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- 5.1 Assessment of any health risk resulting from exposure to radiofrequency (RF) fields depends on the results of well-conducted and reproducible scientific studies, and the need for these is all the greater because any effect of exposure to RF fields at the levels encountered from mobile telecommunications is likely to be subtle. Reports of such studies are mainly found in peer-reviewed journals, although the Expert Group considered evidence from all sources of information available to it.
- 5.2 The World Health Organization (WHO) defines health as the state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. Thus the Expert Group considered ways in which mobile phones and their base stations might jeopardise any of these aspects of the health of people.
- 5.3 We are aware of the concerns about the biological effects and possible health risks of exposure to RF fields expressed by a group of scientists who met in Vienna in October 1998. The evidence reviewed in this chapter addresses the issues in detail.
- 5.4 New telecommunications technologies have been introduced without full provision of information about their nature and without prior discussion within the scientific community about possible consequences for health. The average output power from the antennas of digital mobile phones is lower than that from earlier analogue models, but the maximum powers are greater, the exact patterns of radiation are different and these differences might influence their effects on people. As the costs of mobile phone technology have fallen, their use has increased dramatically and the overall levels of exposure of the population as a whole have therefore increased.

Interaction of Radiofrequency Fields with Tissues

Mechanisms

- 5.5 While risk assessment is generally based on experimental data from biological systems, a consideration of possible mechanisms is nevertheless pertinent, for two reasons. Firstly, as discussed below, the experimental data regarding biological effects of RF fields are fragmentary and inconsistent in many respects, and an understanding of the biophysical mechanisms for reported effects can help to rationalise and understand the data. Secondly, it is necessary to extrapolate data from one exposure condition to others, and for reliable extrapolation some understanding of the underlying mechanisms is needed.
- 5.6 The electric and magnetic fields produced in the body by a nearby electromagnetic source may cause both thermal and non-thermal biological effects. The effects of magnetic fields vary with frequency, and are probably greatest in biological tissue containing small amounts of magnetite. Magnetite (Fe_3O_4) is a naturally occurring oxide of iron. It is a ferrimagnet but behaves similarly in magnetic fields to a ferromagnet such as iron. Magnetite is found in certain bacteria and in the

cells of many animals, including human beings. It is believed to be used by some species of birds and fish to provide magnetic sensitivity, which they employ in navigation. However, no other effects associated with the interactions of electromagnetic fields with magnetite have been demonstrated in animals. It has been calculated that the interaction resulting from the largest RF magnetic fields generated by mobile phones is extremely small (Adair, 1994), and that any other effects of magnetic fields at these frequencies should be even smaller. Indeed, it seems to be generally agreed that any biological effects from mobile phones are much more likely to result from electric rather than from magnetic fields.

Thermal effects

- 5.7** Thermal effects are those caused by the rise in temperature produced by the energy absorbed from oscillating electric fields. The force produced by an electric field on charged objects, such as the mobile ions present in the body, causes them to move, resulting in electric currents, and the electrical resistance of the material in which the currents are flowing results in heating. This heat input causes the temperature to rise and it continues to do so until the heat input is balanced by the rate at which it is removed, mostly by blood flowing to and from other parts of the body. It is estimated that it takes several minutes from the moment RF exposure occurs for the irradiated parts of the body to reach their final equilibrium temperatures. In view of this slow response, the equilibrium temperature arising from the pulsed fields of mobile telecommunications will essentially be determined by the *average* power absorbed. There will, however, be small oscillations about that temperature at the pulse frequency or frequencies.

Heating in the head

- 5.8** It has not yet proved possible to measure these small changes in temperature directly, except those at the outer skin (Adair *et al*, 1999) and, although temperature is a more direct determinant of thermally induced tissue damage, the majority of theoretical studies up to the present time have restricted themselves to the computation of SAR alone (paragraph 4.37).
- 5.9** The relationship between the SAR and the resulting temperature rise is complex, and significantly dependent on antenna configuration, location and frequency. The most problematic feature of a temperature calculation is modelling the effect of blood flow on heat transfer. The traditional continuum heat-sink model developed by Pennes (1948) has been found to give remarkably accurate results in many circumstances, but numerous modifications have been suggested more recently (Arkin *et al*, 1994).
- 5.10** In a recently published study (Van Leeuwen *et al*, 1999) the heat deposition within the head was computed by coupling a finite difference time domain model for SAR with a new thermal model. The thermal model includes the convective effects of discrete blood vessels, whose anatomy was determined using magnetic resonance angiography of a healthy volunteer. For a 915 MHz dipole antenna with a time-averaged power output of 0.25 W (equivalent to a typical mobile phone), this study results in an SAR of about 1.6 W/kg and predicts a maximum brain temperature rise of 0.11°C in the steady state. There is general agreement between the brain temperatures calculated using the Pennes equation and that using the new discrete vessel model, which suggests that the sensitivity of the results to the exact blood flow model may not be critical. However, further work should be done to apply this model to more realistic simulations of mobile phone configuration, and to investigate the effect of different antenna positions and frequencies (particularly in the 1800 MHz band also used by mobile phones).
- 5.11** A recent NRPB study (Wainwright, *in press*) has applied the traditional Pennes thermal model to the SAR patterns predicted by earlier work (Dimbylow and Mann, 1994). The radiation source was modelled as a monopole antenna on a metal box, and both horizontal and vertical orientations

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of the antenna were considered. Computations of the final steady-state temperature rise were carried out for a 0.25 W antenna at frequencies of 900 and 1800 MHz. The highest temperature rises found in the brain were around 0.1°C.

Non-thermal effects

- 5.12** The energy quanta of radiation at 0.9 and 1.8 GHz equal 4 and 7 μeV , respectively (1 μeV is a millionth of an eV). Both these values are extremely small compared with the energy of around 1 eV needed to break the weakest chemical bonds in genetic molecules (DNA). As already noted, it seems impossible, therefore, that RF radiation could damage DNA directly, which might start cells on the path to cancer.
- 5.13** Radiofrequency radiation could, however, produce other effects. In general, detectable changes can arise only if the effect of the electric field within the biological system exposed to RF fields is not masked by *thermal noise*. Thermal noise or random motion, also known as Brownian motion, is due to the thermal energy that all objects possess at temperatures above absolute zero. In solids, the atoms vibrate and in gases and liquids they move erratically to and fro following very frequent collisions with other atoms. So all components of biological tissue – ions, molecules and cells – are in constant motion. The thermal energy of each component has an average value of about kT , where k , Boltzmann's constant, is 86 μeV per degree and T is the absolute temperature measured in kelvin, K ($T = 273 + t$, where t is the temperature in degrees centigrade). The value of T is about 300 K at body temperature so that kT is 26 meV and, if this is much larger than the energy of the motion produced by the electric field, any effect of the field will be completely masked (not detected by any component of the biological tissue). This comparison with thermal noise should then provide a good measure of the minimum electric field necessary to produce detectable biological effects. It should be noted, however, that if there was a special case in which the biological system were resonantly sensitive at the frequency of the electric field and rather insensitive to fields at other frequencies, the comparison would need to be made with the thermal motion taking place at frequencies close to the resonant frequency. If the resonance was very sharp, this would be very much smaller than the total thermal noise, so that quite small electric fields might produce detectable effects in resonant systems of this type, should they exist in biological tissue.
- 5.14** This argument can be used, for example, to see whether non-thermal effects could arise from the motion of the ions discussed above. The ions are driven to and fro by an oscillating electric field, although the extent of the motion is severely reduced by the viscosity of the surrounding liquid. For a field of 100 V/m the movement is in fact less than 10^{-14} m – the diameter of an atomic nucleus – and the energy associated with this motion is less than that of the thermal motion of the ion by about a factor of 10^{15} *. This is so small that it can safely be concluded that this ionic motion could not result in any non-thermal biological effects. The expression (in the footnote) shows that the energy increases with the mass of the charged object, although, for $E = 100$ V/m, it would still appear to be small at these frequencies compared with thermal noise for objects such as cells of average size which have radii around 10 μm (Adair, 1994). Adair notes, however, that it could become significant for larger cells with correspondingly greater masses.
- 5.15** Another mechanism involving cells concerns the attraction between them in the presence of an electric field (Schwan, 1985; Adair, 1994). The electric field polarises the cell, that is to say

* The velocity of the ion is $\mu E = \mu E_0 \sin(2\pi vt)$, where μ , the mobility, is about 10^{-7} $\text{m}^2/(\text{V/s})$ for chloride, the ion of highest mobility, and v , the frequency, is 0.9 or 1.8 GHz. This leads to a maximum displacement of $\mu E_0/2\pi v$ which, for an electric field $E_0 = 100$ V/m, equals 2×10^{-15} m and 10^{-15} m at frequencies of 0.9 and 1.8 GHz, respectively. So the average kinetic energy of an ion of mass m in this field is $m\mu^2 E_0^2/4$ or $m\mu^2 E^2/2$, where E is the rms value of the electric field. For a chloride ion this energy is equal to about 10^{-17} eV, or about 10^{-15} kT .

charges in the cell move so that one side of it becomes positive with respect to the other. The cell is then an electric dipole (like a tiny torch battery) and attracts similarly polarised cells. For typical cells and frequencies below about 100 MHz, the energies involved are calculated to become comparable to thermal noise in electric fields of $E = 300$ V/m. The energies are calculated to become appreciably less for RF fields, but Adair (1994) suggests that, since these values would depend on the detailed structure of the biological elements involved, the possibility of biological effects for fields of this size cannot be excluded.

