours there were statistically significant increased risk estimates for latency periods of 5–10 years and >10 years for both digital and cordless phones. For meningioma significantly increased risk estimates were reported for analogue phones with a 10-year latency and for cordless phones after 5–10 years. For acoustic neuroma all types of phones were associated with significantly increased risk estimates after <5 years since first use, eg a doubling of the risk for analogue phone use (increasing to over three-fold with >5 years' latency). Surprisingly, no analyses according to tumour location were presented in any of the papers.

Cumulative lifetime hours of use were presented with the same categorisation as in the original papers (cut-point at the median hours for controls), showing a clear dose-response pattern only for analogue phone use and acoustic neuroma risk. In addition, new categorisations were presented, with cut-points at 1000 and 2000 hours of use for malignant brain tumours and at 500 and 1000 hours for benign conditions. No rationale for the choice of cut-points was given. Statistically significant increased odds ratios were reported for all exposure categories for malignant tumours and for acoustic neuroma, with the highest risk estimates in the highest exposure category (OR 5.9, 95% CI 2.5–14, for malignant tumours and 5.1, 95% CI 1.9–14, for acoustic neuroma). One paper presented results according to tertiles (Hardell et al, 2006d), with essentially the same pattern of results as when the median was used. Another paper added analyses of the exposure as a continuous variable (Mild et al, 2007), which essentially did not change the overall impression of the results. Analyses stratified according to age at first use were presented in several papers (Hardell et al, 2006a,b; Hardell and Carlberg, 2009), with most details in the latest paper (Hardell and Carlberg, 2009). The highest risk estimates were found among people who started to use a mobile phone before 20 years of age; for astrocytoma in this age group the odds ratio was 5.2 (95% CI 2.2–12) and for acoustic neuroma 5.0 (95% CI 1.5–16) for ever-use of a mobile phone >1 year prior to diagnosis.

Hardell et al, 2010

None of the original studies by Hardell and colleagues included deceased cases, ie proxies were not approached. In the study published in 2002, 35% of the malignant cases had died before being approached, and although an exact percentage cannot be calculated from the data given in the 2006 study, an approximation comes close to 35% also in that study. Having been criticised for omitting deceased cases (Boice and McLaughlin, 2002), Hardell and colleagues conducted a study of the deceased cases, ie those cases that would have been included in the 2002 and 2006 studies had they not died before they could be contacted (Hardell et al, 2010). The study included 535 deceased cases of malignant brain tumours from the two most recent case–control studies, and deceased controls were selected from the cause of death register, matched for year of death, sex, age ±5 years and medical region. Two controls per case were selected: one who had died from another cancer diagnosis and one who had died from another major chronic disease, such as cardiovascular disease, neurological disease, lung disease, gastrointestinal disease, infection and diabetes. A questionnaire on the mobile phone use history of the deceased case was sent to a close relative. Cases had been diagnosed between 1997 and 2003; relatives were contacted between November 2006 and August 2008. The results were very similar to those from the pooling of the two original case–control studies (discussed above), except that no raised risks were found for use of cordless phones. A severe limitation of the study is the reliance upon the

ability of close relatives to report correctly about mobile phone use for distant time periods for a relative who died from a malignant brain tumour several years earlier. The authors discussed that the use of controls who had died from other cancer types or some other malignant disease would offset recall bias when relatives reported on the subjects' past mobile phone use. It seems unlikely, however, that relatives of people who have died from other cancers or from other diseases, such as cardiovascular disease, would believe that mobile phone use had caused the disease from which their relative had died, as is likely to be the case for relatives of many cases of malignant brain tumours, considering frequent headlines in the media during the data collection period about mobile phones causing brain tumours. Reporting on the amount of mobile phone use for a relative 10–20 years earlier must be extremely difficult. An indication of this is seen in the difference in the median cumulative hours of use reported by controls in the original studies, compared with that reported by relatives to controls in this study. The two original studies reported a median of 85 and 80 hours for analogue phone use, 55 and 64 hours for digital phone use, and 195 and 243 hours for cordless phone use. The relatives of deceased controls reported 149 hours for analogue phone use, 183 hours for digital phones use, and 548 hours for cordless phone use, even though the time period covered should be the same.

In a letter to the editor, Hardell et al (2011) presented the results of re-analyses of their previous pooled studies, using various age ranges, including one similar to that used in the Interphone study, as well as analyses of users of cordless phones in the unexposed category. In the age range used in the Interphone study, the Hardell group reported somewhat lowered risk estimates compared with their overall analyses, although it is unclear whether the differences between age groups are statistically significant. Adding users of cordless phones to the unexposed category lowers the risk estimates only marginally. From this letter it is also clear that the risk estimates for temporal lobe tumours are not higher than those for other, less exposed, areas in the brain.

National analyses from Interphone study centres

The Interphone study is an interview-based case–control study on mobile phones and various cancers, conducted by a collaboration of 16 centres in 13 countries (details are given on page 298). Several of the centres within the Interphone collaboration have published data from their centre, or a combination of centres, as well as contributing to the overall Interphone analyses. For several reasons, however, these analyses were not simply subsets of the overall results paper, and therefore need separate consideration. First, many of the centres collected data from a wider age range of subjects than was included in the Interphone study, and often collected information on extra variables. Second, the overall Interphone analyses used pair matching (usually post-hoc), which none of the components alone did, except Germany and France, with consequent exclusion of large numbers of subjects from the overall Interphone analyses. The consequence of these two factors was that, for instance, the Swedish glioma study (Lönn et al, 2005) included 371 cases and 674 controls, but only 222 cases and 222 controls from Sweden (ie 42%) were included in the Interphone publication; the corresponding figure for the Nordic–UK combined glioma analyses (Lahkola et al, 2007) was 43%. Third, the analytical methods and categorisations of the Interphone study differed greatly from those of the individual country analyses, which make comparisons of the two informative rather than duplicative. The core data collection about mobile phone use, however, was the same across the Interphone sites, so is not repeated below. The published national analyses are described below.

Glioma, meningioma and acoustic neuroma: Christensen et al, 2004, 2005

Christensen et al (2005) conducted a case–control study of 252 cases of glioma and 175 of meningioma diagnosed in all of Denmark, during 2000–2002, at age 20–69 years, with 822 population-based controls matched on age and sex, selected from the national population register. Acoustic neuroma was reported in a separate publication with the same study design, including 107 patients and 214 matched controls (Christensen et al, 2004). Mobile phone use data were obtained by interview with the subject or, for 19 glioma and three meningioma patients, a proxy. Response rates were 71% for glioma, 74% for meningioma, 80% for acoustic neuroma and 64% for controls. Regular mobile phone use was not associated with a risk of glioma overall, whereas the risk was significantly decreased for high grade glioma and close to unity for low grade glioma and meningioma and for acoustic neuroma. There were no relations of risk to intensity of use, time since first use, cumulative number of calls or cumulative hours of use. Exclusion of respondents with poor Mini-Mental State Examination scores left the risk below unity for high grade glioma. When analysed by lobe, with temporal and parietal lobes considered as the high exposure part of the brain, there was a small, non-significant deficit in tumours in these lobes in regular mobile phone users compared with non-regular users. For acoustic neuroma, tumours were significantly larger among regular mobile phone users than among non-regular users. Increasing duration of use and time since start of first use did not increase the risk of large tumours.

For 27 cases and 42 controls the authors were able to compare reported phone use from December 2001 onwards with records of network operators, for a mean of 218 days each. This showed a modest correlation of reported and recorded number of calls (kappa 0.31 for cases and 0.28 for controls) but a near-zero correlation for hours of calls.

Glioma, meningioma and acoustic neuroma: Lönn et al, 2004, 2005

Lönn et al (2005), in a population-based case–control study in part of Sweden, obtained data from 371 glioma cases and 273 meningioma cases aged 20–69 years at diagnosis in 2000–2002, and 674 controls from the same area of Sweden, randomly selected from the national population register, stratified on age, sex and residential area. Acoustic neuroma was reported in a separate publication with the same study design, but excluding the most northern part of Sweden (Lönn et al, 2004a). In total, 148 acoustic neuroma patients and 604 matched controls were included. The cases were identified from clinical sources and cancer registries. The participation rates were 74% for glioma, 85% for meningioma, 93% for acoustic neuroma and 71% for controls. Most subjects were interviewed in person, but some (≤5%) were interviewed by telephone, and <1% of cases and <4% of controls (7% of acoustic neuroma controls) gave data by mail questionnaires. For 9% of glioma, 3% of meningioma and 1% of acoustic neuroma patients, information was from a proxy not the cases themselves.

Odds ratios for ever-use of a mobile phone were below unity for glioma and meningioma, significantly so for meningioma (0.7, 95% CI 0.5–0.9). There was no trend of an increase in risk with duration of use, cumulative number of calls or cumulative call time, or relation to analogue/digital phone use or urban/rural use. There was also no indication of a raised risk in separate analyses of risk of glioblastoma, low or high grade glioma, or by lobe of tumour, nor was there any relation between laterality of the tumour and reported side of use of the phone. There was a non-significant raised risk for ipsilateral use for ≥10 years, and for ipsilateral use ≥10 years before diagnosis, but contralateral use was associated with

a non-significantly decreased risk, suggesting that recall bias may have been the explanation. There was no increased risk with the use of DECT phones. For acoustic neuroma the odds ratio for ever-use of a mobile phone was at unity. There was a slightly increased risk with first use of a mobile phone ≥10 years prior to diagnosis, but no trend of increased risk with cumulative number of calls or cumulative call time. There was a significantly increased risk of acoustic neuroma associated with ipsilateral use for ≥10 years, and a slightly reduced risk for contralateral use. There was no increased risk associated with the use of DECT phones.

The authors obtained brief questionnaire data where possible from non-participants, and these showed 34% regular use in the non-participant potential controls compared with 59% in participating controls, but very similar regular use in non-participant cases compared with participant cases. However, less than 20% of non-participants completed such questionnaires, and so it is impossible to determine whether they were representative of non-participants generally.

The study appears to have been well conducted and had relatively high response rates, but has the same limitations as other interview-based case–control studies in terms of misclassification and potential recall bias in exposure data. The results do not suggest an aetiological effect of mobile phone use.

Glioma: Hepworth et al, 2006

Hepworth et al (2006) reported a population-based case–control study of glioma in five areas of the UK. In the northern and southern UK regional groupings cases were aged 18–69 and 18–59 years, respectively, at diagnosis of glioma during 2000–2004; they were identified from hospital clinical sources and from cancer registries. Controls were selected randomly from GP lists, individually matched (in the northern UK) or frequency matched (in the southern UK) on age, sex and GP practice (northern UK) or geographical area (southern UK). Interviews were mainly conducted in person, but 7% of those for gliomas were with proxies. The study included 966 cases and 1716 controls. The response rates were 51% for cases and 45% for controls.

The odds ratio for regular mobile phone use was not raised; nor was there a relation of risk to time since first use, lifetime years of use, cumulative number of calls or cumulative hours of use. This remained true after exclusion of subjects for whom proxies were interviewed, after adjustment for hands-free use, and after censoring a 5-year lag period before diagnosis. There were no significant associations for urban/rural use, or for high and low grade gliomas separately. If non-participation because of death had given rise to participation bias, a greater effect might be expected in high than low grade tumours (ie a real effect would be more evident in low grade tumours), which was not seen. There was a significantly increased risk for gliomas ipsilateral to the reported side of use of the mobile phone (OR 1.24, 95% CI 1.02–1.52), but also a significant reduction in risk for contralateral tumours (OR 0.75, 95% CI 0.61–0.93), suggesting recall bias as the explanation. The odds ratios for ipsilateral and contralateral handedness were 0.78 (95% CI 0.62–0.99) and 1.07 (95% CI 0.85–1.35), respectively. These are of interest because handedness, in contrast to side of mobile phone use, is very unlikely to be affected by recall bias. The lack of relation to handedness therefore argues against a causal effect of phone use, although any true effect of laterality of use on laterality of tumour incidence might be diluted (but not biased) in an analysis based on handedness.

Glioma, meningioma and acoustic neuroma: Schüz et al, 2006, and Schlehofer et al, 2007

In a population-based case–control study in four regions of Germany, Schüz et al (2006a) interviewed 366 cases of glioma and 381 with meningioma aged 30–59 years and diagnosed during 2000–2003, as well as 1494 controls frequency matched on age, sex and region, taken randomly from population registries. For the analyses a 1:2 post-hoc matching of controls to cases was made. The response rates were 80% for glioma (including 11% proxies), 88% for meningioma (1% proxies) and 63% for controls (0.4% proxies). Acoustic neuroma was also included in the German Interphone study (Schlehofer et al, 2007), with the same design as for glioma and meningioma. The study included 97 (89%) cases of acoustic neuroma and 194 controls (55%). Regular use of a mobile phone was not associated with the risk of glioma or meningioma. Use of a mobile phone for ≥10 years was associated with a non-significant raised risk of glioma (OR 2.8, 95% CI 0.9–5.1) but not meningioma (OR 1.1, 95% CI 0.3–3.4), and a non-significant trend in risk with number of years of use. There was no excess risk for temporal lobe glioma or meningioma in users. Cordless phone use and years since first cordless phone use were not related to the risk of glioma or meningioma. Omitting subjects interviewed through proxies changed the results little. For meningioma and low grade glioma the results were similar in separate analyses for males and females, but for high grade glioma there was a significant increased risk in female ever-users (1.96, 95% CI 1.10–3.50), whereas there was a decreased risk in male ever-users (0.78, 95% CI 0.53–1.14). There was also a near-significant trend ($p = 0.06$) in females for risk in relation to time since first regular use, but only one female case (and no female controls) had been first exposed ≥10 years ago. There is no obvious reason why a true aetiological effect would be confined to females, nor is such an effect seen in other studies, so the finding in this study seems likely to be a chance one. For acoustic neuroma, the odds ratio for ever-regular mobile phone use was below unity, and there was a trend towards lower risks with increasing time since first use, numbers of calls and cumulative call time, but the results were based on small numbers of exposed cases. For example, no case had used a mobile phone for >10 years.