- 5.16** Other possible biological effects are associated with cell membranes and the movement of currents through the membrane in either direction. Membranes are known to have strongly non-linear electric properties (Montaigne and Pickard, 1984). When a voltage is applied across the membrane, the current that flows is not always proportional to the voltage. Part of this non-linearity may, in fact, be due to the effect of the electric field on the proteins in the membrane or nearby, which assist the flow of the product currents through the membrane. The membrane also acts as a rectifier. If a voltage is connected across the ends of a wire, the size of the current that flows depends solely on the magnitude of the voltage: if the polarity of the voltage is reversed, the current changes direction but its size is unchanged. However, if the polarity of the voltage applied across a rectifier is reversed, the current changes direction but now its size also changes. So, if an oscillating voltage (electric field) is applied across a rectifier, the total current that flows when the field is in one direction is not balanced by the current when the field is in the other: an AC field produces a net DC current and hence a net flow of products through the membrane. However, the response times of the ion gates are very much slower than the period of microwave frequencies and, using data obtained from measurements on membranes (Montaigne and Pickard, 1984), it has been shown that, for electric fields of 200 V/m, the relative change in the membrane potential is very small (Adair, 1994; see also Foster, 2000a). Therefore no biological effects seem likely from this mechanism.
- 5.17** Many other mechanisms have been proposed by which significant biological effects from RF fields might arise, but very few, if any, appear to stand up to critical analysis of the sort presented above (Foster, 2000b). One, for which there is recent experimental support (Bohr and Bohr, 2000), is that microwave radiation might cause proteins to unfold (denature). The experiments were carried out in a modified microwave oven at 2.45 GHz, a frequency comparable to the likely torsional modes of the protein. The intensity was not specified, but seems likely to have been above ICNIRP guidelines. The experiments were very recent and have not yet been replicated. Another mechanism that has continued to create interest is based on the assumption that biological systems might interact resonantly with microwave fields. This possibility was initially discussed by Fröhlich (1968, 1980) and his work has had a considerable impact (see, for example, Penrose, 1994; Pokorny and Wu, 1998).
- 5.18** Fröhlich was interested in the mechanism through which the chemical energy taken into the body (food) was channelled into highly ordered processes, such as cell building, rather than into heat. His model involves the mechanical vibrations of large molecules or components of biological tissue and the way they interact with each other, which he argued could lead to the existence of a band of frequencies into which energy could be absorbed, plus a particular “coherent state” of vibration. He also considered whether quite small oscillating electric fields might put energy into this state and hence trigger significant biological changes; that it is to say, whether a living biological system might behave in a manner roughly similar to a radio receiver. A radio can detect and amplify an extremely small signal against a background of very much larger signals. It does this when the operator tunes a resonant circuit to the frequency of the carrier wave. The resonant circuit essentially responds only to electromagnetic waves of frequencies (including those generated by thermal noise – see paragraph 5.13) within a narrow bandwidth. The power

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needed to amplify these waves comes from the power supply of the radio. A number of solid state systems behave in similar ways, such as narrow-band optical amplifiers, which are the basis of lasers.

- 5.19** The Fröhlich model has stimulated a range of other work. However, so far there appears to be no direct experimental evidence, and no convincing indirect experimental evidence, for the existence of Fröhlich's coherent state in biological systems. Moreover, the present theoretical treatments of the model do not provide estimates for the magnitude of the electric fields needed to produce biological effects. Fröhlich suggested that the findings of a number of experiments carried out at frequencies of 40 GHz and above on systems such as *E coli* bacteria and yeast cultures (see Fröhlich, 1980) might be (indirect) evidence for his model, since these frequencies lie in the range where cell membranes are expected to resonate mechanically. Four recent attempts to reproduce some of this work have failed to do so (*E coli*: Athey and Krop, 1980; Santo, 1983; yeast cultures: Furia *et al*, 1986; Gos *et al*, 1997), although there have been further reports from Balyaev and colleagues that appear to endorse the earlier research (*E coli*: Balyaev, 1992). A recent appraisal of all this work (Foster, 2000a) notes that the experiments present formidable technical problems and that, while their results may be statistically significant, it may not always be possible to eliminate systematic errors. In view of this appraisal, it is not possible to conclude that this work provides support for the existence of resonant absorption by biological tissue.
- 5.20** Hyland (1998) has suggested that the mechanism proposed in Fröhlich's model might lead to biological effects from electromagnetic fields at the appreciably lower frequencies of mobile phones. This would require the presence of components in the biological tissue with sharp resonant vibrational modes in this frequency range. The frequencies are lower than those expected for most components, although theoretical work (Kohli *et al*, 1981; Van Zandt, 1986; Porkny and Wu, 1998) suggests that DNA polymers and elements of fibre structures (cytoskeletons), such as microtubules and actin filaments, could have modes in this range. However, since these components are surrounded by relatively viscous fluids, their mechanical vibrations would normally be expected to be very highly damped. Thus, resonances they might have out of solution would be almost completely smeared out when they are immersed*. Certainly no evidence of resonant absorption[†] was found from DNA in solution (Gabriel *et al*, 1987), although this might not rule out the possibility that it occurs under the conditions in which DNA exists in tissue.
- 5.21** *CONCLUSION This work on DNA should be repeated under conditions more closely matched to those in tissue and similar measurements should be made on microtubules and actin filaments.*
- 5.22** Another hypothesis is that the interaction with biological tissue depends on the coherence of the electromagnetic fields (see paragraph 4.36). Experimental evidence in support of this idea has been given by Litovitz *et al* (1993, 1997a,b) but not yet independently replicated.
- 5.23** In summarising the physical basis for non-thermal effects, it is convenient to consider separately the situations near to the antenna of a mobile phone and near to a base station.

* Water provides an example of this effect. Water vapour shows strong resonant absorption but the resonances are smeared out in liquid water and absorption occurs over a wide range of frequencies. Scott (1984) and Van Zandt (1986) have, however, proposed models to explain why this might not happen for DNA in solution.

[†] Earlier work on DNA in solution appeared to show strong resonant absorption in this range (Edwards *et al*, 1984). It was shown, however, that this could have been the result of an experimental artefact (Foster *et al*, 1987) and, as noted, the work of Gabriel *et al* (1987), carried out on samples chosen to be as close as possible to those of Edwards *et al*, failed to see any such effects. In this work, three different techniques were used in two different laboratories and the results were essentially identical. It can be concluded, therefore, that DNA in solution does not have resonant modes that couple to microwaves in this range.

Mobile phones

- 5.24 In Chapter 4 it was noted that the *maximum* size of the electric fields produced in the head by the antenna of a mobile phone is around 100 V/m, although the fields inside the brain would be appreciably less. For fields of this size the mechanisms most likely to produce non-thermal biological effects would be through the movement of large cells (paragraph 5.14) or through the attraction between neighbouring cells (paragraph 5.15). At this stage, although there is no experimental evidence to support these mechanisms, the possibility that both of these could produce effects cannot be excluded (Adair, 1994).

Base stations

- 5.25 The maximum size of the electric fields resulting from base stations to which the general public is exposed is around 5 V/m, although the largest field measured to date by NRPB is 2 V/m (Mann *et al*, *in press*). (The corresponding field strengths inside the body will be appreciably smaller.) One mechanism that could lead to biological effects at these relatively low fields is that proposed by Fröhlich and which relies upon the existence in biological tissue of a particular coherent state of mechanical vibration. The absence, even after 30 years, of any convincing evidence for this state, or indeed for any resonant behaviour, would seem to cast considerable doubt on its existence, although it cannot totally be ruled out. It should be noted, however, that Adair (1994) has considered more generally the possibility of energy transfer through a resonant mechanism and his conclusion is that it would be too small to lead to measurable biological effects at any value of electric field.
- 5.26 We conclude that there is little evidence to support resonant behaviour, but further work to investigate this proposed mechanism could be worthwhile.

Experimental Studies

- 5.27 This section considers and interprets research on *in vitro* preparations and on animals (*in vivo*) relevant to the possibility that exposure to RF fields used in mobile telecommunications is associated with adverse health outcomes.

Significance of experiments on molecules, cells and animals

- 5.28 Our principal remit was to report on the possible risks to human health of mobile phones and their base stations. The most direct demonstration of such risks comes from research on people, either through epidemiological studies, which could identify an increased incidence of health problems as a result of exposure to RF fields, or by means of experiments on human volunteers aimed at revealing physiological or behavioural abnormalities resulting from such exposure. However, because of the obvious limitations of human experimentation, more direct methods are necessary to show the underlying biological basis of any health hazards. These involve laboratory studies of biological systems and animals.
- 5.29 Experimental observations on biological molecules (eg solutions of enzymes), and on *in vitro* preparations of isolated cells or tissue samples, could define the mechanism of any action of radiation on living organisms. A great deal of research has been performed on such preparations, particularly on cultured animal or human cells. Such work could, in principle, give insight into the basic mechanisms responsible for more complex effects seen in whole animals or people (eg tumour formation, changes in brain activity and even alterations of behaviour). The results of work on simple molecular and cellular preparations are often easier to interpret, since the nature of any effects can be more precisely defined and the conditions of the preparation (including its

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temperature) can be more accurately assessed and controlled than in whole animals. However, even when clear effects are defined *in vitro*, it is often difficult to extrapolate from them to a health risk for people.