Temporal lobe tumours were a slightly lower proportion of gliomas in regular users than in non-regular users. There was no relation of risk to cumulative number of calls, cumulative duration of calls or intensity of use (per day).

The German study also examined glioma and meningioma risk in relation to whether subjects had a DECT cordless phone base station within 3 m of their bed (presumably at home, although this was not stated), as a proxy for continuous low level RF field exposure at night (Schüz et al, 2006b). There was no evidence of an association for having (presumably 'ever', although this was not stated) such exposure for glioma (OR 0.82, 95% CI 0.29 –2.33) or meningioma (OR 0.83, 95% CI 0.29–2.36), and there was no trend in risk with time since first exposure. All these analyses were based on very small numbers of cases, however.

Glioma, meningioma and acoustic neuroma: Klaeboe et al, 2007

Klaeboe et al (2007) interviewed 289 patients with glioma, 207 with meningioma and 45 with acoustic neuroma diagnosed during 2001–2002 at age 19–69 years, and 358 controls, in southern Norway. In total, 36% of the glioma interviews were through proxies. Almost half of the interviews were by telephone. Controls were chosen from the national population register within strata by age and geographical area. Participation rates were 74% for cases and 69% for controls.

The risks of glioma were significantly diminished and those of meningioma and acoustic neuroma non-significantly diminished in regular users of mobile phones. There was no trend of glioma or acoustic neuroma risk with duration of regular use, time since first regular use or cumulative use, while for meningioma there was some indication of a trend for each of these variables (it was not stated whether this was significant), but no significantly raised risk in the highest categories. Adjustment of analyses for hands-free use, and exclusion of proxies, did not alter the results substantially. There were no significant relations to analogue or digital phone use, and odds ratios for reported use ipsilateral and contralateral to the side of the tumour were close to unity and not significant.

Of the controls who declined to take part in the study, 65% answered a short questionnaire. From this questionnaire, 54% of these non-participants were regular users of mobile phones compared with 63% of participant controls, ie there was evidence of a potential slight bias of participants being more often users, although the non-participant questionnaire was only attempted for those who declined to take part rather than all non-participants, eg these who had died or could not be contacted.

Glioma and meningioma: Hours et al, 2007

Hours et al (2007) conducted interviews with 96 glioma, 145 meningioma and 109 cranial nerve neuroma patients resident in Paris or Lyon, France, and diagnosed at age 30–59 years in 2001–2003. The cases were ascertained from hospitals, without cancer registry information. This was therefore a relatively small study and not population based. In addition, 241 controls were included, chosen at random from electoral rolls within matching on sex, age and place of residence. Participation rates were 60% for glioma, 78% for meningioma, 78% for neuroma and 75% for controls. For 12 glioma and two meningioma patients information was obtained through proxies.

The study found no raised risk of glioma, meningioma or cranial nerve neuroma with regular mobile phone use, and no significant relations of risk to duration of use, cumulative hours of use, mean call length and cumulative number of calls, although for glioma the odds ratios for the top quartile of each of these variables were non-significantly raised (in the range 1.53–1.96). There was a near-significant trend in glioma risk per 80 hours of cumulative use (OR 1.02, 95% CI 1.00–1.04). There was no significant relation of risk to side of use: for glioma the odds ratios for ipsilateral and contralateral use were similar, for meningioma that for ipsilateral was slightly higher than for contralateral use, and for cranial nerve neuroma the risk for ipsilateral was lower than for contralateral use. There was a significantly raised odds ratio for glioma if a subject had used two or more phones rather than only one (OR 2.06, 95% CI 1.02–4.18), but this was not significant after adjustment for potential confounders.

Glioma and meningioma: Takebayashi et al, 2008

Takebayshi et al (2008) conducted in-person interviews with 88 glioma patients and 132 meningioma patients diagnosed at age 30–69 years from hospitals in Tokyo and other adjacent cities (21 of 30 eligible hospitals agreed to participate). They also interviewed 683 controls. Recruitment was during 2000–2004. Participation rates were 59% for glioma patients, 78% for meningioma and 51% for controls. Controls were selected by random digit dialling to home fixed-line phones of the general population, individually matched on age, sex and area of residence. This gave a potential for bias in that mobile phone users (or others) with no fixed-line phone would not be included. Acoustic neuroma was presented in a

separate publication (Takebayashi et al, 2006), where the same study design was used. Interviews were conducted with 101 (84%) acoustic neuroma cases and 339 (52%) individually matched controls.

The investigators used a brief non-participant questionnaire for controls who declined to participate in the full interview; this was obtained for just over half of the non-participants. The age- and sex-adjusted percentage of regular users was marginally higher in the brief questionnaire respondents (66% for the glioma controls and 55% for the meningioma controls) than in the full participants (65% and 51%, respectively).

Regular use of a mobile phone was not associated with a significant risk of glioma, meningioma or acoustic neuroma. There was no trend in risk with cumulative years of use or cumulative call time. The odds ratios for ≥10 years of use were 0.58 (95% CI 0.09–3.86) for glioma and 1.35 (95% CI 0.31–5.93) for meningioma. Only one case of acoustic neuroma had used a mobile phone for ≥10 years. The odds ratio for at least 8 years of use was 0.79 (95% CI 0.24–2.65). There were no effects of analogue plus digital phone use or of digital use only (no one used only analogue phones). There was no significant effect of laterality of phone use: for glioma the odds ratio was 1.24 for reported ipsilateral use and 1.08 for contralateral use; for meningioma the corresponding odds ratios were 1.14 and 0.68, respectively, and for acoustic neuroma 0.90 and 0.92, respectively.

The investigators estimated the SAR at the site of the tumour by combining information from phantom intracranial SAR distribution for 76 phones on the Japanese market, with computed tomography data on the location of the tumour. There was no trend of risk with SAR or with cumulative SAR years or cumulative SAR hours. The highest quartile categories for these SAR variables showed non-significant raised risks for some variables, more for glioma than for meningioma, but these were not consistent or significant. There were no material differences in SAR indices between the actual tumour location and an axis-symmetrical location opposite the tumour across the saggital plane. Acoustic neuroma was not included in the analyses of SAR levels.

Glioma: Hartikka et al, 2009

Hartikka et al (2009) conducted a case–case analysis of glioma within the Finnish Interphone study to assess whether mobile phone use was related to location of the tumour. The rationale behind the analyses is that RF field exposure from mobile phones declines rapidly from the source, and most of the exposure is absorbed within a few centimetres from the phone. If RF field exposure from the phone is causally related to the risk of glioma, it would be expected that tumours would occur at locations close to where the handset is held. A subset of glioma cases (99 in total), for whom radiological imaging was available, was included in the analyses. Two neuroradiologists evaluated the radiological images and recorded the midpoint of each tumour on a 1 cm x 1 cm x 1 cm grid. The shortest distance from the midpoint of the tumour to the assumed location of the mobile phone was estimated. Analyses were based on small numbers and, although modestly non-significantly elevated odds ratios were observed for several indicators of mobile phone use, no consistent dose-response patterns were found, with the lowest risk estimates in the highest exposure categories. The highest risk estimates were found for contralateral and short-term use. The study was too small for any conclusions to be drawn, but it has illustrated an innovative method to investigate the potential effect of mobile phone use on glioma risk.

Pooled analyses, subsets of the Interphone study

Two pooled analyses have been conducted of data for glioma (Lahkola et al, 2007) and meningioma (Lahkola et al, 2008) from five north European countries involved in the Interphone study. These consisted of the data from Denmark, Norway, Sweden and the southern UK regional grouping described above, as well as the data from Finland, which have not been published separately. The numbers of subjects, age ranges and control sources from the published countries are described above. For Finland, 266 glioma patients, 334 meningiomas and 870 controls were recruited from 98% of the population of the country, ie excluding Northern Lapland and Åland. Participation rates were 81% for glioma patients and 90% for meningioma patients, and 42% for controls. Telephone interviewes were conducted for 3% of glioma patients and 3% of meningioma patients, and 7% of controls.

Overall, the glioma analyses included 1521 cases and 3301 controls. The risk of glioma was significantly diminished for regular mobile phone use (OR 0.8, 95% CI 0.7–0.9) and there were no significant risks in categories by years since first use, lifetime years of use, cumulative number of calls and cumulative hours of use. The linear trend in risk with cumulative hours of use was significant when analysed as a continuous variable (1.006 per 100 hours, 95% CI 1.002–1.010) but not when analysed in categories. There was a non-significant raised risk in the top decile (determined from the control data) of cumulative years of use, for >1475 hours (OR 1.13, 95% CI 0.86–1.48), but not for the top decile of number of calls. The risks for cumulative hours of use, and cumulative number of calls, ≥10 years before the reference date were not significantly raised. There were no increased risks for the use of analogue or digital phones, considered separately, and the results for glioblastoma separately were similar to those for glioma overall as were results for men and women separately.

The risks were non-significantly raised for regular reported use of the phone ipsilateral to the tumour (1.13, 95% CI 0.97–1.31) and decreased for contralateral use (0.75, 95% CI 0.64–0.88). The odds ratios for first ipsilateral and contralateral use ≥10 years ago were 1.39 (95% CI 1.01–1.92) and 0.98 (95% CI 0.71–1.37), respectively, with p-trends for duration of ipsilateral and contralateral use of 0.04 and 0.11, respectively (the corresponding odds ratios for ≥10 years of use were closer to 1.0 and not significant). Whereas the laterality results overall suggest reporting bias, those for ipsilateral use for ≥10 years and duration of use are marginally significant and not accompanied by comparable compensatory opposite findings for contralateral use, leaving the possibility of long-term risks.

The meningioma analyses included 1209 cases and 3299 controls. The risk in regular users was significantly lower than in non-regular users (OR 0.76, 95% CI 0.65–0.89). It was not raised in relation to years since first use, lifetime years of use, cumulative hours of use and cumulative number of calls, nor was there any material increase for those in the top decile of number of calls (OR 0.86, 95% CI 0.60–1.24) or of hours of use (OR 1.13, 95% CI 0.82–1.57) or when only use ≥10 years before the reference date was considered. The results were similar in subdivisions of the data by age, sex and analogue/digital phones, except that the odds ratio for cumulative hours of use of digital phones, analysed as a continuous variable, was significantly raised (OR 1.008 per 100 hours, 95% CI 1.002–1.014). The odds ratio for analogue phones, which generally have greater power output, was not significantly raised, however. There was a significant linear association of cumulative hours of use to the risk of meningioma, when hours of use were considered as a continuous variable (OR 1.005 per 100 hours, 95% CI 1.001–1.010), but this was consequent on a small number of very high values, which reflected implausibly high reported mean

daily hours of use. When subjects who reported more than 2 hours per day of use were excluded, no relation remained.

The risks of meningioma were not raised for reported regular use ipsilateral (0.81, 95% CI 0.66–0.99) or contralateral (0.67, 95% CI 0.54–0.83) to the tumour, nor were there significant or materially raised risks in analyses of years since first use, lifetime years of use or cumulative hours of use, by laterality.

The combined north European analyses, as for the studies from which they derive, and indeed as for the other Interphone studies considered separately, showed reduced odds ratios for regular use of a mobile phone, no overall evidence for causation of brain tumours by mobile phone use and inconsistently raised risks in relation to the reported cumulative hours of use but not the cumulative number of calls. It should be noted that the hours of use per day, in contrast to the number of calls per day, was a calculated, not a reported, variable. Study subjects were asked about the number and mean duration of calls they made per day on average, and these were then multiplied together to calculate cumulative time per day. Some of the highest values appeared improbable. The subjects were not asked, however, whether this calculated number was a good representation of their hours per day of use – it is possible that the subjects would not have agreed the improbably high values had they been asked.

There were also some, but not consistent or strong, indications of raised odds ratios for glioma in relation to use ≥10 years ago.

To test the hypothesis that tumours in mobile phone users occur more frequently in locations in the brain where the RF field exposure from the mobile phone is highest, ie close to where the handset is held, the methods developed by Hartikka et al (2009) were applied to data from seven Interphone study centres: the five north European centres mentioned above, and the German and Italian centres (Larjavaara et al, 2011). Based on radiological images, neuroradiologists recorded the midpoint of each tumour on a 1 cm x 1 cm x 1 cm grid. The main exposure indicator was the shortest distance between the midpoint of the tumour to the typical location of the mobile phone. To avoid potential recall bias, self-reported laterality of phone use was not taken into consideration when estimating the distance. Case–case analyses were performed including 873 glioma cases. The distance between the exposure source (ie mobile phone) and the tumour midpoint did not vary with mobile phone use. The distance was slightly shorter in cases who had never used a mobile phone regularly compared with regular users, and among subjects who reported the preferred side of mobile phone use contralateral to the tumour. The distance was longer for cases with the highest cumulative call time and for duration of use >10 years. None of the distance differences was statistically significant. The odds ratio for a location <5 cm from the exposure source was 0.80 (95% CI 0.56–1.15), and for duration of use >10 years 0.85 (95% CI 0.39–1.86). The results do not suggest that gliomas occur more often within the area of the brain that receives the highest RF field exposure during mobile phone use. The potential influence from recall bias in self-reported amounts of mobile phone use and from selection bias is minimised by the case–case design.

A study based on five other Interphone study centres (Australia, Canada, France, Israel and New Zealand) assessed the risk of brain tumours in relation to the estimated absorption of RF energy from mobile phones (Cardis et al, 2011a). Estimation of the total RF energy absorbed was based on self-reported call duration and laterality of mobile phone use, location of the tumour centre determined by neuroradiologists or estimated by a computer algorithm, frequency band, communications system and

network characteristics, summed over all mobile phones that the subject had used. An accompanying paper describes the details of the exposure assessment (Cardis et al, 2011b). Only cumulative call time and tumour location were significant predictors of the total cumulative specific energy, accounting for 43% and 13% of the variance, respectively. The analyses included 551 glioma cases and 1720 controls, and 674 meningioma cases and 1796 controls. The original matching of controls was not kept; instead a post-hoc matching was performed to take into account differences in the timing of the interview between cases and the original controls. Exposure indices were categorised into quintiles and results were reported for both total cumulative specific energy and cumulative call time. For glioma, the odds ratio in the highest quintile of cumulative call time was 1.25 (95% CI 0.88–1.77) in the subset of subjects with information available on tumour centre. The corresponding result for total cumulative specific energy was 1.35 (95% CI 0.96–1.90). When tumour laterality was not included in the estimation of total cumulative specific energy, to avoid potential recall bias when reporting the preferred side of phone use, the odds ratio was 1.23 (95% CI 0.89–1.72), ie almost identical to the risk estimate based solely on cumulative call time. For meningioma, the odds ratio in the highest category of total cumulative specific energy was slightly lower than for cumulative call time, and even lower when tumour laterality was not included.

Analyses of the total cumulative specific energy during three periods of time before diagnosis were also performed: <3, 3–6 and >7 years. No rationale was given for the choice of these particular time windows. In the >7-year time window, all odds ratios for glioma were raised, although only statistically significantly in the category with the highest total cumulative specific energy (OR 1.91, 95% CI 1.05–3.47). In the <3-year time window, all odds ratios were below unity, except in the highest category of total cumulative specific energy, some of them statistically significantly reduced. For meningioma, most odds ratios were close to or below unity, except in the highest category of total cumulative specific energy in the >7-year time window (OR 2.01, 95% CI 1.03–3.93). In case–case analyses, comparing mobile phone use in cases with tumours located in the region of the brain with the highest exposure, to those with tumours located in less exposed areas (similar to the Hartikka et al analyses discussed above), risk estimates did not increase with cumulative call time. Having started to use a mobile phone >10 years earlier was more common among cases with a tumour in the highest exposed area (OR 2.80, 95% CI 1.13–6.94), but the risk was reduced in the 5–9 year period (OR 0.72, 95% CI 0.27–1.90).

Estimation of the total cumulative specific energy was done to reduce exposure misclassification caused by other factors that influence the level of RF field exposure at different locations in the brain. Such exposure misclassification is likely to be non-differential, and would therefore dilute risk estimates should an increased risk exist. It should not, however, lead to spuriously increased risk estimates. Estimated total cumulative specific energy is not, however, free from potential recall bias; self-reported information on cumulative call time is the most important determinant of the exposure level, and other factors make only minor contributions to the overall estimate. Results from analyses of cumulative call time were almost identical to those when using the total cumulative specific energy. Thus, reducing non-differential RF field exposure misclassification did not result in stronger risk estimates, which would have been expected if RF field exposure was aetiologically related to brain tumour risk. Analyses of cumulative call time in different time windows before diagnosis were not presented; therefore, it is not possible to assess whether they differ from the corresponding results for total cumulative specific energy in these subgroups.

The main Interphone paper (see below) presented cumulative hours of mobile phone use for short-term (0–4 years since first use), medium-term (5–9 years) and long-term (>10 years) users separately. In the time-window analyses of total specific energy by Cardis et al (2011a,b), however, all subjects were included in all time windows. Thus, it is not only the chosen cutpoints that differ between the Cardis et al study and the original Interphone study. This makes comparisons between the Cardis et al study and other studies difficult. In addition, the quintiles used by Cardis et al do not correspond exactly to 20% in each category. For example, for both glioma and meningioma over 24% of controls were in the lowest quintile.

One pooled analysis has been conducted with data for acoustic neuroma (Schoemaker et al, 2005). This included data from the five north European countries described above for the pooled analyses of glioma and meningioma and, in addition, the northern UK regional grouping. Acoustic neuroma results have been published separately for Denmark, Norway and Sweden (Christensen et al, 2004; Lönn et al, 2004a; Klaeboe et al, 2007). Overall, the pooled analysis included 678 cases of acoustic neuroma and 3553 controls. In the Nordic countries, controls were randomly selected from population registers stratified on sex, age and region. In the UK, controls were randomly selected from general practice (GP) lists. The participation rate among cases was 83% and among controls 51%.

Regular mobile phone use was associated with a slightly reduced odds ratio, 0.9 (95% CI 07–1.1), and there were no trends with any measure of amount of use or time since start of mobile phone use; the odds ratio for ≥10 years since first use was 1.0 (95% CI 0.7–1.5). There were no material differences between the results for analogue and digital mobile phone use.

The odds ratios for regular use ipsilateral to the tumour was 0.9 (95% CI 0.7–1.1) and for contralateral use 1.1 (95% CI 0.9–1.4). A raised risk was reported for ≥10 lifetime years of ipsilateral use (OR 1.8, 95% CI 1.1–3.1), and a slightly reduced risk for the corresponding contralateral use (OR 0.9, 95% CI 0.5–1.8). The odds ratio for ≥10 years since first ipsilateral use was 1.3 (95% CI 0.8–2.0) and for contralateral use 1.0 (95% CI 0.6–1.7).

Overall, the results do not support an association between mobile phone use and acoustic neuroma risk. The increased risk for ≥10 years since first use reported in the Swedish study was not confirmed in the pooled analysis. Instead, a raised risk was seen for ≥10-years' duration of ipsilateral use. With no overall risk increase in this exposure category, it seems unlikely that the raised risk would reflect causality.

Glioma and meningioma: Interphone Study Group, 2010

The Interphone study was set up to provide more powerful analyses of brain tumour (and acoustic neuroma and parotid gland tumour) risk in relation to mobile phone use than any previous study (Cardis et al, 2007; Interphone Study Group, 2010). The study included 16 centres in 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK) which used a common core protocol and questionnaire. The questionnaire was administered by interviewers reading the questions from, and entering responses into, an on-screen program on a laptop computer (except in Finland, where a paper questionnaire was used). The interview asked about patterns of use and type of phone (identified by use of show cards) for each phone used, for every respondent who had been a regular phone user, defined as an average of at least one call per week for 6 months or more.

The study recruited glioma and meningioma patients aged 30–59 years at diagnosis during periods of 2–4 years during 2000–2004 (the exact period varying by centre). In all countries, except France and Japan, the cases were population based; in the latter two countries they were hospital based. Controls were selected on a population basis from various sources, depending on the country – mainly population registers and electoral rolls, but GP lists in two centres and random digit dialling in two others. Controls were individually matched to cases in seven centres and frequency matched in the remainder. The matching ratio was stated to be 1:1, except in Germany where it was two controls per case. Matching variables were age, sex and region of residence as well as, in Israel, ethnic origin. At the analysis stage, individual matching was conducted post-hoc for centres that had collected controls with stratified matching, to give one control per case (or two in Germany). (The total numbers of controls presented, however, are not exactly the same as the number of cases in all countries except Germany plus twice the number of German cases.) All exposure variables except time since first use of a mobile phone were censored at 1 year before the reference date (date of diagnosis for cases and the equivalent date calculated for controls). Risks in relation to 'deciles' of cumulative number and duration of calls were calculated, with the cut-points of the deciles stated to be based on the distribution in controls who were regular users. (Although in practice these were not actual tenths of the controls in the paper – for instance, the top 'decile' of cumulative hours of use was considerably less than a tenth of the controls in the paper.) The cumulative use variables were calculated, adjusted for hands-free use.

The study centres interviewed 2765 eligible glioma cases, 2425 meningioma cases and 7658 controls. Because of the use of post-hoc matching, however, only 2708 glioma cases with 2972 controls, and 2409 meningioma cases with 2662 controls, were included in the analyses. Participation rates were 65% (range across centres 37–92%) for glioma and 78% (57–92%) for meningioma cases, and 53% (35–74%) for controls. In total, 94% of interviews for glioma cases and 95% for controls (not stated for meningioma) were conducted face-to-face, although the percentages were much lower than this in two countries (Italy and Norway) where most interviews were by telephone. Interviews were with proxies for 13% for glioma and <2% for meningioma cases, and 1% for controls. For 11% of glioma and 5% of meningioma cases, and 5% of controls (17%, 9% and 8%, respectively, of regular users), there were missing data regarding mobile phone use for which imputation was used to fill the gaps.

Significantly reduced odds ratios of glioma and meningioma were found for regular users of mobile phones. There was no relation of risk to cumulative number of calls or years since first use. The odds ratio for first use ≥10 years ago were 1.0 (95% CI 0.8–1.3) for glioma and 0.8 (95% CI 0.6–1.1) for meningioma. For cumulative hours of use there was no appearance of a linear trend in risk (although trend tests were not presented). Odds ratios were below 1.0 for the lower nine deciles of hours, and above 1.0 for the top, tenth, decile (≥1640 hours): 1.4 (95% CI 1.0–1.9) for glioma and 1.1 (95% CI 0.8–1.6) for meningioma. The individuals with the highest cumulative hours of use included many with highly implausible values of hours per day, who were largely glioma cases: for instance, 10 glioma cases but no controls reported ≥12 hours of use per day. For both glioma and meningioma, the risk for ≥1640 hours was far greater in individuals who had started use <5 years before the reference date (OR 3.8, 95% CI 1.2–11.4, for glioma and 4.8, 95% CI 1.5–15.4, for meningioma) than for those with longer term use (odds ratios in the range 0.9–1.3).

Examining risk by lobe of the brain, odds ratios for regular use of phones were <1 for meningioma and glioma of each of the temporal lobe, parietal and frontal lobes, and other anatomical locations. For each of these locations separately, there were no apparent trends in risk with time since first use, cumulative hours of use or cumulative number of calls; no trend tests were presented. The risk of glioma of the temporal lobe was significantly raised for the top decile of cumulative hours of use (OR 1.87, 95% CI 1.09–3.22), but not for the top decile of number of calls (OR 1.10, 95% CI 0.65–1.85). Odds ratios of both glioma and meningioma tended to be greater ipsilateral to the reported side of use of the phone than contralateral: for regular users, odds ratios for glioma were 0.84 (95% CI 0.69–1.04) and 0.67 (95% CI 0.52–0.87) for ipsilateral and contralateral use, respectively, and for meningioma 0.86 (95% CI 0.69–1.08) and 0.59 (95% CI 0.46–0.76), respectively. Tests of trend in risk with cumulative call time and cumulative number of calls by laterality were not presented, but there appeared to be a tendency, although not strong or consistent, for odds ratios of ipsilateral meningioma and glioma to be greater at higher levels of these variables. For contralateral tumours, however, odds ratios for all levels of these exposure variables were below 1.0, except for glioma in the top decile of exposure (1.25, 95% CI 0.64–2.42). The odds ratio for the top decile of cumulative hours for glioma ipsilateral to reported phone use was 1.96 (95% CI 1.22–3.16).

The risks were not raised for regular use of analogue or digital phones, considered separately. Significantly raised risks were seen in the highest decile of cumulative call time for meningioma in digital phone users (OR 1.84, 95% CI 1.17–2.88) and glioma in analogue phone users (OR 1.95, 95% CI 1.08–3.54). There was no appreciable effect modification by age or sex for any of the above results.

Acoustic neuroma: Interphone Study Group, 2011

The Interphone study also investigated acoustic neuroma risks, based on 1105 cases and 2145 controls (Interphone Study Group, 2011). The methods were essentially as described above for glioma and meningioma. The participation rates were 82% for cases and 53% for controls. Less than 1% of case and control interviews were with proxies. In total, 16 otherwise eligible cases and 5513 otherwise eligible controls were not included in the analyses because of the use of post-hoc matching.