- 5.30** Laboratory studies on animals play an essential role in evaluating the integrated reactions of various, intact systems of the body, particularly the nervous, endocrine (hormone) and immune systems. These systems are largely responsible for homeostasis – the essential maintenance of the internal environment. The complex, co-ordinated, interdependent response of these systems when challenged by potentially damaging stimuli cannot be defined through experiments on molecules or isolated cells.
- 5.31** The environment and parameters of exposure to RF radiation can be made virtually the same for all animals in each group; well-matched “control” animals can be identically treated except that they receive no exposure. Valid comparisons can then be made between the exposed and control groups to determine if exposure causes any effects. The precision of this type of study also allows dose–response relationships to be determined.
- 5.32** Of course, phenomena seen in experimental animals do not necessarily imply a health risk for people. In particular, an effect found in only one animal species may be specific to that type of animal and not relevant to people.
- 5.33** Although rodents differ from people in some aspects of their physiology, mice and rats are frequently used in biomedical research. This is mainly because genetically homogeneous strains of rodents are available for research and because they are easy to breed and maintain. Another advantage of rodents accrues from the fact that they have been so widely used for research in the past and consequently much is known of their normal physiology. Moreover, mice have been the preferred species for research on genetic mechanisms and for experimental work involving transgenesis (the modification of genes).
- 5.34** Appropriate animal studies provide the opportunity to test whether lifetime exposure to well-characterised RF radiation causes cancer, something that is obviously impossible using human volunteers. While epidemiological studies do allow human populations to be studied, they are generally not able to assess RF exposure accurately. Research on animals can also demonstrate influences of RF exposure on susceptibility to cancer promotion and progression, as well as on various physiological functions, including behavioural performance in tasks involving learning, memory, etc. It is important to note, however, that the interpretation of any such behavioural effects in small animals is not straightforward. For instance, if radiation affects the performance of mice in tests of learning (as has been claimed: see paragraphs 5.80–5.92), one might imagine that it could influence this aspect of brain function in people. However, given the small size and somewhat different functional and anatomical organisation of the mouse brain, such a result could not easily be extrapolated to suggest a similar effect on memory in people.

Stimulus conditions

- 5.35** As described above, high levels of RF radiation cause heating by inducing small electric currents and increasing the movement of molecules. However, the rise in temperature in the brain caused by the use of a mobile phone for more than a few minutes (the time taken to reach thermal equilibrium) is estimated to be only about 0.1°C (Van Leeuwen *et al*, 1999). Moreover all cells in the body have a mean thermal energy proportional to the absolute temperature T (paragraph 5.13) and the energies of individual cells fluctuate about this mean energy as they interact with other cells, extracellular fluids etc. Any increase in energy caused by radiation is

superimposed on this background of fluctuating energies and would have to begin to be comparable in size to these to cause any additional biological hazard.

- 5.36** Experimental studies have employed a bewildering variety of exposure conditions, with respect to the RF carrier frequency, whether it is continuous, amplitude modulated or pulsed, and, particularly, its intensity. High intensities, above present guidelines (see paragraphs 6.19–6.31), can cause significant heating (ICNIRP, 1998a,b), which itself can lead to a variety of pathological effects in cells and tissues.
- 5.37** We have considered the whole range of research reports, including those that employed intensities that caused heating, since they might provide clues to the mechanism of effects at more modest levels of exposure. However, we have concentrated on studies that used intensities below 50 W/m^2 (5 mW/cm^2) and/or SARs below 1 W/kg , which are less likely to have involved significant heating (see paragraph 5.8). We have also taken note of studies in which investigators used higher intensities but have attempted to prevent what they considered to be significant rises in temperature. It must be noted, however, that it is difficult to be sure of the absence of thermal effects. The absorption of RF energy is necessarily accompanied by temperature increases, which can be minimised, but not prevented. Whole-body SARs less than 1 W/kg have been shown to cause thermoregulatory responses in animals. In the case of pulsed fields, the average SAR is obviously much lower than the peak SAR during pulses, which can generate quite rapid, transient heating and quite large electric fields. This probably accounts for many of the effects, such as ‘microwave hearing’ (see paragraphs 5.76–5.79), that have been described at low average SARs.
- 5.38** We were struck by certain inconsistencies and inadequacies in the scientific literature on the biological effects of RF radiation. Many studies in this field have been exploratory and preliminary in nature, and claims of effects have sometimes been based on single experiments rather than a consistent series of hypothesis-driven investigations. In some cases, study design and statistical analysis have been inadequate, and apparent effects may have been artefactual or due to random variation. Indeed, the field is troubled by failures to replicate previous studies and by a lack of theoretical explanation of some effects that have been claimed. There may also be biases arising from selective publication and non-publication of results. Finally, even for effects that appear to be well substantiated, the biological significance and the implications for health are often unclear.
- 5.39** A considerable problem in the interpretation of experimental reports is that many of them have given insufficient detail concerning exposure conditions, including the important SAR value. Moreover, in the case of pulsed fields, when SAR values are quoted it is often unclear whether these refer to the average SAR or to the peak SAR during pulses. It is very important to make this distinction, since the peak SAR can be 1000 or more times the mean value.
- 5.40** Current mobile phone systems utilise RF radiation between about 800 MHz and 2 GHz, which fall in the microwave part of the spectrum. Emerging telecommunications technologies under development may use up to 60 GHz. Paging systems and two-way radios employ frequency bands down to about 150 MHz. Thus, we have focussed on experimental studies involving RF radiation between 100 MHz and 60 GHz.
- 5.41** *CONCLUSION* We consider that, in future, researchers in this field should provide full details of the experimental conditions used, including the maximum specific absorption (SA) per pulse, for pulsed radiation.

Biological issues

- 5.42** With regard to possible influences on the head, we have concentrated primarily on functional changes in the brain and consequent changes in behaviour. With regard to whole-body exposure, we have concentrated on possible effects on carcinogenic processes, on reproduction and development, on immune responses, on the cardiovascular system and on overall longevity.

Nervous system: can RF exposure cause functional changes in the brain and affect behaviour?

- 5.43** There is particular concern about the possible effects on the brain and behaviour of repeated, acute exposure to RF fields, largely because mobile phones are conventionally held close to the head. Recent reports in the media, for instance, have implied that the use of mobile phones can cause memory loss, changes in attention, and variation of blood pressure (see Chapter 3).

- 5.44** There is a vast literature on the effects of RF fields on isolated nerve cells (neurons), on cultured nervous tissue, on living brain slices, on brain function in experimental animals, on the blood–brain barrier and on behavioural measures of brain function (see, for example, UNEP/WHO/IRPA, 1993; Cleary, 1995; Hermann and Hossmann, 1997; Repacholi, 1998; D’Andrea, 1999; Jokela *et al*, 1999; Royal Society of Canada, 1999). The behaviour of animals, in particular, can be a very sensitive indicator of adverse health consequences. Early signs of potential insult are often behavioural rather than anatomical (Salzinger, 1994). Behavioural experiments on animals are used to investigate the biological basis of memory, and studies with non-human primates can serve as a model of human cognitive functions. Work on people is reviewed below (paragraphs 5.176–5.200) and here we deal specifically with *in vitro* studies and work on animals. Much of the research, especially the early studies, was conducted with high levels of RF exposure, or low average levels using high peak-power pulses (which are characteristic of radar and quite unlike emissions from telecommunications systems). Few relevant experiments have used low level fields with characteristics similar to those used in telecommunications systems (UNEP/WHO/IRPA, 1993; Repacholi, 1998; Royal Society of Canada, 1999).

Effects on cell membranes: do RF fields affect the movement of substances across membranes?

- 5.45** The lipid bilayer membrane that surrounds cells and the internal membranes within cells are vitally important for normal cellular function. Embedded in the external membrane are important protein molecules. Some act as receptors, detecting extracellular molecules (such as growth factors, hormones and neurotransmitters) and triggering changes in the conductivity of associated ion channels (see below) or activating signalling pathways within the cell. Other membrane proteins, called pumps, actively transport ions across the membrane, using energy derived from the energy source ATP. Yet others are channels that serve as conduits through which ions (eg sodium, potassium, chloride and calcium ions) can move across the membrane. Changes in the conductivity of ion channels, which increase or decrease the flow of ions across the membrane, cause changes in the intracellular potential of the cell. In the case of a neuron, this can affect its excitability and the amount of transmitter substance that it produces at the end of its fibre (or axon) where it makes contact with another nerve cell. Calcium acts as a signalling molecule, influencing a variety of intracellular molecular pathways, as well as having direct electrical effects within or around the cell.
- 5.46** Inside neurons, calcium is held in internal stores, from which it can be released into the cytoplasm. It can enter neurons from the extracellular space through selective ion channels associated with one class of neurotransmitter receptor (the NMDA-receptor). It can also move in

or out of the cell (depending on the internal concentration and electric potential) through calcium channels, the permeability of which is affected by the intracellular potential. In the terminals of nerve fibres, where they form junctions (called synapses) with other neurons, the amount of transmitter substance released when a nerve impulse arrives depends on the entry of calcium caused by the change of intracellular potential.