The odds ratio for acoustic neuroma with ever-regular use of a mobile phone was 0.85 (95% CI 0.69–1.04), and for ≥10 years after first use was 0.76 (95% CI 0.52–1.11). There was no trend of risk with time since first use, cumulative number of calls or cumulative call time. For cumulative call time, the highest odds ratio was for the tenth (highest use) decile of reported exposure (≥1640 hours) (1.32, 95% CI 0.88–1.97) and the lowest was for the ninth (ie adjacent) decile (0.48, 95% CI 0.30–0.78). In part, the increased risk in the top decile reflected implausible reported levels of use: 16 (1.4%) cases and 22 (1.0%) controls reported ≥5 hours average use per day, most of whom contributed to the ≥1640 cumulative hours category. The increased odds ratio in the tenth decile derived mainly from long-term (≥10 year) users (OR 1.93, 95% CI 1.10–3.38), but with greatly decreased risks in long-term users for intermediate-use categories (eg 0.39, 95% CI 0.20–0.74, for the penultimate category).

Overall odds ratios were not appreciably greater for reported ipsilateral than contralateral phone use, but were somewhat so for the top deciles of cumulative call time and cumulative number of calls. There was no trend in risk with cumulative call time or cumulative number of calls for reported ipsilateral use.

Analyses were also presented with the 5 years before the reference date censored. The pattern of results in these analyses, and the lack of trends, was similar to that with a 1-year lag, but with the odds ratio for regular use somewhat greater (0.95, 95% CI 0.77–1.77) and, in general, most odds ratios greater – greatest for the tenth decile of cumulative call time (2.79, 95% CI 1.51–5.16) and second decile of cumulative number of calls (2.32, 95% CI 1.39–3.87). The odds ratio for ≥10 years since first use was 0.83 (95% CI 0.52–1.19). These analyses need to be treated with some caution. On the one hand, the latent period for acoustic neuroma is likely to be several years, so an analysis censoring several recent years might be appropriate. On the other hand, the selection of these analyses for presentation may have been post-hoc – the same analyses were not presented for brain tumours in the Interphone study, even though the same argument in favour of them could be made for meningioma as for acoustic neuroma.

The Interphone data do not give any convincing evidence that acoustic neuroma is caused by use of mobile phones. There was a curious similarity, however, between the Interphone acoustic neuroma results and those for brain tumours, in the raised risk in the top decile of cumulative hours of use. This appears to have reflected, to some extent, excess reporting of implausible values for daily use by cases compared with controls but, in addition, it raises the possibility that the result may stem to some extent from the controls: in eight of the study centres, over 50% of the controls used in the acoustic neuroma analyses had been used also in the glioma and meningioma analyses, so if there were a shortfall in high cumulative users in these controls, by chance or by bias, it would have affected the results of analyses for each tumour type similarly. Whatever the reason, the lack of trend for cumulative use (and lowest odds ratio for the ninth decile) argues against an aetiological explanation.

Other studies

Sato et al (2011) performed a case–case study of acoustic neuroma including 787 cases from 22 hospitals throughout Japan that were willing to participate (51% of invited cases, representing approximately 7% of all cases in Japan) (see Table 8.5). Separate analyses were made using latency periods of either 1 year or 5 years, including only cases who were mobile phone users and with no tumour symptoms at the corresponding reference date. Analyses using a 1-year latency period included 180 cases who reported a preferred side of mobile phone use, and the corresponding analyses for a 5-year latency period included 150 cases. Regular mobile phone use until 1 year before diagnosis was associated with a risk estimate of 1.08 (95% CI 0.93–1.28), and until 5 years 1.14 (95% CI 0.96–1.40). An average duration of mobile phone use of >20 minutes per day was associated with a risk estimate of 2.74 (95% CI 1.18–7.85) for a 1-year latency period, and 3.08 (95% 1.47–7.41) for a 5-year latency period. Analyses of tumour size among cases with >20 minutes of mobile phone use per day indicated a possibility of detection bias, as tumours in cases with ipsilateral mobile phone use tended to be smaller than in subjects with contralateral phone use. No differences in tumour size were found among cases using a mobile phone ≤20 minutes per day. Furthermore, analyses of the distribution of left- and right-sided tumours indicated that recall bias might have affected retrospective reports of side of mobile phone use.

Aydin et al (2011) performed a case–control study of mobile phone use and childhood brain tumours, with data from Denmark, Norway, Sweden and Switzerland. It included all children aged 7–19 years diagnosed with a brain tumour during the period 2004–2008. Two matched controls per case were randomly selected from population registers, and information on mobile phone use and potential

TABLE 8.5 Case–case study of mobile phone use and risk of brain tumours

Study	Country	Tumour type	Number of cases	Age at diagnosis	Prevalence of ever-use	Odds ratios (95% CI) ever-use
Sato et al, 2011	Japan	Acoustic neuroma	180 (1-year latency) 150 (5-year latency)	All ages	Included only mobile phone users	1.08 (95% CI 0.93–1.28) 1.14 (95% CI 0.96–1.40)

confounding factors was collected through personal interviews with the child and at least one parent. For about one-third of the subjects, information was available from mobile phone operator records. In total, 352 cases (83% of those eligible) and 646 controls (71%) participated in the study. The odds ratio for regular mobile phone use (defined as at least once per week for a period of at least 6 months) was 1.36 (95% CI 0.92–2.02). There was no evidence of a dose-response pattern; the odds ratio for children who started to use a mobile phone more than 5 years prior to diagnosis was 1.26 (95% CI 0.70–2.28). The risk estimates were not higher in the areas of the brain that were closest to where the mobile phone was held, eg for ipsilateral tumours or in the temporal lobe.

In the small subsample for whom traffic records were available, the overall risk was not reported, but an increased risk was observed in the top quartile of time since first subscription (OR 2.15, 95% CI 1.07–4.29 for >2.8 years since first subscription), with a significant trend in risk with time since first subscription ($p = 0.001$). However, risk estimates did not increase with increasing cumulative duration of calls. The authors noted that the observed association in the small subgroup >2.8 years since first subscription was not compatible with the brain tumour incidence trends among children and adolescents overall in recent years, as there is no evidence that they have increased. The study had limited power. The other main limitation of the study is that the retrospectively self-reported amount and duration of past mobile phone use gave potential for both differential and non-differential exposure misclassification. Use of operator records to determine exposure is likely to have reduced non-differential exposure misclassification, although the incomplete and non-random availability of such data in the study is a concern. The raised odds ratio based on operator data for the longest time since first subscription is in the direction that would be expected if there were causality, but the evidence from the study overall is not consistent and does not give substantial evidence for causality.

8.3.2.2 Cohort studies

An update of the Danish cohort study from 2002 (Johansen et al, 2001) was published in 2006 (Schüz et al, 2006b) (Table 8.6). The cohort was described in detail in the last AGNIR review, and only a brief description is included here. The cohort consists of 420,095 people whose first mobile phone subscription was registered between 1982 and 1995. In the 2001 publication the cohort was followed from first date of subscription until the end of 1996, emigration or death, whichever occurred first; the update continued the follow-up through 2002. Incident cases of cancer were identified through linkage to the national Danish cancer registry. Standardised incidence ratios (SIR) were calculated comparing the cancer incidence in the cohort to that of the general Danish population controlling for sex, age in 5-year age groups and calendar period in 5-year periods. In the updated publication, members of the subscriber cohort were excluded from the calculation of national incidence rates.

TABLE 8.6 Cohort studies of mobile phone (ever) use and the risk of cancer

Study	Country	Number in cohort	Age (years)	Person-years of follow-up	Endpoint	Diagnosis	Number of cancer deaths/ cases	Standardised incidence ratio (95% CI), ever-use
Schüz et al, 2006b	Denmark	420,095	≥18	3,572,155	Incidence	All cancer	14,249	0.93 (0.92–0.95) male 1.03 (0.99–1.07) female
						Brain and NS	580	0.96 (0.87–1.05) male 1.03 (0.82–1.26) female
						Glioma	257	1.01 (0.89–1.14)
						Meningioma	68	0.86 (0.67–1.09)
						Nerve sheath tumours, cranial	32	0.73 (0.50–1.03)
						Nerve sheath other and unspecified	100	0.97 (0.79–1.18)

The overall cancer incidence in the cohort was slightly reduced among men (SIR 0.93, 95% CI 0.92–0.95), and close to unity among women (SIR 1.03, 95% CI 0.99–1.07). The reduced incidence in men was mainly attributed to smoking-related cancers; risk estimates for brain and nervous system tumours were close to unity for both men and women. Women had an increased risk of smoking-related cancers, driven by statistically significantly raised risks of cervical cancer and kidney cancer. No raised risks were indicated in analyses of glioma, meningioma and nerve sheath tumours separately. Analyses of different latency periods showed a slight reduction of the SIR for brain and nervous system tumours among people with <1 year since first mobile phone subscription, although this was not statistically significant. For 1–4 and 5–9 years since first subscription, risk estimates were close to unity, and for ≥10 years a significantly reduced SIR was reported (SIR 0.66, 95% CI 0.44–0.95).

Using subscriber lists to assess mobile phone use is subject to misclassification of the exposure. Most importantly, only private subscriptions could be linked to a specific person, which means that people with corporate subscriptions could not be included in the exposed cohort. Furthermore, the person having a subscription may not necessarily be the user of the mobile phone. This type of exposure misclassification would lead to a dilution of the risk estimates, should a true risk exist, but is not expected to lead to spurious increased or decreased risk estimates. Thus, exposure misclassification does not appear to explain the reduced risk for brain tumours associated with long-term mobile phone use. To assess the magnitude of the effect of exposure misclassification on the risk estimates, the controls from the Danish Interphone case–control study were matched to the cohort of subscribers to compare self-reported mobile phone use with operator records. Of the controls identified in the subscriber cohort, 61% reported that they used a mobile phone regularly (at least once per week over a period of 6 months or more). Of the controls that were not found in the subscriber cohort, only 16% reported regular mobile phone use. The cohort of mobile phone subscribers was established during a period when mobile phone use was still uncommon in the population. In total, there were 723,421 subscriptions in Denmark during 1982–1996. Of these, 200,507 were corporate subscriptions, constituting a little less than 5% of the population aged ≥18 years old in 1996 (www.dsk.dk). An additional 102,819 subscriptions could not be linked to a person. This means that approximately 7% of the comparison population were incorrectly classified as non-subscribers, ie as unexposed despite being exposed. When the exposure is uncommon, however, such exposure misclassification will affect the risk estimates only marginally. It is therefore unlikely that such misclassification can explain the lack of association between mobile phone use and brain tumour risk in this study. The subjects in the cohort were found to have an average annual income that was higher than in the general Danish population, and it has been discussed whether a so-called 'healthy mobile phone subscriber effect' could explain the reduced risk of brain and nervous system tumours, similar to the 'healthy worker effect' in studies of occupational exposures. The higher average socioeconomic status in the mobile phone subscriber cohort is likely to explain the difference in the lower incidence of smoking-related cancers, but for brain tumours there is little evidence for an association with socioeconomic status. If anything, there seem to be a higher brain tumour incidence in higher socioeconomic groups (Wigertz et al, 2010)

Schüz et al (2011a) extended follow-up of this cohort for acoustic neuroma to the end of 2006 (Table 8.7). They also gained data on the highest educational level attained, disposable income and marital status for the 'user' and 'non-user' cohorts, by matching to data on people aged >30 years in another, existing,

TABLE 8.7 Cohort studies of long-term mobile phone use and the risk of cancer

Study	Country	Number in cohort	Age (years)	Person years of follow-up	Endpoint	Diagnosis	Number of cancer deaths/ cases	Standardised incidence ratio (95% CI), long-term use
Frei et al, 2011	Denmark	358,403	≥30	3,763,322	Incidence	CNS tumour	846 89 (≥13 years) 6 (≥13 years)	 1.03 (0.83–1.27) male 0.91 (0.41–2.04) female
						Glioma	356 37 (≥13 years)	 0.98 (0.70–1.36) male
Schüz et al, 2011a	Denmark	2,883,665 (including non-subscribers)	≥30	22,884,931 462,430 (men, ≥11 years)	Incidence	Acoustic neuroma	806 15 (≥11 years)	(Whole population) 0.87 (0.52–1.46) male

Danish cohort study, enabling adjustment for potential confounding by socioeconomic status. Acoustic neuromas were ascertained from a clinical database at the main treatment centre in Denmark and from the national cancer registry.

A mobile phone subscription for ≥11 years was not related to an increased risk of acoustic neuroma in men (RR 0.87, 95% CI 0.52–1.46) or women (0 observed, 1.6 expected), after adjustment for the above socioeconomic variables. Because there were comparatively few female long-term subscribers, several of the remaining analyses were solely for men.

In total, 48% of acoustic neuromas in subscribers of each sex were right-sided, and the proportion was not greater in long-term male subscribers, whereas the authors, when analysing data from the Danish part of the Cosmos study (Schüz et al, 2011b), found that Danish mobile phone users tended to use their phones on the right rather than the left – 53% stated preferential right-sided use, 35% left and 13% no preference (Schüz et al, 2011a). The percentage of acoustic neuromas that were right-sided did not change over time (1999/2000 to 2005/2006) among long-term male users or among non-long-term users. The size of acoustic neuromas was not larger in male long-term users than in non-long-term users.

Frei et al (2011) updated the Danish cohort study with a follow-up of brain tumours (and of all cancers combined) to the end of 2007. As for acoustic neuroma, they collected information on educational level attained, disposable income and marital status. Incident cases of brain tumours and other cancers were identified through the Danish national cancer registry.

Being a mobile phone subscriber was not associated with a significantly raised risk of cancer overall or of central nervous system tumours, nor was subscription for ≥13 years associated with raised risks of these outcomes. The relative risk of central nervous system tumours in men for ≥13 years' subscription was 1.03 (95% CI 0.83–1.27, based on 89 exposed cases) and in women was 0.91 (95% CI 0.41–2.04, based on 6 exposed cases). The corresponding result for glioma in men was 0.98 (95% CI 0.70–1.36, based on 37 exposed cases); the number of women was too small for the corresponding analysis. For male subscribers for ≥10 years the relative risk for glioma was 1.04 (95% CI 0.85–1.26, 117 exposed cases), and for females 1.04 (95% CI 0.56–1.95, 10 exposed cases). The corresponding results for meningioma were a relative risk of 0.90 (95% CI 0.57–1.42) for men and 0.93 (95% CI 0.46–1.87) for women.

As discussed above, using subscriber lists to assess exposure will be subject to exposure misclassification. The most recent update of the Danish cohort study cannot be used to assess risk in short-term users, as a considerable proportion of the comparison population will also be short-term mobile phone users. Earlier updates of the cohort were suitable for studying the effects of short-term use, and the results did not indicate any risk increases. In this latest update, it is only the analysis of long-term mobile phone use that is informative, and where the proportion of misclassified people in the comparision population is still negligible. These findings do not indicate effects on brain tumour or acoustic neuroma risk after long-term mobile phone use.

8.3.2.3 Brain tumour incidence trends

Given the change in the prevalence of mobile phone use over the last two decades, from virtually none to near 100% in some age groups, an increase in brain tumour incidence would be expected to be evident in cancer registry data, should a substantial aetiological effect exist. Conversely, a lack of increase in the

incidence would constitute evidence against a substantive effect of mobile phone use on brain tumour risk. Studies of brain tumour incidence trends in the Nordic countries (1974–2003) (Deltour et al, 2009, 2010; Vrijheid et al, 2009a), the USA (1992–2006) (Inskip et al, 2010; Kohler et al, 2011) and the UK (1998–2007) (de Vocht et al, 2011) have not found an increase in brain tumour incidence that could be attributed to mobile phone use; time trends for brain tumours, or glioma when analysed separately, were flat, despite a large proportion of mobile phone users in these countries. Thus, the considerable risk increases after short durations of phone use reported in some of the analyses described above, notably certain results from Hardell and colleagues and from the Interphone study, are incompatible with the observed incidence trends. Similarly, incidence trends for acoustic neuroma in the UK (Nelson et al, 2006) and the Nordic countries (Larjavaara et al, 2011b) do not correspond to temporal trends of mobile phone use in the population.

Other factors could, of course, influence incidence trends but seem unlikely to have masked an effect of mobile phone use, if there were one. Decreases in the prevalence of other risk factors for brain tumours might in theory hide a putative increase due to mobile phones, but no factors are known that cause brain tumours and are of sufficient prevalence. It is implausible to postulate that there are highly prevalent unknown risk factors that could have exactly counterbalanced mobile-phone-related trends over long periods in several different countries. The development of new diagnostic techniques would tend to increase apparent incidence rather than the opposite. Introduction of computed tomography in the 1970s and magnetic resonance imaging in the mid-1980s can be seen as a slight upward trend until the middle of the 1980s (Inskip et al, 2010; Kohler et al, 2011). Changes of classification systems might appear as changes in registered incidence of specific diagnostic subcategories of brain tumours, but would not have affected incidence trends for broader categories such as glioma and meningioma. Completeness of cancer registration is a factor that may affect incidence rates. This is known to be a problem for benign tumours such as acoustic neuroma that tend to be under-reported (Howitz et al, 2000; Tos et al, 2004; Nelson et al, 2006), but is unlikely to have affected recent incidence trends for malignant tumours such as glioma, because completeness of registration, except in the elderly, has been high for many years. A validation study of the completeness of the Swedish cancer registry found under-reporting of all nervous system tumours combined (including benign tumours) in the elderly (>70 years), but 94.5% completeness for people younger than 70 years at diagnosis (Barlow et al, 2009). The Finnish cancer registry reported a completeness of 98.6% for malignant central nervous system tumours (Teppo et al, 1994).

Deltour and colleagues estimated the probabilities of detecting different levels of putative increased risks of glioma from mobile phone use in population data on glioma incidence trends (Deltour et al, 2011), based on incidence data from the Nordic countries from 1979 to 2008. Increased relative risks of 1.2 after a maximum induction period of 5 years, 1.5 after a maximum of 10 years and 2.0 after a maximum of 15 years would be detected in incidence trends with 100% probability. For heavy use (1640 cumulative hours of use) with an induction period of 1 year, corresponding to the top decile category analyses in the Interphone study, an increased risk of 2.0 would be detected with 100% probability, and a risk increase of 1.5 with 98% probability.

In order to conduct ecological studies well, information is required on trends in mobile phone use in different subgroups of the population – for instance, by age and sex. Currently, however, data are only

available for national populations overall. It is possible to extract from existing case–control studies information about controls' reported past use of mobile phones, but such data will be affected by possible selection bias from non-participation related to phone use, as well as exposure misclassification. Data from mobile phone companies on past usage patterns would therefore be very valuable.

8.3.2.4 Discussion

The epidemiological results on the risk of brain tumours and acoustic neuromas in relation to mobile phone use differ between the studies by Hardell and colleagues, which find raised risks, very substantially so in some subsets of the data, and those by all other investigators, that in general find decreased risks. The Hardell group has published multiple re-analyses, and pooled analyses, of different combinations of their own data so that there is far less evidence from this group than might appear from the number of papers and analyses. It is unusual to conduct so many re-analyses of the same dataset and this gives rise to a potential for apparently raised risks to be found as a consequence of multiple testing.

There are no clear methodological reasons for the differences between the results of Hardell and colleagues and those of the remainder of investigators, but subtle aspects of the methods of data collection and analysis, not assertainable from the published reports, may be the reason for these differences (Ahlbom et al, 2009). To be reliable, epidemiological results need to be replicated by other investigators and, in this instance, the similar results of all investigators except the Hardell group, with no methodological inferiorities in these other investigators' studies overall, suggest that the results of the Hardell group are the problematic ones.

Many studies report reduced risk estimates associated with mobile phone use, most notably in the Interphone studies, but also in earlier studies with both case–control and cohort designs (Muscat et al, 2000; Inskip et al, 2001; Schüz et al, 2006b). One likely explanation for at least part of the risk reduction in case–control studies is selection bias caused by non-response. The Interphone study investigators conducted a study among non-responders to assess the potential magnitude of the effect on the risk estimates caused by such selection bias (Vrijheid et al, 2009b). Among refusals who agreed to answer a short non-responder questionnaire, 50% of cases and 56% of controls were mobile phone users, compared with 66% of cases and 69% of controls among the original participants. Thus, regular mobile phone use was related to the likelihood of participation among both cases and controls. As refusal was more common among controls than among cases, it was estimated that this would lead to a downward bias in the risk estimates by 5–15%.

An appendix to the main Interphone study discusses a method to adjust for selection bias, where the analyses are restricted to regular mobile phone users, ie a post-hoc shifting of the reference category from non-regular mobile phone use to the lowest category of mobile phone use, while excluding non-regular users. This analysis is based on the assumption that selection bias is the only or predominant reason for the reduced risk estimates in users, and that this bias is less or none between different categories of user. If this assumption is incorrect, however, new bias may be introduced and any gain in validity is questionable, because the odds ratios can be distorted in any direction, and the results will be difficult or impossible to interpret. There are, indeed, several reasons to believe that selection bias is not the only cause of the reduced risks. Risk estimates for glioma in the lowest exposure categories are

considerably lower than those for meningioma, and far below what would be expected by selection bias alone. Selection bias caused by non-participation among controls would be expected to affect glioma and meningioma results in a similar way. Another potential explanation for some of the risk reduction is prodromal symptoms, which could make cases less likely to start a new habit close in time to their brain tumour diagnosis, ie reversed causality. If this is the case, restriction to regular users only would introduce an upward bias of the risk estimates. The results when restricted to regular users show a statistically significant increased risk of glioma within less than 5 years of mobile phone use (OR 1.68, 95% CI 1.16–2.41), but reduced risks for meningioma persist also after this adjustment. It is highly implausible that mobile phone use would increase the risk of glioma after such a short latency period, and at the same time protect against meningioma. Most importantly, an increased risk after such a short induction period would, in the light of the widespread mobile phone use during the last decade, result in an increase in brain tumour incidence. There is no evidence of increasing brain tumour incidence trends since the introduction of mobile phones (see Section 8.3.2.2), which speaks strongly against the validity of analyses restricted to regular mobile phone users.

For acoustic neuroma, a second form of selection bias might have affected the results. Hearing difficulties during phone use might accelerate diagnosis, leading to artefactually raised odds ratios for users.

Dose-response

One of the classic criteria to judge whether relationships of exposures to outcomes in epidemiological studies represent aetiological effects is the presence or absence of a dose-response effect (Hill, 1965), ie that if a relationship is truly aetiological then, in general, higher doses would be expected to be associated with greater risks. With the exception of some results from studies by the Hardell group, which are outliers from the rest of the literature and uncorroborated by other investigators, the studies have not shown such a gradient. In particular, the results of the largest study, the Interphone combined analyses, show no convincing evidence of a dose-response: for each of glioma, meningioma and acoustic neuroma, for the lower nine of ten deciles of cumulative hours of use the odds ratios were below or close to unity, and for the top decile the odds ratio was modestly above unity; for cumulative number of calls, no odds ratios in the top five exposure deciles were above unity; and for glioma and to a lesser extent acoustic neuroma the top decile of cumulative hours was driven, at least in part, by clearly implausible reports of hours of use per day, more often in cases than controls, ie probable reporting bias.

Duration-response and time since first use

In principle, an aetiological interpretation of an epidemiological association is supported by the presence of a duration-response effect, ie that exposure over a longer period is associated with greater risk. The studies on mobile phone use and brain tumours do not show such an effect, and in particular this is true of the Interphone study – the largest study, with the greatest power to examine longer durations of use.

Examination of risks by time since first use of mobile phones gives evidence on a different aspect of aetiology, the lag period between exposure and tumour manifestation, although in practice because few users discontinue use after they have started, the results of the two analyses tend to be similar. Raised risks have not generally been found in the longest duration examined – in the Interphone study ≥10 years (in practice, largely 10–14 years). This suggests that aetiological effects do not occur within approximately 10–14 years. Given the lack of a biological model for a carcinogenic effect of RF field exposure on cancer

aetiology, and the lack of epidemiological evidence for such an effect, there is uncertainty as to what lag period would be appropriate to be investigated. On the one hand, it has been argued that as RF field exposure does not damage DNA, it cannot initiate cancer, and therefore that if there is an effect it would be on cancer promotion, and hence relatively rapid, within a few years. On the other hand, it could be argued that given an unknown mechanism, the lag period is necessarily unknown, and that for tumours with a long latency (meningiomas and acoustic neuromas, but not many gliomas), effects might not be manifest for many years. At present, the epidemiological data suggest that there is not a material effect within approximately 10 years from first use, from levels and types of RF field exposure so far experienced. The more-limited data for longer periods do not indicate an effect, but are weaker evidence.

Laterality, anatomical location and lobe

In principle, since RF fields are greatly attenuated by passage through brain tissue (see Chapter 2), if there is an aetiological effect of RF field exposure from mobile phones it should easily be detectable by a raised risk ipsilateral to the side of phone use in people who are unilateral users. In a cohort study this could provide a powerful analysis, as reporting of the side of use would not be biased by the presence of a subsequent tumour. Unfortunately, however, in recall-based case–control studies, which are the only data available on laterality, potential recall bias makes laterality data extraordinarily difficult to interpret: if the relative risk is raised for reportedly unilateral use and symmetrically diminished for reportedly contralateral use, with an overall relative risk of about unity, then reporting bias is the likely explanation, since there is no other plausible reason for the diminished contralateral risk and no overall evidence of aetiology. If the overall risk is raised, however, then greater risk ipsilateral than contralateral is compatible with aetiology, but also compatible with reporting bias, whereas if contralateral and ipsilateral risks are similar, this would argue against aetiology.