- 5.47** In neurons in certain parts of the brain (especially a structure called the hippocampus, and in the cerebral cortex, particularly in young animals), changes in the level of intracellular calcium resulting from incoming synaptic activity can lead to long-term alterations in the “strength” of synaptic inputs on to the neurons. Such long-term potentiation and long-term depression are thought to be involved in the mechanisms of memory and learning (see Kandel *et al*, 2000).
- 5.48** Repacholi (1998) has recently concluded from a World Health Organization review of the literature that RF fields, continuous or pulsed, can affect membrane channels, mainly at fairly high intensities, but even at levels that do not cause significant heating. There have been reports of decreased rates of channel formation, decreased frequency of channel openings, and increased rates of rapid, burst-like firing (see UNEP/WHO/IRPA, 1993). However, there is no clear understanding of how low intensity RF fields have such effects.
- 5.49** Cleary (1990a,b 1995) has reported, in reviews of the literature, that the flux of positively charged sodium and potassium ions across cell membranes can also be affected by RF exposure, over a wide range of frequencies (27 MHz to 10 GHz). Although most of these experiments involved very high SARs (up to 200 W/kg), he reported that effects can be produced at much lower intensities, without what he considered to be a significant rise in temperature. However, they seem to occur over a temperature “window” from 17.7 to 25°C, which might imply that the RF energy facilitates lipid phase transitions in the membrane near the phase transition temperature (Tenforde and Liburdy, 1988). In the human body, cells are always well above this temperature window and therefore the effect is unlikely to occur *in vivo*.
- 5.50** RF exposure has been reported to influence the ATP-dependent sodium/potassium pump in the membranes of human red blood cells, and this effect might also perhaps be mediated by membrane phase transitions (Allis and Sinha-Robinson, 1987; Liu *et al*, 1990).
- 5.51** Effects on receptor proteins and their associated ion channels have also been described. For instance, Philippova *et al* (1994) found that 900 MHz radiation, at SARs of 1 and 100 W/kg, specifically affects the binding of odorant molecules to receptor protein in the membranes of olfactory receptor neurons in the rat. They attributed this to shedding of this particular protein from the membrane, probably because of increased peroxidation of membrane lipids (see Phelan *et al*, 1992). Liburdy and Vanek (1987) have also reported protein shedding from membranes as a result of RF exposure. Radiation at very low power densities can affect the ion channels associated with transmitter receptors: D’Inzeo *et al* (1988) reported a decrease in the frequency of opening of sodium channels associated with acetylcholine receptors in muscle membranes as a result of exposure to 9.75 GHz radiation at only 10–20 $\mu\text{W}/\text{m}^2$, which might cause a decrease in the excitability of the muscle.
- 5.52** *CONCLUSION* There is evidence that RF fields can affect membrane proteins and can change the movement of ions across membranes. Some of these effects seem to occur in cells only at temperatures well below normal body temperature or with RF intensities that cause significant heating. However, some evidence suggests that RF radiation at levels produced by mobile phones might influence ion channels and other membrane proteins of neurons in the brain under normal conditions. This might cause subtle changes in cell function, but the significance of such effects

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for human health is uncertain. Moreover, these effects have not been independently confirmed, which is important given the frequent lack of reproducibility of RF biological effects.

Calcium efflux

- 5.53** In view of the vital role of calcium in the function of neurons and other cells, considerable work has been done on the effects of RF fields on calcium movement in brain tissue (see Adey, 1981; UNEP/IRPA/WHO, 1993; Repacholi, 1998; Jokela *et al*, 1999; Royal Society of Canada, 1999; Table 5.1).
- 5.54** At high intensities, 2.8 GHz radiation pulsed at 350 pulses per second (pps) – with peak SARs of several tens of thousands of watts per kilogram – can cause an increase in the incorporation of radiolabelled phosphorus into important phosphoinositide signalling molecules (Gandhi and Ross, 1989). Phosphoinositides mediate the release of calcium from internal stores, which could alter calcium-dependent processes inside the cell. In turn, this could lead to a rise in extracellular calcium because of movement through the cell membrane, which could electrically stabilise the membrane by charge-screening the surface. This would be expected to reduce the excitability of neurons.
- 5.55** Several studies, starting with the work of Bawin *et al* (1975), have involved measurement of the efflux of calcium out of large explants of brain tissue, prelabelled by incubation in medium containing radioactive calcium. Bawin *et al* (1975) reported that exposure to 147 MHz fields at intensities too low to cause heating increased the efflux of calcium from chick brain, but only if the field was amplitude modulated at 16 Hz. The RF carrier frequency alone had no obvious effect. This observation was confirmed by Blackman *et al* (1979, 1980a,b), who used a number of different frequencies of amplitude modulation (3–30 Hz) and found that the effect was maximal at 16 Hz. This led to the view that modulation at or near 16 Hz might be critically important and a number of other studies using this frequency of amplitude modulation have also reported increases in the diffusion of calcium out of isolated fragments of nerve cells and cultured human neuroblastoma cells (see Table 5.1). Such calcium efflux may partly reflect movement of calcium out of neurons. Indeed, Kittel *et al* (1996), using electron microscopy to identify labelled calcium in a particular part of the brain (the medial habenular nucleus), found that exposure of mice *in vivo* to 2.45 GHz RF fields, amplitude modulated at 16 Hz, caused a reduction in the number of calcium-containing vesicles inside nerve cells and an increase in the amount of calcium precipitated on the surface of the cells. However, calcium efflux from brain explants almost certainly involves a number of other factors, including the release of calcium bound or adherent to membranes and simply trapped in the interstices of the tissue. It is also likely to be influenced by temperature.
- 5.56** Adey (1989, 1993) has suggested that changes in calcium efflux may be due to an amplification process in which weak electric fields might be set up in the tissue at the extremely low frequency of amplitude modulation, and that these might act as a “trigger” for the initiation of long-range co-operative events within the cell membrane. However, there is no obvious theoretical basis for such effects which would seem to require the presence of a non-linear mechanism operating on the timescale of the carrier frequency. This is not the case for ion-gating mechanisms.
- 5.57** A number of subsequent studies in other laboratories have failed to detect an increase in calcium efflux from brain explants *in vitro* (see UNEP/WHO/IRPA, 1993), but they generally used different conditions of stimulation (see Table 5.1).
- 5.58** There have been only two attempts to determine if such efflux of calcium occurs *in vivo*. Adey *et al* (1982) exposed cats to 16 Hz amplitude-modulated 450 MHz fields (SAR of 0.29 W/kg) and

Table 5.1 Effects in calcium efflux on nervous tissue

Model	Exposure conditions	Result	Reference
Chick brain, <i>in vitro</i>	147 MHz CW; 0.5–35 Hz AM; 10–20 W/m ²	Increase in efflux, maximum effect at 16 Hz AM. No effect of carrier frequency alone	Bawin <i>et al</i> , 1975
Chick brain, <i>in vitro</i>	147 MHz or 50 MHz ; 3–30 Hz AM	Increase in efflux at 16 Hz AM, dependent on intensity	Blackman <i>et al</i> , 1979,1980a,b
Chick brain, <i>in vitro</i>	450 MHz; 16 Hz AM	Increase in efflux dependent on intensity	Sheppard <i>et al</i> , 1979
Human neuroblastoma cells	147 or 915 MHz CW; 16 Hz AM	Increase in efflux dependent on intensity and modulation	Dutta <i>et al</i> , 1984, 1989
Synaptosomes (isolated fragments of nerve cells)	450 MHz; 16 Hz AM	Increase in efflux	Lin-Lui and Adey, 1982
Mouse brain: medial habenula nucleus, <i>in vivo</i>	2.45 GHz; 16 Hz AM	Number of calcium-containing vesicles reduced, level of calcium precipitation on surface of neurons increased	Kittel <i>et al</i> , 1996
Cat cortex, <i>in vivo</i>	450 MHz; 16 Hz AM	Sustained increase in efflux	Adey <i>et al</i> , 1982
Rat brain, <i>in vitro</i>	1 GHz pulsed; 10 or 20 ms pulses; 16 or 32 pps for 20 min; 5–150 W/m ²	No effect on efflux	Shelton and Merritt, 1981
Rat brain, loaded with radiolabelled calcium <i>in vivo</i> , exposed <i>in vitro</i>	1 GHz or 2.45 GHz pulsed; 10 ms pulses at 16 pps for 20 min; 0.29–2.9 W/kg	No effect on efflux	Merritt <i>et al</i> , 1982
Rat brain, loaded with radiolabelled calcium <i>in vivo</i> , exposed <i>in vivo</i>	2.06 GHz pulsed; 10 ms pulses at 8, 16 or 32 pps, OR 2.06 GHz CW; SAR 0.12–2.4 W/kg; 20 min	No effect on efflux	Merritt <i>et al</i> , 1982
Chick cerebral hemispheres, <i>in vitro</i>	147 MHz; 16 Hz AM; 7.5 W/m ²	No effect on efflux	Albert <i>et al</i> , 1987

AM = amplitude modulated CW = continuous wave

reported changes in calcium ion-exchange in the cerebral cortex. However, Merritt *et al* (1982) did not find such an effect in the brain of anaesthetised rats.

5.59 *CONCLUSION* Although the weight of evidence suggests that RF exposure at average levels, too low to cause significant heating, does increase the release of calcium from brain tissue, there are contradictory results. The suggestion that these effects occur specifically with fields that are amplitude modulated at extremely low frequencies is intriguing but difficult to interpret. Further, this finding is of no obvious relevance to mobile phone technology, where the amplitude modulation within the critical frequency band is very small (see paragraph 4.13). If such effects occur as a result of exposure to mobile phones, their implications for cell function are unclear and no obvious health risk has been suggested. Nevertheless, as a precautionary measure, amplitude modulation around 16 Hz should be avoided, if possible, in future developments in signal coding.

Neuronal excitability

5.60 Any tendency for calcium to move out of neurons and to accumulate on the surface of membranes would be expected to stabilise them electrically and hence to decrease the general excitability of neurons. Such effects have been described by Arber and Lin (1984, 1985), who reported an increase in membrane conductance and a decrease in the spontaneous firing of

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impulses in neurons of the snail *Helix aspersa* when exposed for an hour to continuous and amplitude modulated 2.45 GHz radiation. The effects were abolished by the application of ethylenediamine tetraacetic acid (EDTA), which chelates calcium. However, they occurred at a high RF intensity and clearly depended on a rise in tissue temperature. McRee and Wachtel (1980) described a decrease in the electrical amplitude of impulses and a reduction in the excitability of the frog sciatic nerve when exposed to 2.45 GHz radiation, but only at high levels. Wachtel *et al* (1975) and Seaman and Wachtel (1978) also described a decrease in spontaneous activity of neurons isolated from the marine gastropod *Aplysia* at relatively high intensities.