Most studies that have investigated risk by laterality have found greater risks ipsilateral than contralateral to phone use, and in the Interphone study, where it was investigated in some detail, this applied for glioma and meningioma to virtually all categories of time since first use, cumulative hours of use and cumulative numbers of calls, with no consistent tendency for ipsilateral/contralateral ratios to be greater with higher and longer categories of exposure – the data therefore suggest considerable reporting bias, and leave open, but give no consistent support to, the possibility of an additional aetiological component. For acoustic neuroma, ipsilateral risk (in the comparable analyses to those for glioma and meningioma) was not raised overall, and was only raised in the top categories of time since first use, cumulative number of calls and cumulative hours of use, but with no dose- or duration-response effects for these variables.

A second anatomical aspect of the tumours could give evidence on potential aetiology. Because of the rapid attenuation of RF fields as they pass through brain tissue, a real aetiological effect should raise the risk of tumours at sites close to the phone antenna rather than those distant. The Interphone study collected information from neuroradiology on the exact location of brain tumours, to enable such analyses. Using this information, analyses have been published from Japan and Finland, and two pooled analyses of separate subsets of Interphone study centres have been published. None of these gave any clear evidence of a relation.

A cruder version of the same principle has been to conduct analyses of mobile-phone-related risk by lobe of the tumour. These analyses are complicated by lack of agreement, and clarity, on which lobes

are the most exposed: different papers have analysed different combinations of lobes that they deemed to be most exposed. For instance, Hardell et al in 1999 analysed tumours in the temporal, occipital and temporoparietal lobes, grouped together, as the most highly exposed lobes, but in 2002 the same group analysed temporal tumours as the most exposed. Overall, the literature does not suggest consistently greater risks of brain tumours in relation to phone use in any particular lobe.

Type of signal

Average output powers from analogue phones are higher than those from digital phones, as they have higher specified powers and do not have adaptive power control. Higher risk estimates for brain tumours would therefore be expected for use of analogue phones, should a true causal effect exist. There are, however, also other differences, eg that digital phones, such as GSM phones, use pulsed signals. For these reasons, studies have sometimes presented the results of analogue and digital phones separately, in addition to overall analyses. Hardell and colleagues presented all analyses stratified on type of phone, with no overall analyses, except in a few later re-analyses of their data. As analogue phones were introduced in the 1980s, and digital phones at the beginning of the 1990s, the majority of long-term use is of analogue phones. It is therefore not possible to clearly distinguish a potential effect of analogue phone use from that of long-term phone use. There is also a considerable overlap in the type of phones that people have used; the majority of analogue phone users have later started to use a digital phone. Cordless phone use was included in only a few studies: all of the Hardell group's studies and two of the national Interphone studies. The average output power levels from cordless phones are considerably lower than those from analogue and digital mobile phones and, thus, a potential effect on brain tumour risk would be expected to be higher from use of mobile phones than from cordless phones. So far, only the Hardell group has reported increased risks of brain tumours associated with cordless phone use. None of the Interphone studies found any associations with cordless phone use. Overall, there are no consistent differences in risk estimates that can be attributed to the type of mobile phone signals.

8.3.2.5 Summary

The number of epidemiological studies on mobile phone use and the risk of brain tumours and acoustic neuroma has increased considerably since the previous AGNIR report on RF fields in 2003. Overall, the evidence from the new studies combined with the previous evidence does not demonstrate a raised risk of brain tumours or acoustic neuroma within 15 years of mobile phone use. Data on longer latencies and long-term or heavy use are, however, still limited.

Methodological problems were identified in relation to both case–control studies using self-reported exposure information and cohort studies based on subscriber data. Recall bias could lead to overestimated risks or even spurious effects, non-differential exposure misclassification could dilute risk estimates should an effect exist, and selection bias in case–control studies could lead toward artefactually reduced risk estimates. These problems add uncertainty to interpretation of the results.

Data from cohort studies and examination of cancer incidence trends in various Western countries give no indication of raised risks in relation to mobile phone use. Data on secular trends in phone use are only available for national populations overall, not subdivided by demographic variables, however.

In conclusion, despite methodological shortcomings, the available data do not suggest a causal association between mobile phone use and fast-growing tumours such as malignant glioma in adults. For slow-growing tumours such as meningioma and acoustic neuroma, and for long-term users, ie more than around 15 years, the absence of association reported thus far is less conclusive because the current observation period is still relatively short. In addition, there is currently only one study available on brain tumour risk in children and adolescents, which has inconclusive results.

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9 Conclusions

9.1 Exposures, Interaction Mechanisms, Dosimetry and Sources

Exposure of the general public from low level man-made radiofrequency (RF) electromagnetic radiation is now essentially universal, arising from a wide range of devices operating over a range of frequencies and signal characteristics. Sources are used for communications, medical diagnosis, treatment and surgery, and a wide range of industrial applications. The widespread introduction of RF devices for public use has resulted in a general increase in the average exposure of the general public above natural background levels. Nevertheless, exposures remain below internationally accepted guideline levels.

Modern communications protocols use power control and spectral efficiency methods to reduce interference between devices using the same frequency channels at distant locations, and also to maintain battery life. As a result, the trend in instantaneous exposure to a member of the public from mobile communications devices will probably be downward. Short-range wireless local area networks are being established in homes, public places and educational institutions. The personal exposure from the associated group of sources is expected to be very low, but generalisations are very difficult, depending on locations and synchronisation of the aerials and their emissions.

Standard computational models for dosimetry are now available for adults, but have been shown to be inadequate for age-dependent studies, and for fetal dosimetry. New models, together with improved measurements of dielectric properties, are improving knowledge in this area.

Mild, localised hyperthermia is the most likely mechanism for any biological response. Whilst many new modulation and pulsing methods are being introduced, it is extremely unlikely that demodulation of the carrier frequency, under such conditions, causes any independent biological response.

Industrial procedures, including sputtering, welding and induction heating are well established, of which RF dielectric heating gives rise to the highest occupational exposures. In a medical context, the operators of both surgical and medical diathermy devices may be exposed to high levels of RF fields. For individual members of the general public, by far the highest single-event exposures to RF fields arise during medical applications, including those associated with surgical diathermy, medical diathermy and magnetic resonance imaging.

For overall, long-term exposure of the general public, mobile phone handsets are not only highly prevalent, but they also produce the highest exposures encountered during everyday life, primarily of cranial tissues. Public exposure levels from other man-made sources such as Wi-Fi and monitoring equipment, and other digital communications devices including radio and TV masts and microwave link antennas, are considerably lower than those from mobile phone handsets.

9.2 Cellular Studies

There are now several hundred studies in the published literature that have looked for effects on isolated cells or their components when exposed to RF fields. None has provided robust evidence for an effect. Furthermore, where reported effects were investigated by independent replications the effects were not found. The evidence for a direct or indirect genotoxic effect is unconvincing, as is the possibility of synergistic effects with known carcinogens. The apparent effect on stress proteins described in the previous review by AGNIR in 2003 has not been replicated in most of the newer studies. The reported direct effects of RF fields on cell membranes and isolated proteins, although interesting, lack independent verification and therefore should be interpreted with caution.

In general, the reported effects are small, often close to the lower limits of detection. Research into the biological effects of RF field exposure suffers from too many poorly designed and inadequately controlled experiments. These can lead to false positives which tend to be published because of the publication bias for positives in the scientific literature. At present there is no known pattern of exposure conditions that has been shown consistently to cause a biological effect from exposures below guideline levels.

9.3 Animal Studies

Many new studies have been published since 2003 and these have employed a wide range of biological models, exposure levels and signal modulations. The most reliable effects remain associated with exposures that result in marked elevations in whole-body temperature. There is no clear evidence of harmful effects with low level exposures, although some studies have continued to report subtle biological changes, often following single, acute exposures. It is noteworthy that several large-scale studies investigating the initiation and development of cancer have all been robustly negative, and a lack of effect has been seen regarding effects on auditory function.

Studies investigating effects on the brain and nervous system in adults have not produced consistent evidence of weak-field effects. In particular, recent studies do not indicate that low level exposures are associated with changes in gene expression or in altered permeability of the blood-brain barrier. Two well-performed studies, one in juvenile rats and one in aged mice, have reported that improvements in learning and memory may occur following exposure to mobile phone signals, but these studies are as yet unreplicated.

9.4 Neurocognitive Effects in Humans

Studies of cognitive function and human performance measures do not suggest acute effects of RF field exposure from mobile phones and base stations.

Neurophysiological studies of brain function are inconsistent. The methods and sample sizes in some recent studies have improved, compared with those considered in the previous AGNIR review. Four of six recent studies using vascular and metabolic measures suggest possible effects of RF fields on brain function. However, only one involved a large sample size, and the actual RF field exposures were unclear.

EEG studies have also produced mixed results. Small increases in alpha-band EEG power have been reported during or after exposure. However, the effects are small and inconsistent between studies, so the reliability and biological significance of these findings still remain unclear. Further research in large representative samples, and in independent laboratories, would be required before this evidence can be considered convincing.

Existing studies of cognitive and neurophysiological effects in children do not support the hypothesis that they are any more susceptible to RF field effects than adults. However, these studies have been few in number, and most have used small sample sizes. There is still insufficient good quality evidence to draw strong conclusions about potential effects of RF fields in children.

9.5 Symptoms in Humans

Since the 2003 AGNIR report, a substantial amount of research has explored the potential link between exposure to RF fields and symptoms. The overall evidence from the numerous experimental studies that have been conducted suggests that no causal link exists for short-term exposures. These studies also suggest that people are unable to detect the presence of RF fields. These findings apply to both healthy participants and to people who report being sensitive to various types of electromagnetic field. This does not undermine the importance of the symptoms that are experienced, but it does suggest that causes other than those related to RF fields should be considered.

With regard to RF field exposures over the longer term, early observational studies concerning the effects of RF fields from mobile phone handsets or base stations suffered from several methodological flaws which limit the conclusions that can be drawn from them. In particular, assessing exposure through self-report or based on objective distance from a local base station is problematic, while confounding variables may account for many of the associations that were observed. More recent studies employing personal exposure meters offer many advantages over this work and have typically demonstrated no association between exposure and symptom presence, although a possible association with behavioural disorders in children is of note, but as yet unreplicated. At present, insufficient good quality evidence is available to draw conclusions as to the role of long-term exposure to RF fields in causing symptoms.

9.6 Other (Non-cancer) Effects in Humans

Few studies of potential effects of parental RF field exposure on reproductive outcomes have been published since the previous AGNIR report. The evidence on the effect of RF fields on sperm quality is weak; however, some suggestive positive results, although not very convincing, give justification for further studies with improved methods. The evidence on effects on male subfertility and on female sexual function and fertility is very limited, and allows no conclusions. Effects on spontaneous abortions have been addressed in four studies: neither the one positive finding, nor the three negative ones, give convincing evidence because of methodological limitations in study designs. Studies of the risk of congenital malformations associated with parental RF field exposure have similar limitations, and the few positive findings need to be re-examined in studies with independent exposure assessment and sufficient

statistical power. Similarly, the retrospective assessment of exposure status in the two positive studies relating to prenatal exposure and child development limit the conclusions that can be drawn from them.

Human studies on the effects of RF field exposure on cardiovascular function, although limited in number, have provided no substantial evidence of adverse health effects. Overall, since 2003 there is no new evidence from human exposure studies that indicates any other non-cancer morbidity resulting from RF field exposure below current guideline levels. It should be noted that research in this area remains quite limited and, in particular, there is a lack of research evidence available regarding RF field exposure in children.

9.7 Cancer in Humans

Compared with the AGNIR review in 2003, a great deal more epidemiological evidence is now available. The studies of occupational exposure to RF fields, and those of residence near radio and TV transmitters, do not indicate that RF field exposure from these sources causes cancer. However, these studies have considerable weaknesses, particularly in exposure assessment, such that they do not give strong evidence against such a possibility. The overall results of epidemiological studies to date do not demonstrate that the use of mobile phones causes brain tumours or any other type of malignancy, nor do they suggest that causation is likely. They give considerable evidence against a material causal effect on brain tumour risk within 10 years since first use, and to a lesser extent within 15 years, but give far less information about longer periods. There is very limited information on risks of childhood tumours.

As mobile phone use has proved very difficult to measure retrospectively in recall-based studies, and has become ubiquitous over a relatively short period of time, considerable weight needs to be given to evidence from national brain tumour incidence trends. So far, these give no indication of any risk, but continued surveillance of them is not difficult and would be valuable.

10 Research Recommendations

10.1 Exposures, Interaction Mechanisms, Dosimetry and Sources

Emphasis should be placed on studies into the characteristics, exposures and dosimetry associated with new and emerging radiofrequency (RF) technologies, especially those to which the public are likely to be exposed, such as smart meters and airport security scanners. The detailed exposure characteristics associated with each existing and new mobile phone operating protocol should be quantified, by direct measurement if necessary, including operation specifically during missed calls and standby mode. In experimental studies any real device used as an exposure source should be fully characterised, including the quantification of associated SAR distributions.

Surveys should be carried out on the personal exposure of occupationally exposed personnel, including specific groups, such as those operating surgical diathermy units, who may necessarily be exposed to high levels of RF fields. Quantitative surveys should be carried out of exposure to members of the public, for public information and to provide guidance for epidemiological studies. Where appropriate, epidemiological studies should be accompanied by dosimetric assessment of the sources used. Age-dependent methods for computational dosimetry should be further developed, with specific emphasis on fetal and child exposure.