5.61 On the other hand, Chou and Guy (1978) found no obvious electrophysiological changes in the frog sciatic nerve exposed to 2.45 GHz (continuous or pulsed) at modest intensities. A slight increase in conduction velocity was found at a very high level and was probably dependent on the temperature rise, since it could be mimicked by a 1°C rise in temperature. Wang *et al* (1991), found no change in the membrane resting potential, electric capacitance, or the properties of impulses in dorsal root ganglion cells exposed *in vitro* to continuous-wave 2.45 GHz radiation under temperature-controlled conditions; recordings were made using sensitive patch-clamp techniques. Linz *et al* (1999), who also employed whole-cell patch-clamping, found no effect of low intensity continuous or pulsed RF fields on the membrane potential, action potentials or calcium and potassium currents of isolated heart muscle cells.

5.62 *CONCLUSION* There is good evidence that exposure to high intensity RF fields, sufficient to cause a significant rise in tissue temperature, reduces the excitability of neurons. Exposure that does not cause an increase in temperature produces no obvious effects.

Neurotransmitter systems

5.63 Changes in the amount of neurotransmitter substance released by nerve terminals could alter brain function. Since release is dependent on intracellular calcium levels, there has been concern that it could be affected by RF radiation.

5.64 Modak *et al* (1981) reported that RF exposure caused a decrease in the concentration of the important transmitter acetylcholine in the mouse brain, but they employed a very intense 2.45 GHz single pulse, causing a 2–4°C rise in temperature. The rate-limiting step in the synthesis of acetylcholine is the uptake of choline by nerve cells. In an extensive series of experiments, Lai and colleagues (Lai *et al*, 1987, 1989a,b, 1990, 1991, 1994) have reported that 20 minutes of exposure of rats to pulsed 2.45 GHz radiation at low intensities causes an increase in choline uptake and a reduction in the concentration of acetylcholine receptors, whereas exposure for 45 minutes has the opposite effects (Table 5.2). These effects were found to be prevented by pretreatment of the animals with naltrexone (which blocks opioid receptors) or with corticotrophin-releasing hormone. Although the average intensities used in these studies were relatively low, the findings might depend on thermal effects, especially since acetylcholine is known to be involved in transmission in the parts of the hypothalamus responsible for temperature regulation, which is acutely sensitive to temperature change. Moreover, as discussed below, the studies by Lai *et al* used radar-like pulses of quite high peak intensity that are capable of eliciting auditory responses in animals, which themselves might have behavioural effects.

5.65 Dutta *et al* (1992) detected an increase in the activity of the enzyme acetylcholinesterase (which hydrolyses acetylcholine) in cultured human neuroblastoma cells exposed to low intensity RF fields, amplitude modulated at 16 Hz. Curiously, these effects were reported to occur over an SAR “window” – ie within a narrow range of SAR values, but not at lower or higher intensities. On the other hand, Galvin *et al* (1981) and Millar *et al* (1984), who examined the effects of continuous and pulsed 2.45 GHz RF fields on purified solutions of acetylcholinesterase, detected

Table 5.2 Effects on cholinergic systems

Model	Exposure conditions	Results	References
Rat brain	2.45 GHz pulsed; 2 μ s pulses at 500 pps; 0.6 W/kg	Exposure for 45 min decreased choline uptake and concentration of acetylcholine receptors. Exposure for 20 min opposite effect seen. Effects blocked with naltrexone	Lai <i>et al</i> , 1987, 1989a,b, 1990, 1991, 1994
Human neuroblastoma cells	147 MHz; 16 Hz AM	Increase in acetylcholinesterase activity at 0.02 and 0.05 W/kg. No effect at 0.005 or 0.1 W/kg	Dutta <i>et al</i> , 1992
Solution of acetylcholinesterase	2.45 GHz CW or pulsed; 16.7 ms pulses, 10–90 pps; up to 100 W/kg	No effects	Galvin <i>et al</i> , 1981; Millar <i>et al</i> , 1984
Guinea pig	3 GHz CW or pulsed; 400 pps (no pulse width specified); 35–250 W/m ²	Decrease in acetylcholinesterase activity	Baranski <i>et al</i> , 1972

AM = amplitude modulated CW = continuous wave

no influence on the activity of the enzyme, even with SARs up to 100 W/kg. The use by Dutta *et al* of 16 Hz amplitude modulation, the frequency of modulation reported to produce calcium efflux (see paragraphs 5.53–5.59) might have been critical, although it is not clear how such modulation can have a specific effect on tissues. Without a theoretical basis, the non-linear dependence of effects on intensity (the SAR window phenomenon) is very surprising: the possibility that such window effects are merely due to chance variation, or some undefined experimental artefact should be kept in mind.

5.66 In contrast to the above, Baranski *et al* (1972) reported a decrease in the activity of acetylcholinesterase in guinea pigs exposed to pulsed RF fields at high power densities, but they attributed this to thermal effects.

5.67 Attention has also focussed on the amine transmitters norepinephrine (noradrenaline) and serotonin (5-hydroxytryptamine), which may determine arousal and mood, but, more pertinently, are involved in the hypothalamic mechanisms that regulate body temperature (Brück and Hinckel, 1990). Amine transmitters are released in many parts of the brain by the terminals of axons from cell groups in the brain stem. The various changes in levels of these transmitters and their metabolites after acute and long-term exposure to RF (see, for example, Snyder, 1971; Grin, 1974; Merritt *et al*, 1977; Inaba *et al*, 1992) may well be due to short-term and adaptive responses to thermal effects, since most of the experiments involved quite intense stimulation (see Hermann and Hossmann, 1997).

5.68 *CONCLUSION Most of the work on neurotransmitter systems has used high power densities and has probably revealed thermoregulatory or other responses to temperature change. However, in view of the essential role of neurotransmitters in brain function and the involvement of specific transmitter systems in the regulation of emotion, memory, sleep, etc, this area deserves further investigation, including the assessment of these functions in human subjects.*

Electroencephalograms (EEGs) in animals

5.69 Electrophysiological experiments in animals have mainly involved the recording of “gross” potentials from the brain with electrodes placed on or within the brain. Since the work of Adey and his colleagues in the early 1970s, there has been interest in the possibility that exposure to low levels of pulsed RF alters the electrical activity of the brain in cats and rabbits (Table 5.3).

Table 5.3 Effects on EEG rhythms in animals

Model	Exposure conditions	Results	References
Cats	147 MHz; 1–25 Hz AM; up to 10 W/m ² . SAR estimated as 0.015 W/kg (WHO, 1993)	Changes in EEG conditioned rhythms	Bawin <i>et al</i> , 1973, 1974
Rats and rabbits	2.375 GHz; 7 h/day for 30 days; 0.1–5 mW/m ²	Changes in EEG	Shandala <i>et al</i> , 1979
Rats	425 MHz; 100 W/m ² AND 2.45 GHz; 50 W/m ² ; from late gestation until 92 days old	No effects on spontaneous or evoked EEG	McRee <i>et al</i> , 1979
Rats	2.45 GHz CW; 2.7 W/kg; 7 h	No consistent changes in spectral power	Mitchell <i>et al</i> , 1989
Rats	2.45 GHz CW or AM at 16 Hz	Changes in spectral power with SARs in brain of 8.4 W/kg and above	Thuroczy <i>et al</i> , 1994

AM = amplitude modulated CW = continuous wave

- 5.70** Bawin *et al* (1973, 1974) exposed cats, which had been previously conditioned to produce selected EEG rhythms in response to a light flash, to low level RF fields. Changes were reported in the performance of the conditioned EEG response task and in various other behavioural parameters. It was argued that the fields acted directly on brain tissue causing a minute release of calcium (see paragraphs 5.53–5.59), resulting in changes in membrane excitability (see paragraphs 5.60–5.62), which could possibly affect EEG rhythms.
- 5.71** Takashima *et al* (1979) reported changes in the EEG of rabbits following exposure to a modulated RF field of 1–10 MHz, a frequency range outside the main interest of the present document. Following long-term exposure, changes in the frequency spectrum of the EEG were reported, with enhanced low frequency components and reduced higher frequency activity, similar to the changes that occur during drowsiness. Single, short-term exposures to modulated 1–30 MHz fields were without effect. The SAR could be estimated to be about 1 mW/kg and no rise in body temperature was detected during exposure. This study, however, employed few animals and there might have been artefacts due to the presence of implanted metal electrodes in the head during irradiation.
- 5.72** There have also been reports of subtle effects on the EEG in rats and rabbits exposed to RF fields within the frequency range of interest (Shandala *et al*, 1979; Thuroczy *et al*, 1994). However, the most consistent effects have been found at high intensities. Neither of these studies relates directly to mobile phone exposures, and neither the stimulation conditions needed or the nature of changes in the EEG are firmly established. McRee *et al* (1979) described experiments by Rosensteig of the US Environmental Protection Agency, who exposed rats to RF from late fetal life until adult. He saw no changes in either the spontaneous EEG or the electrical responses evoked by flashes of light (visual evoked responses). Mitchell *et al* (1989) reported the findings of a joint project on this subject carried out in the USA and the former Soviet Union. Both groups exposed rats to fairly intense continuous-wave RF fields for seven hours. Interestingly, both teams found small but statistically significant reductions of power in the EEG, but in different parts of the frequency spectrum.
- 5.73** *CONCLUSION Studies of the EEG in animals have generally not employed conditions that are directly relevant to mobile phone technology, and the results have been mixed. However, some experiments have produced evidence of non-thermal effects from RF fields on brain activity.*

Experiments on human volunteers, with exposure conditions similar to those experienced in using a mobile phone, have been more informative (see paragraphs 5.188–5.193).