10.2 Cellular Studies

Despite the increase in the number of reported studies, there is still no cellular model that can be consistently shown to respond to exposure to RF fields and hence there is still a need for a robust cellular model that can be transferred between independent laboratories. Until this need is met there will always be doubts that any reported effects are real.

Studies on possible synergistic effects of RF fields combined with known stressors, either physical or chemical agents, would benefit from further experimentation to clarify if these present a potential hazard. Further research is also required into the effect of RF field exposure on cell membranes and protein structure; more studies are needed to establish if the reported effects are real.

10.3 Animal Studies

Further studies investigating the genotoxic or carcinogenic potential of RF fields are not considered a priority at this time. The available data strongly suggest that RF fields neither cause adverse effects on DNA integrity nor increase the likelihood of any type of tumour. Nevertheless, this recommendation should be considered again following publication of the results of the large-scale US National Toxicology Program project that is currently underway (http://ntp.niehs.nih.gov).

Although most studies investigating neurobehavioural changes in adult animals have not produced consistent evidence of weak-field effects, a few studies have produced positive and potentially important results. One such study used a transgenic mouse model of Alzheimer's disease and reported significant improvements in learning following long-term exposure, in both transgenic and non-transgenic animals. Another study suggested that the behavioural impairments caused by exposure to microwaves in rats were blocked by simultaneous exposure to a temporally incoherent magnetic field. The suggestion that repeated low level exposure to a RF field could protect against and ameliorate age-related declines in behaviour in both normal and transgenic animals is particularly intriguing; both of these suggestions merit independent replication using well-characterised exposure systems incorporating detailed dosimetry.

Few studies have yet investigated the effects of exposure of young or immature animals to RF fields on the development of the brain and nervous system, but one study has reported that medium-term exposure of juvenile animals may significantly improve performance of a behavioural task. Therefore, additional studies investigating the immediate and late consequences of acute and repeated exposure of very young and juvenile animals on behaviour are recommended. These studies should include well-controlled, head-only exposures using mobile-phone-like signals and a wide battery of behavioural tasks.

10.4 Neurocognitive Effects in Humans

The evidence continues to suggest that exposure to RF fields from mobile phones does not cause cognitive effects. Therefore, studies of cognitive performance are not a research priority.

Some studies have reported small effects of RF fields on EEG and other markers of brain function. However, the consistency between these results is still limited, and they do not yet form a convincing body of evidence. More research is therefore required in this area. Future studies should be based on adequate sample sizes, agreed exposure and analysis protocols, and replication in independent laboratories. Future research should also consider whether any effects of RF fields on neural function are relevant for health.

Finally, there is still a lack of research on possible effects of RF fields on neural function in children. Provocation studies in children remain a priority.

10.5 Symptoms in Humans

A substantial number of good quality experiments have now tested whether short-term exposure to RF fields can trigger acute symptoms. Given the consistency of their findings, further studies using this approach are not a high priority.

Additional studies are required to clarify the association between long-term exposure to RF fields and the onset of behavioural problems among children or of symptoms. Future research on this would benefit from using personal exposure meters, a longitudinal design and a large sample size. In practice, studies using these features are likely to be costly and difficult to perform. Nonetheless, they would offer substantial benefits in comparison to previous observational studies in this area, many of which have been of poor quality.

10.6 Other (Non-cancer) Effects in Humans

Investigations currently available on male reproductive function are of insufficient quality. AGNIR would only favour conducting further studies in this area if a study design could be put forward that overcame the potential selection bias in available investigations, and with independent exposure assessment.

Prospective studies would be of benefit in clarifying the association between prenatal exposure to RF fields and the development of behavioural problems among children.

Although there is insufficient justification to undertake cohort studies solely to investigate the risks of non-cancer chronic diseases in relation to RF field exposures, it is desirable that, where cohort studies of occupationally highly exposed groups or of phone users are undertaken, they should include, where possible, cause-specific mortality and measures of morbidity, such as hospital admissions, in their outcomes investigated.

10.7 Cancer in Humans

The most pressing deficiencies in reaching firmer conclusions about cancer risk in relation to RF field exposure are the lack of information on brain tumour and acoustic neuroma risks after 15 or more years of mobile phone use, as well as the risks of brain tumours after childhood exposures.

Further case–control studies based on recall of mobile phone use are unlikely to be decisive in resolving the current uncertainties because they will suffer from the same potential problems of recall bias and misclassification that afflict the published studies. These should not therefore be a priority.

Studies of highly exposed occupational groups would be of considerable interest provided that they have good exposure assessment.

Very low exposure levels and great difficulties in valid exposure assessment leave it unlikely that studies of risks in relation to environmental exposures (eg from broadcasting and phone masts) will substantially contribute to discovering whether RF field exposure is carcinogenic.

Cohort studies of phone use have considerable potential to illuminate assessment of carcinogenicity. Future follow-up of existing cohort studies would be of interest, but cohort studies would need to combine high quality exposure assessment with very large size, an extremely difficult combination. They will also take many years of follow-up to reach persuasive conclusions. An advantage of cohort studies, however, is that they could also allow follow-up of other outcomes as well as cancer.

Monitoring of secular trends in incidence of brain tumours from good quality population-based cancer registries is both relatively inexpensive and likely to be informative within the next few years. Trends should if possible be analysed by histological type and anatomical location. In the UK specifically, it would be desirable to conduct a study of brain tumour incidence trends by age and sex (and, if possible, also by region, histological type and anatomical location) in relation to phone use trends in the country. To maximise the insight that can be gained from this, data would need to be obtained from the telephone companies on trends in mobile phone use by age, sex and region.

Appendix A
Wi-Fi in Schools: Results of an HPA Study

The aim of the study was to investigate the types of Wi-Fi equipment used by children in schools in the UK and assess the exposure of pupils to the RF fields associated with such devices.

The study involved the assessment of the electric field strengths and the radiated powers around a selection of laptops and access points, representing the most popular Wi-Fi equipment used in UK schools (Peyman et al, 2011). Dosimetric modelling techniques were also used to assess the localised specific energy absorption rates (SARs) in models of adults and children (Findlay and Dimbylow, 2010). Finally, data on the proportion of the time for which devices transmit during typical school lessons were acquired in real classrooms (Khalid et al, 2011).

The exposures were assessed in the context of guidelines of the International Commission on Non-Ionizing Radiation Protection (ICNIRP) (see Appendix B). For the general public, ICNIRP advises a basic restriction of 0.08 W kg^{-1} for whole-body SAR, to be averaged over 6 minutes. The corresponding reference level in terms of equivalent wave power density is 10 W m^{-2}. Where low power radio transmitters are used near to the body, the localised SAR in the head and trunk should not exceed 2 W kg^{-1}, which involves an averaging mass of 10 g and an averaging time of 6 minutes.

The results from the three elements of the study are summarised below.

A1 Electric Field Strengths around Selected Wi-Fi Devices during Transmission and Calculated Radiated Powers

In total, 15 laptops and 12 access points were investigated under controlled conditions in a laboratory (Peyman et al, 2011). There are different manufacturers producing WLAN equipment and there are several different technical standards to which equipment can be designed. The devices selected in this study operated with an equivalent isotropically radiated power limited by emission standards to 100 mW in the 2.4 GHz band, 200 mW in Band A (5.15–5.35 GHz) and 1000 mW in Band B (5.470–5.725 GHz).

The electric field strength measurements were performed around the devices using a Seibersdorf Precision Conical Dipole (PCD) 8250 broadband antenna and a Q-par Angus QSH12N10S horn antenna to cover the 2.4 and 5 GHz bands, respectively. The laptops were connected to transmit through access points and the measurements were made in an anechoic chamber in the far-field region with respect to the devices under test. A manual positioning system was constructed which enabled the devices to be rotated in two orthogonal planes and sampling of the radiation pattern at any angle. Where the maximum field strength was encountered, additional measurements were performed as a function of distance from the device.

As the emissions produced during normal tasks such as streaming of video over Wi-Fi were found to be too irregular and gave too low a duty factor, LanTraffic, commercially available WLAN traffic generator software, was used to maintain a constant flow of data. An Agilent N9020A MXA signal analyser was used to monitor the traffic between the device under test and the WLAN receiving device. The signal analyser enabled the direct measurement of Wi-Fi burst power irrespective of duty factor (the proportion of time for which a device transmits). A protocol was developed for measuring the Wi-Fi equipment emissions and software was written to control the signal analyser and capture the measured emission data. Pilot measurements were made to refine the measurement protocol and data analysis methods were developed.

Preliminary measurements showed that for a given position, the field strength around laptops fluctuated between two (and sometimes three) distinct levels. This is because of switched diversity, the process of rapid switching of the signal between multiple transmitting antennas within each laptop, which is used to counteract fading. It was possible to distinguish the emissions from the various antennas using the signal analyser.

The spherically integrated radiated power for laptops ranged from 5–17 mW in the 2.4 GHz band and from 1–16 mW in the 5 GHz band (Table A1). For access points, the hemispherically integrated powers ranged from 3–28 mW at 2.4 GHz and from 3–29 mW at 5 GHz. However, given that some of the access points had symmetrical structures with regard to the unmeasured hemisphere, it might be reasonable to assume that these devices had total powers that were double the hemispherically measured powers. Thus, while the maximum radiated powers from access points are greater than those from laptops, the variation in the values is large and it is difficult to generalise.

The maximum power density values for the laptops and access points at 0.5 m were 22 and 87 mW m^{-2}, respectively, decreasing to 4 and 18 mW m^{-2} at 1 m distance. Consistent with the low radiated powers, these power density values are well below the ICNIRP reference level of 10 W m^{-2}.

A2 Modelling Wi-Fi Equipment used by Children, to Predict the SAR of Energy in the Body

As the SAR cannot easily be measured in humans and because it is difficult to measure power densities very close to transmitting antennas, computer modelling was used to assess the localised SARs arising from Wi-Fi equipment in models of adults and children (Findlay and Dimbylow, 2010). In order to assess compliance with exposure guidelines, localised and whole-body SAR values were calculated in a 10 year old sitting voxel model from exposure to electromagnetic fields at 2.4 and 5 GHz. Both plane wave exposures of the model and exposures from antennas in the near field were investigated for a variety of exposure conditions.

Using a sitting voxel model of a 10 year old child, and considering an exposure scenario of a Wi-Fi device operating at 2.4 GHz with an output power of 100 mW and a duty factor of one (ie the device is transmitting continuously), the highest localised SAR values in the head and torso were calculated as 5.7 and 14.4 mW kg^{-1}, respectively. These values are substantially lower than the limit of 2 W kg^{-1} basic restriction advised by the ICNIRP for the general public. Moreover, the reported SAR value in the head represents less than 1% of the SAR previously calculated in the head for a typical mobile phone exposure condition.

TABLE A1 Spherically integrated radiated power for all Wi-Fi devices under test (Peyman et al, 2011)

		Spherically integrated radiated power (mW)	
Device	**ID**	**IEEE 802.11g/b standard (2.4 GHz)**	**IEEE 802.1a standard (5 GHz)**
Laptops	LT01	9	–
	LT02	17	–
	LT03	15	–
	LT04	12	9
	LT05	5	4
	LT06	11	–
	LT07	11	16
	LT08	9	5
	LT09	16	1
	LT10	10	6
	LT11	9	13
	LT12	15	–
	LT13	8	–
	LT14	11	4
	LT15	8	–
Access points	AP01	20	–
	AP02	24	9
	AP03	28	29
	AP04	8	–
	AP05	6	–
	AP06	5	–
	AP07	12	29
	AP08	9	–
	AP09	3	3
	AP10	10	25
	AP12	14	7
	AP13	8	–

A3 Proportion of Time for which Individual Wi-Fi Computers Transmit during Typical School Lessons

A series of school visits was arranged to assess the proportion of time for which individual Wi-Fi computers transmitted during typical school lessons. A small convenience sample of six primary and secondary schools was visited to make measurements during classroom lessons. Two methods were employed: the first using a Wi-Fi packet capture system, which allowed all network wireless communications to be examined on a packet-by-packet basis, and the second using specially designed transmit time accumulator counter devices attached to the laptops. For the 146 individual laptops investigated, the

range of duty factors was from 0.02–0.91%, with a mean of 0.08% (standard deviation, SD, of 0.10%). The duty factors of access points from seven networks ranged from 1.0–11.7% with a mean of 4.79% (SD 3.76%). Data gathered with transmit time measuring devices attached to the laptops showed similar results. Within the present limited sample, the ranges of duty factors from laptops and access points were found to be broadly similar for primary and secondary schools.

Applying these duty factors to the computer modeling results above, the maximum time-averaged power density from a laptop at 2.4 GHz would be 220 $\mu W\ m^{-2}$, at a distance of 0.5 m, and the peak localised SAR predicted in the torso region of a 10 year old child model, at 34 cm from the antenna, would be 80 $\mu W\ kg^{-1}$.

Under a pessimistic scenario assuming a classroom with 30 laptops and an access point emitting maximal power densities at a distance of 0.5 m and operating with maximal duty factors, personal exposure in the classroom could reach 16.6 $mW\ m^{-2}$, compared to the ICNIRP international guideline reference level of 10 $W\ m^{-2}$.

A4 References

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Appendix B
ICNIRP Exposure Guidelines

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) developed guidelines in 1998 for limiting exposure to time-varying electric, magnetic and electromagnetic fields up to 300 GHz (ICNIRP, 1998). The guidelines are intended to provide protection against known adverse health effects, and various studies of exposed human populations, biological studies and the dosimetry of electric and magnetic fields were considered in establishing the advised restriction. New guidelines were published in 2010 for limiting exposure in the range from 1 Hz to 100 kHz (ICNIRP, 2010). A comprehensive review of RF field exposure studies was also performed (ICNIRP, 2009a), resulting in ICNIRP restating the RF field parts of its 1998 guidelines (ICNIRP, 2009b). ICNIRP considered that for frequencies above 100 kHz, the scientific literature published since 1998 did not necessitate an immediate revision of its guidance on limiting exposure (ICNIRP, 2009b). The NRPB (now part of the HPA) published its own review of the evidence relevant to developing exposure guidelines (NRPB, 2004a) and advised that the UK should adopt the ICNIRP guidelines (NRPB, 2004b). This continues to be the central pillar of advice on RF field exposure from the HPA.

The guidelines on restrictions on exposure to electromagnetic fields recommended by ICNIRP are based on biological data relating to thresholds for adverse *direct* and *indirect* effects of acute RF field exposure. Direct effects are those resulting from the interactions of electromagnetic fields with the human body. For exposure to RF fields above 10 MHz, which include microwaves, the restrictions are intended to prevent the adverse effects of whole- and partial-body heating. Indirect effects are those resulting from an interaction between electromagnetic fields, an external object such as a vehicle or other mechanical structure, and the human body. For these effects restrictions on exposure to RF fields are intended to avoid burns.

Recommendations to prevent adverse direct effects are based on information on the interactions of RF fields with body tissues and are termed *basic restrictions*. Compliance with the basic restrictions cannot, however, be easily determined directly. *Reference levels* are therefore recommended as values of measurable field quantities for assessing whether compliance with the basic restrictions has been achieved. In developing the restrictions in its guidelines, ICNIRP has generally incorporated reduction factors below the levels where adverse effects may begin to occur. Moreover, for members of the public, it has generally included a reduction factor of up to five over and above that used in developing exposure restrictions for workers.

The following is a summary of the ICNIRP exposure guidelines for reference with regard to the exposures considered in this review.

The ICNIRP guidelines on basic restrictions are summarised in Table B1. Theoretical dosimetric considerations enable the basic restrictions in terms of current density and specific (energy) absorption rate (SAR) to be related to the external field quantities of electric and magnetic field strength which, in the far field, can be expressed in terms of power density. At frequencies above 10 GHz, where energy absorption is essentially confined to the surface tissues, exposure is expressed in power density (in W m^{-2}).

The simple assumptions used in deriving these external field strength levels result in conservative values for the reference levels implying that, if exceeded, further investigation is needed to demonstrate whether there is compliance with the basic restrictions. This is the reason why apparent exposure above readily measured field strength levels is not in itself confirmatory evidence of non-compliance with the recommended basic restrictions, but indicative of a need for more extensive exposure assessment.

The power density levels for frequencies above 10 GHz are given in Table B2 and the external field strength reference levels for occupational and public exposure are shown in Tables B3 and B4, respectively.

TABLE B1 ICNIRP (1998) basic restrictions for time-varying electric and magnetic fields for frequencies up to 10 GHz

Exposure characteristics	Frequency range	Current density for head and trunk (mA m^{-2}) (rms)	Whole-body average SAR (W kg^{-1})	Localised SAR (head and trunk) (W kg^{-1})	Localised SAR (limbs) (W kg^{-1})
Occupational	Up to 1 Hz	40	–	–	–
	1 – 4 Hz	40/*f*	–	–	–
	4 Hz – 1 kHz	10	–	–	–
	1 – 100 kHz	*f*/100	–	–	–
	100 kHz – 10 MHz	*f*/100	0.4	10	20
	10 MHz –10 GHz	–	0.4	10	20
General public	Up to 1 Hz	8	–	–	–
	1 – 4 Hz	8/*f*	–	–	–
	4 Hz – 1 kHz	2	–	–	–
	1 – 100 kHz	*f*/500	–	–	–
	100 kHz – 10 MHz	*f*/500	0.08	2	4
	10 MHz – 10 GHz	–	0.08	2	4

Notes

a *f* is the frequency in hertz.

b Because of electrical inhomogeneity of the body, current densities should be averaged over a cross-section of 1 cm^2 perpendicular to the current direction.

c For frequencies up to 100 kHz, peak current density values can be obtained by multiplying the rms value by $\sqrt{2}$ (~1.414). For pulses of duration t_p the equivalent frequency to apply in the basic restrictions should be calculated as $f = 1/(2t_p)$.

d For frequencies up to 100 kHz and for pulsed magnetic fields, the maximum current density associated with the pulses can be calculated from the rise/fall times and the maximum rate of change of magnetic flux density. The induced current density can then be compared with the appropriate basic restriction.

e All SAR values are to be averaged over any 6-minute period.

f Localised SAR averaging mass is any 10 g of contiguous tissue; the maximum SAR so obtained should be the value used for the estimation of exposure.

g For pulses of duration t_p the equivalent frequency to apply in the basic restrictions should be calculated as $f = 1/(2t_p)$. In addition, for pulsed exposures in the frequency range 0.3–10 GHz and for localised exposure of the head, in order to limit or avoid auditory effects caused by thermoelastic expansion, an additional basic restriction is recommended. This is that the specific absorption should not exceed 10 mJ kg^{-1} for workers and 2 mJ kg^{-1} for the general public, averaged over 10 g of tissue.

TABLE B2 ICNIRP (1998) basic restrictions for power density for frequencies between 10 and 300 GHz

Exposure characteristics	Power density ($W\ m^{-2}$)
Occupational exposure	50
General public	10

Notes

a Power densities are to be averaged over any 20 cm^2 of exposed area and any $68/f^{1.05}$-minute period (where f is in GHz) to compensate for progressively shorter penetration depth as frequency increases.

b Spatial maximum power densities, averaged over 1 cm^2, should not exceed 20 times the values above.

TABLE B3 ICNIRP (1998) reference levels for occupational exposure to time-varying electric and magnetic fields (unperturbed rms values)

Frequency range	*E*-field strength ($V\ m^{-1}$)	*H*-field strength ($A\ m^{-1}$)	*B*-field (μT)	Equivalent plane wave power density, S_{eq} ($W\ m^{-2}$)
Up to 1 Hz	–	$1.63\ 10^5$	$2\ 10^5$	–
1–8 Hz	20,000	$1.63\ 10^5/f^2$	$2\ 10^5/f^2$	–
8–25 Hz	20,000	$2\ 10^4/f$	$2.5\ 10^4/f$	–
0.025–0.82 kHz	$500/f$	$20/f$	$25/f$	–
0.82–65 kHz	610	24.4	30.7	–
0.065–1 MHz	610	$1.6/f$	$2.0/f$	–
1–10 MHz	$610/f$	$1.6/f$	$2.0/f$	–
10–400 MHz	61	0.16	0.2	10
0.4–2 GHz	$3f^{½}$	$0.008f^{½}$	$0.01f^{½}$	$f/40$
2–300 GHz	137	0.36	0.45	50

Notes

a f as indicated in the frequency range column.

b Provided that basic restrictions are met and adverse indirect effects can be excluded, field strength values can be exceeded.

c For frequencies between 100 kHz and 10 GHz, S_{eq}, E^2, H^2 and B^2 are to be averaged over any 6-minute period.

d For peak values at frequencies up to 100 kHz see Table B1, note (c).

e Between 100 kHz and 10 MHz, peak values for the field strengths are obtained by interpolation from the 1.5-fold peak at 100 kHz to the 32-fold peak at 10 MHz. For frequencies exceeding 10 MHz it is suggested that the peak equivalent plane wave power density, as averaged over the pulse width, does not exceed 1000 times the S_{eq} restrictions, or that the field strength does not exceed 32 times the field strength exposure levels given in the table.

f For frequencies exceeding 10 GHz, S_{eq}, E^2, H^2 and B^2 are to be averaged over any $68/f^{1.05}$-minute period (where f is in GHz).

g No *E*-field value is provided for frequencies <1 Hz, which are effectively static electric fields. Electric shock from low impedance sources is prevented by established electrical safety procedures for such equipment.

TABLE B4 ICNIRP (1998) reference levels for general public exposure to time-varying electric and magnetic fields (unperturbed rms values)

Frequency range	*E*-field strength ($V\ m^{-1}$)	*H*-field strength ($A\ m^{-1}$)	*B*-field (μT)	Equivalent plane wave power density, S_{eq} ($W\ m^{-2}$)
Up to 1 Hz	–	$3.2\ 10^4$	$4\ 10^4$	–
1–8 Hz	10,000	$3.2\ 10^4/f^2$	$4\ 10^4/f^2$	–
8–25 Hz	10,000	$4{,}000/f$	$5{,}000/f$	–
0.025–0.8 kHz	$250/f$	$4/f$	$5/f$	–
0.8–3 kHz	$250/f$	5	6.25	–
3–150 kHz	87	5	6.25	–
0.15–1 MHz	87	$0.73/f$	$0.92/f$	–
1–10 MHz	$87/f^{½}$	$0.73/f$	$0.92/f$	–
10–400 MHz	28	0.073	0.092	2
0.4–2 GHz	$1.375f^{½}$	$0.0037f^{½}$	$0.0046f^{½}$	$f/200$
2–300 GHz	61	0.16	0.20	10

Notes

a *f* as indicated in the frequency range column.

b Provided that basic restrictions are met and adverse indirect effects can be excluded, field strength values can be exceeded.

c For frequencies between 100 kHz and 10 GHz, S_{eq}, E^2, H^2 and B^2 are to be averaged over any 6-minute period.

d For peak values at frequencies up to 100 kHz see Table B1, note (c).

e Between 100 kHz and 10 MHz, peak values for the field strengths are obtained by interpolation from the 1.5-fold peak at 100 kHz to the 32-fold peak at 10 MHz. For frequencies exceeding 10 MHz it is suggested that the peak equivalent plane wave power density, as averaged over the pulse width, does not exceed 1000 times the S_{eq} restrictions, or that the field strength does not exceed 32 times the field strength exposure levels given in the table.

f For frequencies exceeding 10 GHz, S_{eq}, E^2, H^2 and B^2 are to be averaged over any $68/f^{1.05}$-minute period (where *f* is in GHz).

g No *E*-field value is provided for frequencies <1 Hz, which are effectively static electric fields. Perception of surface electric charges will not occur at field strengths less than 25 $kV\ m^{-1}$. Spark discharges causing stress or annoyance should be avoided.

B1 References

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Appendix C
Publications of the Advisory Group on Non-ionising Radiation

1 Electromagnetic Fields and the Risk of Cancer. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **3**(1), 1–138 (1992).

2 Electromagnetic Fields and the Risk of Cancer. Summary of the views of the Advisory Group on Non-ionising Radiation on epidemiological studies published since its 1992 report. *Doc NRPB,* **4**(5), 65–9 (1993).

3 Health Effects Related to the Use of Visual Display Units. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **5**(2), 1–75 (1994).

4 Electromagnetic Fields and the Risk of Cancer. Supplementary report by the Advisory Group on Non-ionising Radiation. *Doc NRPB,* **5**(2), 77–81 (1994).

5 Health Effects from Ultraviolet Radiation. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **6**(2), 7–190 (1995).

6 Use of Sunbeds and Cosmetic Tanning. Statement by the Advisory Group on Non-ionising Radiation. *Radiol Prot Bull,* No. 218, 11–15 (1999).

7 The Solar Eclipse. Statement by the Advisory Group on Non-ionising Radiation. Chilton, NRPB Information Servics P8/99 (1999).

8 ELF Electromagnetic Fields and the Risk of Cancer. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **12**(1), 1–179 (2001).

9 Possible Health Effects from Terrestrial Trunked Radio (TETRA). Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **12**(2), 1–80 (2001).

10 ELF Electromagnetic Fields and Neurodegenerative Disease. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **12**(4), 5–24 (2001).

11 Health Effects from Ultraviolet Radiation. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **13**(1), 5–282 (2002).

12 Health Effects from Radiofrequency Electromagnetic Fields. Report of an independent Advisory Group on Non-ionising Radiation. *Doc NRPB,* **14**(2), 5–177 (2003).

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17 Brain Tumour Risk in Relation to Mobile Telephone Use: Results of the Interphone International Case–Control Study. Statement from the Advisory Group on Non-ionising Radiation. Available at www.hpa.org.uk

Health Protection Agency
2nd Floor
151 Buckingham Palace Road
London
SW1W 9SZ
www.hpa.org.uk

Centre for Radiation, Chemical and Environmental Hazards
Chilton
Didcot
Oxfordshire
OX11 0RQ
T: +44(0)1235 831600
F: +44(0)1235 833891
E: ChiltonInformationOffice@hpa.org.uk

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