Thermoregulatory behaviour

5.74 Mammals employ various physiological and behavioural mechanisms to regulate and stabilise their body temperature and thermoregulatory behaviour can be exhibited when RF exposure is sufficiently intense to generate heat. These studies have been well described by UNEP/WHO/IRPA (1993), who concluded that thermoregulatory responses from RF exposure were similar to those elicited by conventional radiant heat sources. However, the overall response depends on the distribution of RF absorption and thus on the RF frequency. At frequencies below 10 GHz, RF fields are more deeply penetrating than infrared radiation and thus less effective in stimulating superficial temperature-sensitive receptors in the skin, which are particularly involved in local and whole-body thermoregulatory responses (Adair, 1983; Adair *et al*, 1999). Thermoregulatory responses depend largely (but not exclusively) on the total heat load to the animal. Such responses can be elicited by whole-body SARs that are comparable to the basal metabolic rate (which in people is about 1 W/kg). It is therefore important to distinguish between whole-body and partial-body exposures. The latter can be of the order of 1 W/kg for mobile phones, even though the total heat added to the body is negligible.

Motor activity

5.75 Measurement of locomotion is often used to assess gross levels of brain activity and arousal. Some animals decrease their motor activity in order to lower their endogenous heat production, as part of their thermoregulatory behaviour. Acute and long-term RF exposures have been reported to reduce spontaneous motor activity in rodents. Typical studies are described by UNEP/WHO/IRPA (1993) and summarised in Table 5.4. A lifetime study reported that activity

Table 5.4 Effects on motor activity

Method	Exposure conditions	Results	References
Rats	2.45 GHz pulsed; 2.5 µs pulses at 120 pps; 6.3 W/kg; 30 min	Immediate decrease; no effect after 2 h	Hunt <i>et al</i> , 1975
Rats	2.45 GHz CW; 2.7 W/kg; 7 h	Decrease; plus less responsive to novel acoustic stimuli	Mitchell <i>et al</i> , 1988
Rats	918 MHz CW; 3.6–4.2 W/kg; 10 h/night for 3 weeks	Decrease in activity and changed time-distribution of activity	Moe <i>et al</i> , 1976
Rats	2.45 GHz CW; 0.14 W/kg and 0.7 W/kg; 7 h/day for 14 weeks	No effects at 0.14 W/kg. Decreased activity 30 days after exposure at 0.7 W/kg	D'Andrea <i>et al</i> , 1986a,b
Rats	2.45 GHz CW; 1.2 W/kg and 915 MHz CW; 2.5 W/kg; 8 h/day; 5 days/week for 16 weeks	Decrease using 2.45 GHz, but no change overnight. No effect at 915 MHz	D'Andrea <i>et al</i> , 1979, 1980
Rats	3 or 10.7 GHz CW; 185 h or 3 GHz pulsed; 1.3 µs pulses at 769 pps; 0.15–0.3 W/kg; 408 h	No effect. Other stereotypic activities also not affected	Roberti <i>et al</i> , 1975
Rats	2.45 GHz pulsed; 10 µs pulses at 800 pps; pulse-modulated at 8 Hz; 0.15–0.4 W/kg; 2–27 months	No effect except for a decrease in activity during first test session. Lifetime exposure of rats	Johnson <i>et al</i> , 1983 Guy <i>et al</i> , 1985

CW = continuous wave

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levels were reduced after 6 weeks continuous exposure of young rats to 2.45 GHz pulsed RF fields at up to 0.4 W/kg. However, activity returned to control levels during subsequent exposure for up to 27 months.

Auditory responses

- 5.76** Animals may perceive auditory sensations when their heads are exposed to radar-like pulsed RF fields. Auditory perception of pulsed RF fields, the so-called “microwave hearing” effect, is an established phenomenon, which is produced by thermally generated sounds, due to minute thermoelastic expansion effects within the soft tissues of the head, which are conveyed to the inner ear by conduction through bone (UNEP/WHO/IRPA, 1993). The transient temperature increase and the duration of the increase (determined by the RF pulse width except for very short widths) determine whether the RF-induced acoustic vibrations can be perceived. There are good theoretical reasons to believe that microwave hearing does not occur with mobile phone signals. The acoustic sound pressure generated by a RF pulse is proportional to the rate of temperature increase. To produce audible acoustic vibrations requires a very high transient rate of heating of tissues in the head, around 1°C per second, which is considerably higher than is produced by current pulsed mobile phone signals. Thus the effect has little relevance to health effects of mobile phone signals, but must be kept in mind when interpreting animal studies that employed radar-like pulses.
- 5.77** Responses to pulsed RF fields can be detected by recording from the auditory nerve or other parts of the auditory pathway in the brain (Taylor and Ashleman, 1974; Chou and Guy, 1979; Chou *et al.*, 1982; Seaman and Lebowitz, 1989). These responses are in all respects identical to ordinary hearing phenomena and there is little doubt that they are perceived as sound by the animal. Chou *et al.* (1985) estimated the threshold in the rat at about 1 mJ/kg for pulses briefer than 35 µs (1 mJ/kg in a pulse lasting 35 µs is equivalent to a peak SAR of 30 W/kg). It is well established that these auditory sensations produce behavioural effects in awake animals. Animals might be slightly stressed if they can hear pulsed RF fields, and this should be taken into account when considering any behavioural effects of RF exposure.
- 5.78** Exposure to very intense pulsed RF fields is reported to suppress the startle response and evoke body movements in conscious mice (NRPB, 1993; Sienkiewicz *et al.*, 1993; UNEP/WHO/IRPA, 1993). The startle response was suppressed by 1 µs pulses with SAs of 200 mJ/kg (equivalent to a peak SAR of 200,000 W/kg), and body movement was elicited by 10 µs pulses with SAs of 2000 J/kg (peak SAR 20,000,000 W/kg) – far above the threshold for auditory perception. Although the mechanism for these effects is not well established, such intense pulses certainly elicit microwave hearing, and it is conceivable that some effects derive from the high electric fields associated with these intense pulses as well as from transient heating.
- 5.79** *CONCLUSION* Auditory perception of intense pulsed RF fields may elicit behavioural responses. This phenomenon has not been explored using conditions that are directly relevant to mobile phone technology, but it is unlikely to occur at the peak intensities of pulsed fields associated with mobile phones.

Learning and memory

- 5.80** To detect changes in learned behaviour, operant techniques are used that investigate behavioural responses, such as pressing a lever following a visual or auditory cue. Spatial memory can be tested in a radial-arm maze, in which a food pellet is placed at the end of each arm and the time is determined for the animal to collect all the food pellets. Animals must remember which arm they have entered so as to collect all the pellets in the shortest time. This technique provides a means of assessing the performance of specific learned tasks in a highly quantified and standardised

manner. However, threshold values for changes in behaviour will depend on many factors, such as the complexity of the task being performed. To quote a single threshold value for a range of tasks would be an oversimplification.

- 5.81** Results of earlier studies on rodents have shown that the threshold at which acute RF exposure disrupts learned operant behaviour lies between 2.5 and 8 W/kg whole-body SARs, with an associated rectal temperature rise of about 1°C. Deficits in the performance of a previously learned behaviour occur following long-term exposure to 2.45 GHz fields at SARs as low as 2.3 W/kg whole-body exposure. The initial acquisition of operant learned tasks by rats appears to be more sensitive to disruption by RF fields, the thresholds for long-term exposure to pulsed 2.8 GHz fields being between 0.7 and 1.7 W/kg whole-body exposure (UNEP/WHO/IRPA, 1993). The pulsed fields used in many of these studies involved brief, rather intense pulses such as those produced by radar equipment, which may have elicited auditory sensations in the animals, a potential confounding factor in the interpretation of the studies.
- 5.82** There is a distinct difference in response between rodents and primates. Changes in operant performance responses in primates occur at higher threshold RF exposures. Such changes were detected from acute exposure of rhesus and squirrel monkeys to 1.3–5.8 GHz fields at whole-body SARs of 4–5 W/kg. Exposure of rhesus monkeys to the RF field at which they absorb the maximum amount of energy (resonant frequency, 225 MHz) resulted in reduced task performance at a whole-body SAR of 2.5 W/kg. As with rodents, these changes in performance were accompanied by a raised body temperature of about 1°C (UNEP/WHO/IRPA, 1993). Since primates are much closer in size to people than are rodents, these data were used as the basis for standards limiting RF exposure.
- 5.83** Under some circumstances, ongoing learned behaviour can be stopped by exposure above a threshold corresponding to a whole-body SAR of about 4 W/kg. Many factors are known to modify this value, however, including the frequency of the applied field, the ambient temperature and relative humidity, and the animal size and species. Under the most adverse environmental conditions, changes in behaviour may be observed with whole-body SARs as low as 1 W/kg.
- 5.84** This interpretation is supported by the results of a study investigating working memory. Mickley *et al* (1994) found that acute exposure to 600 MHz fields at an SAR of up to 10 W/kg for 20 minutes produced significant deficits in memory in rats only when the exposure caused rises in rectal and brain temperatures of at least 1°C. These changes were correlated with an increase in expression of the *c-fos* gene in the cortex (see paragraph 5.119). The authors concluded that the observed changes in memory and behaviour were dependent on a rise in body temperature.
- 5.85** However, some studies conducted on rats exposed to pulsed RF fields appear to challenge the conclusion that learning is disturbed only when radiation produces significant increases in body temperature. In experiments by Lai *et al* (1989a) on spatial learning, rats had to learn to forage for food pellets located at the ends of the arms of a radial-arm maze, using cues in the environment. Animals exposed for 20 minutes to low level, pulsed 2.45 GHz fields (average whole-body SAR of 0.6 W/kg), immediately before daily training sessions in the maze, were reported to show improved learning for the first two days, although final performance and overall accuracy were not affected. The RF fields did not cause a measurable rise in colonic temperature. However, the performance of the exposed animals was generally less stable than that of the controls, which raises questions about the significance of this result.
- 5.86** Later, Lai *et al* (1994) reported that rats acutely exposed to pulsed 2.45 GHz fields (whole-body SAR 0.6 W/kg), for 45 minutes each day, immediately before testing in the maze, consistently made *more* errors than did the control animals. Further work suggested that this apparent effect

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on learning might be due to effects of RF exposure on nerve pathways in the brain that use endogenous opioid neurotransmitters.

- 5.87** In the same laboratory, Wang and Lai (2000) have also reported RF-induced changes in spatial memory as assessed in a circular water maze, in which rats had to learn to escape from the water by swimming to a submerged platform that they could not see. Male rats that had been acutely exposed for 60 minutes to pulsed 2.45 GHz fields (pulse width 2 μ s, 500 pps), at a fairly high whole-body SAR of 1.2 W/kg, took longer to find the platform than did control animals during the training sessions. In a “probe trial” without the platform present, the exposed animals spent less time swimming in the quadrant of the maze that should have contained the platform than did control animals. They also spent more time trying to climb up the sidewalls of the maze, as if they had no recollection of the task. It was concluded that exposure had disrupted spatial reference memory functions and that the exposed animals had to use other, less efficient learning strategies to locate the platform. However, the energy per pulse in this study can be calculated to be 2.4 mJ/kg (peak SAR of 2400 W/kg), which would have caused rapid, transient heating. This level of pulse energy almost certainly exceeds the threshold for microwave hearing in rats (Chou *et al*, 1985; see paragraph 5.76). Since the slight stress caused by explicit noise can modify behaviour, it is possible that the results reported in some of the studies by Lai *et al* were due to microwave hearing. It is also conceivable that the electric fields associated with such a high peak SAR might have caused non-thermal effects on nerve cells. If the findings are due to the high peak-pulse energy, they are not relevant to human exposure to mobile phone radiation, which has different modulation characteristics.
- 5.88** For both the Lai *et al* (1994) and Wang and Lai (2000) studies, there are also statistical problems that suggest internal inconsistencies in the results. These studies involved investigation of spatial memory in either a radial-arm or water maze using a time (ie training session) \times group (exposed *versus* non-exposed) design. In both studies large time effects were observed, such that the animals became more adept at the task as the training progressed. However, in neither study was there a group \times time interaction, indicating that the exposure was affecting the rate at which the task was learned.
- 5.89** Sienkiewicz *et al* (2000), using an experimental design very similar to that of Lai *et al* (1994), exposed mice to 900 MHz RF radiation pulsed at 217 Hz at a whole-body SAR of 0.05 W/kg. The behaviour of the animals was tested each day for 10 days in an eight-arm radial maze, either immediately after exposure for 45 minutes, or after delays of 15 and 30 minutes. There were no significant differences in either the original performance of the exposed animals, the rate at which their learning increased or the final levels of performance. However, the animals tested immediately after exposure took longer to complete the task and exhibited a more erratic performance than the other animals. It is possible that these changes may have been induced by a mild stress associated with auditory perception of the field. This experiment was not an exact duplication of the Lai *et al* (1994) study, since it used mice, rather than rats, an eight-arm instead of a twelve-arm maze, and a much lower SAR.
- 5.90** Overall, these and other studies (see D’Andrea, 1999) provide weak evidence for a specific effect of RF fields on spatial memory, and some artefact associated with exposure may have affected the performance of the rats in those experiments in which effects were found. In particular, it is possible that the animals may have perceived the pulsed RF fields and this may have contributed to the observed behavioural changes. A summary of the results of earlier studies is given by UNEP/WHO/IRPA (1993) and more information about recent work is given in Table 5.5.

Table 5.5 Studies on learning

Model	Exposure conditions	Results	References
Rats, 12-arm maze	2.45 GHz pulsed; 2 μ s pulses; 500 pps; 0.6 W/kg; 20 min/day for 10 days	Fewer errors for two days, no effect overall	Lai <i>et al</i> , 1989a
Rats, 12-arm maze	2.45 GHz pulsed; 2 μ s pulses; 500 pps; 0.6 W/kg; 45 min/day for 10 days	More errors each day	Lai <i>et al</i> , 1989a, 1994
Rats, Water maze	2.45 GHz pulsed; 2 μ s pulses; 500 pps; 1.2 W/kg; 60 min/session; 2 sessions/day for 3 days	Took longer to locate submerged platform	Wang and Lai, 2000
Mice, 8-arm maze	900 MHz pulsed; 576 μ s pulses; 217 pps; 0.05 W/kg; 45 min/day for 10 days	No effect	Sienkiewicz <i>et al</i> , 2000
Operant tasks: rats	2.8 GHz pulsed; 2 μ s pulses; 500 pps; for 30 min	Impaired acquisition threshold at 1.7 W/kg whole-body exposure	Schrot <i>et al</i> , 1980
Operant task: rats	360, 480, 500, 600 MHz CW; up to 25 min or 55 min	Threshold for reduced performance > 4–6 W/kg whole-body exposure	D'Andrea <i>et al</i> , 1976, 1977
Operant task: rats	2.45 GHz CW; 110 5 h sessions over 22 weeks	Impaired performance at 2.3 W/kg whole-body exposure	Mitchell <i>et al</i> , 1977
Operant task: rats	2.45 GHz CW; 60 min	Threshold for reduced performance > 2.5–8 W/kg whole-body exposure	Sanza and de Lorge (1977); de Lorge and Ezell (1980)
Operant task: rhesus monkey	1.2 GHz CW; SAR 0.8 or 1.6 W/kg; 120 min	No effect	Scholl and Allen, 1979
Operant task: rhesus monkey	225 MHz CW OR 1.3 GHz pulsed; 3 μ s pulses; 370 pps OR 5.8 GHz pulsed; 0.5 or 2 μ s pulses; 662 pps	Threshold for impaired performance 2.5 W/kg (at 225 MHz) or 4–5 W/kg (at 1.3 and 5.8 GHz) whole-body exposure	De Lorge, 1984
Working memory task: rats	600 MHz (CW); SAR 0.1–10 W/kg; 20 min	Impaired performance at 1 °C rise in body and brain temperature (>9 W/kg) whole-body exposure	Mickley <i>et al</i> , 1994

CW = continuous wave

5.91 The hippocampus (a forebrain structure, buried on the inside of the temporal lobe) has been implicated in spatial learning in many animals, and in the laying-down of “episodic”, personal memories in people. Damage to the hippocampus interferes with these forms of learning and certain synaptic connections between neurons in the hippocampus are capable of rapid and long-lasting changes in transmission efficiency, which might constitute the cellular basis of the memory trace. The hippocampal slice preparation, in which the activity of neurons and the efficiency of synaptic transmission can be directly measured, *in vitro*, is widely used to investigate these cellular mechanisms (Kandel *et al*, 1991). Wood *et al* (2000) have recently used this technique to examine the effects of RF fields on electrical activity in the hippocampus. Short-term exposure to very low intensity 700 MHz radiation in the absence of any detectable increase in temperature resulted in transient changes in evoked and spontaneous activity. Curiously, the changes were very variable, but exposure at about 0.001 W/kg generally led to a decrease in activity. It is difficult to interpret these results, especially the variability of the effects,

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but if they were to occur *in vivo*, they might influence learning and memory. It must be emphasised, however, that the human hippocampus lies deep in the human brain, where very little energy is absorbed from a mobile phone.

- 5.92** *CONCLUSION* Increases in core temperature of 1°C or more certainly lead to changes in the performance of well-learned tasks and other simple behaviours. However, there is no consistent experimental evidence that exposure to low level RF fields affects learning and memory in animals. The studies of Lai and co-workers challenge these conclusions and suggest that spatial learning can be disturbed at average SARs below 1 W/kg. However the peak-pulse energy was much higher than that associated with mobile phones, the effects reported were statistically weak and they have not been reproduced by Sienkiewicz *et al* (2000) using 900 MHz fields. D'Andrea (1999) has speculated that some cognitive tasks may show particular sensitivity to RF exposure, and effects on these behaviours may occur at SARs below those required to disrupt simple, well-learned tasks. Few studies have yet explored this possibility. The hippocampal slice preparation shows great potential for the study of RF field effects: more research is indicated. However, studies on human subjects are needed to assess whether fields associated with mobile phones have any effect on memory or learning.

Blood–brain barrier

- 5.93** Early work suggested that the blood–brain barrier, which normally prevents large molecules from crossing into the cerebrospinal fluid from the blood, might be susceptible to low level pulsed RF fields. Effects on permeability of the barrier have been investigated by comparing the penetration into the brain in exposed and control animals after intravenous injection of various compounds. Interest began when Frey *et al* (1975) reported increased penetration of the blood–brain barrier of anaesthetised rats after acute low level exposure to pulsed or continuous-wave 1.2 GHz fields. Oscar and Hawkins (1977) then reported that the acute exposure of anaesthetised rats to pulsed 1.3 GHz fields at similar SARs increased the uptake of radiolabelled saccharides. However, later, more rigorous studies indicated that the early studies might have been confounded by various factors including alteration in cerebral blood flow, the effect of the anaesthetic, and changes in renal clearance (Blackwell and Saunders, 1986; UNEP/WHO/IRPA, 1993).
- 5.94** Two studies (Neubauer *et al*, 1990; Salford *et al*, 1994) have reported increased blood–brain barrier permeability to protein (albumin) following RF exposure at SARs as low as 0.016 W/kg. Later studies (Fritze *et al*, 1997a; Nagawa and Uneo, 1999) have, however, failed to confirm these results.
- 5.95** *CONCLUSION* The available evidence for an effect of RF exposure on the blood–brain barrier is inconsistent and contradictory. Recent, well-conducted studies have not reported any effects.

Studies of melatonin

- 5.96** Melatonin is a hormone secreted by the pineal gland, which controls our diurnal rhythm (day–night cycle). Peak levels are produced in people during the night (in the dark period). Melatonin affects the mammalian reproductive system, as well as other physiological and biochemical functions (Reiter, 1991). The function of the pineal gland is strongly influenced by visible radiation, because signals from the optic nerve affect the suprachiasmatic nucleus in the hypothalamus, which in turn regulates the secretion of melatonin from the pineal gland. The cyclical pattern of light and dark imposes seasonal as well as circadian rhythms in some mammals (Reiter, 1993). Melatonin is an efficient scavenger of free radicals, which can damage cells, and there is evidence that melatonin has a protective effect against cancer. Thus, changes in melatonin secretion could conceivably alter tumour initiation and promotion (NRC, 1997; NIEHS, 1998).

- 5.97** There are reports that extremely low frequency (ELF) electromagnetic fields may affect pineal function, although the data are inconsistent. This has led to the “melatonin hypothesis”, suggesting a link between ELF fields and cancer (Stevens, 1987). This raises the question whether exposure to RF fields might also have an effect on the pineal gland. Radiofrequency photon energies are much higher than those at ELFs, lying between the ELF and visible parts of the electromagnetic spectrum. In contrast to visible radiation, neither ELF fields nor RF fields directly affect photopigments in photoreceptors in the eye, and they are therefore very unlikely to affect pineal function by the same anatomical pathway as does visible radiation. It is conceivable that RF fields might influence the synthesis or secretion of melatonin by the pineal gland through a direct influence on either the suprachiasmatic nucleus or the pineal gland itself, although there is no obvious theoretical reason to expect such influences.
- 5.98** Only a few studies testing effects of RF exposure on melatonin synthesis have been conducted. Stark *et al* (1997) studied dairy cattle herds located in the vicinity of a short-wave (3–30 MHz) radio antenna. Their data showed no chronic effect on salivary melatonin levels, although a short-term rise in melatonin was noted when the antenna was energised after being turned off for three days. In a laboratory study specifically designed to study pineal function of rats and hamsters exposed to very low level 900 MHz fields for up to six hours, no effects on nocturnal melatonin production were found (Vollrath *et al*, 1997).
- 5.99** *CONCLUSION Although few studies have been conducted, they do not suggest that exposure to RF fields affects pineal function or melatonin production. Relevance to the use of mobile phones could, in any case, be assessed only through laboratory studies of people because of species differences in the pattern of circadian rhythms. It must also be emphasised that the hypothalamus and pineal gland are much further from the surface of the head in people than in animals. Therefore, even if there were an effect on melatonin production in animals resulting from a direct interaction of fields within the brain, it would be much less likely to occur in people.*

Effects on the eye

- 5.100** The lens of the eye is potentially sensitive to RF exposure because it lacks a blood supply and therefore has reduced ability to dissipate heat. Further, the fibres that make up the bulk of the lens have only a limited capacity for repair and hence the effects of minor insults tend to accumulate, resulting in clouding of the lens (cataract).
- 5.101** Many studies conducted to determine the threshold for RF-induced cataracts have concluded that very high exposures are needed for at least 1 hour to produce lens cataracts (UNEP/WHO/IRPA, 1993). The single acute exposure threshold to produce a cataract at 2.45 GHz corresponds to an SAR in excess of 100 W/kg for more than 1 hour, with the temperatures in the eye exceeding 43 °C. Repeated subthreshold exposures at levels just below this threshold would finally produce a cataract, provided that the accumulated damage could not be repaired before the next exposure (Carpenter, 1979). Near-continuous, long-term RF exposures at moderate intensity (100 W/m²; peak SAR in the head 17 W/kg) did not produce cataracts in rabbit eyes (Guy *et al*, 1980).
- 5.102** Degenerative changes have been reported in various eye tissues of primates after exposure to pulsed RF fields (Table 5.6). Studies in this area have been summarised by Kues and Monahan (1992a) and Lu *et al* (2000). Localised exposure of the eyes of anaesthetised monkeys to pulsed 2.45 GHz fields at an SAR in the eye of 2.6 W/kg for several hours resulted in lesions in the corneal endothelium (Kues *et al*, 1985) and increased the vascular leakage from the blood vessels of the iris. Lesions in the cornea were also induced by exposure to 2.45 GHz fields, with pulsed fields being more effective than continuous-wave radiation. Topical pretreatment with the ophthalmic drug timolol maleate (used for treatment of glaucoma) appeared to reduce the

threshold for these effects to 0.26 W/kg (Kues *et al*, 1992). Intermittent exposure over a 10-week period resulted in early degenerative changes in the retina, which were also exacerbated by application of timolol maleate. In contrast, Kamimura *et al* (1994) reported that they were unable to induce corneal, lenticular or retinal lesions in the eyes of non-anaesthetised macaque monkeys exposed to continuous-wave (but not pulsed) 2.45 GHz radiation at levels exceeding the threshold for continuous-wave-induced corneal damage described by Kues *et al* (1985).

Table 5.6 Effects of RF fields on the eye

Model	Exposure conditions	Results	References
Rabbits	2.45 GHz; 100 W/m ² ; 17 W/kg; 23 h/day for 180 days	No cataracts produced	Carpenter, 1979
Anaesthetised monkeys	2.45 GHz pulsed; 10 µs pulses at 100 pps; 26 mJ/kg per pulse; average SAR 1.3–3.9 W/kg; 3 exposures of 4 h	Lesions in corneal endothelium, increased vascular leakage in iris	Kues <i>et al</i> 1985, 1992; Kues and Monahan, 1992a
Rabbits and macaque monkeys	60 GHz; 100 W/m ² ; 8 h, plus 4 h/day for 5 days	No effects on the eye	Kues <i>et al</i> , 1999
Non-anaesthetised monkeys	2.45 GHz CW	No effects	Kamimura <i>et al</i> , 1994
Monkeys	1.25 GHz pulsed; 5.59 µs pulses; 0.59, 1.18 and 2.79 pps; peak SAR 1.3 MW/kg; average SAR in retina 4.3, 8.4 or 20.2 W/kg; 4 h/day, 3 days/week for 3 weeks	No effects on retinal structure. Electric responses of retinal cells slightly increased at higher SARs	Lu <i>et al</i> , 2000
Non-anaesthetised monkeys	1.25 GHz pulsed; 0.5 µs pulses; 16 pps; 0.4 W/kg OR 2.7 GHz; 1 µs pulses; 20 pps; 2.6 W/kg	Transient changes in electrical activity induced by repeated exposure	Kues and Monahan, 1992b
Monkeys	5.6 GHz pulsed; 2.3 µs pulses at 100 pps; 1 W/kg	No effect on visual function	D’Andrea <i>et al</i> , 1992

CW = continuous wave

5.103 Transient changes in the electrical activity of the retina of the eyes of monkeys, in response to light stimulation, have been reported following repeated exposures to pulsed 1.25 or 2.7 GHz fields (Kues and Monahan, 1992b). Changes in electrical responses were attributed to field-induced degeneration of the photoreceptors, particularly of the cones. However, D’Andrea *et al* (1992) reported a lack of effect on visual function of monkeys exposed to pulsed 5.6 GHz RF radiation. This disparity seems puzzling in view of the fact that the average SAR was quite similar in the two studies. However, it is possible that the difference between these two studies is explained by differences in the peak SAR per pulse in the pulsed radiation. Taking into account pulse duration and frequency, peak SARs in the study of Kues and Monahan (1992b) can be calculated to be 50,000 and 130,000 W/kg, while that in the work by D’Andrea *et al* (1992) was 4,000 W/kg. This highlights the crucial importance of specifying the energy per pulse in research using pulsed radiation. Very recently, Lu *et al* (2000) have described a slight enhancement of electrical responses from the retina in monkeys exposed to 1.25 GHz RF fields pulsed at low rates with intense pulses (peak retinal SAR 1,300,000 W/kg), but without any obvious change in retinal structure.

- 5.104** *CONCLUSION* The intensities of pulsed RF fields employed in these studies were well above the SAR and specific absorption that could occur in the eye from the use of current mobile phones. However, the studies do raise important concerns about possible adverse health effects in the eye from high peak-power, pulsed RF fields.

Overall conclusions of effects on the nervous system

- 5.105** *The potential of RF fields to affect the nervous system has been addressed using a variety of model systems. The most consistent evidence indicates that changes in neuronal excitability, neurotransmitter function, and innate and learned behaviours will occur when exposure induces significant heating, such that core body or local tissue temperatures increase by about 1°C or more. The evidence for effects in the absence of heating is generally not consistent and convincing. However, some studies suggest that low level exposure at specific frequencies of amplitude modulation and energy levels may affect membrane proteins, the flux of calcium and other ions across the membranes of neurons, and EEG rhythms. The relevance of these results to mobile phone technology and to human health is unclear.*
- 5.106** *Despite much publicity, the evidence for an effect on spatial memory in rats in the absence of whole-body heating is weak. In addition, there are differences in the pattern of RF energy deposition between rodents and people. This makes direct extrapolation from these animal studies to changes in human cognitive performance uncertain. The tissue penetration of RF fields means that, while the intensity of exposure is fairly uniform within the small brain of a rodent, only regions close to the ear will be effectively exposed in the much larger human brain. Primate brains, however, not only have greater anatomical similarity to those of people, but also have similar proportions, resulting in a better model of the distribution of absorbed energy.*

Cancer-related studies: can RF exposure affect carcinogenic processes?

- 5.107** The DNA in our chromosomes, which controls the growth and function of our cells, is normally remarkably stable: indeed, there are a variety of mechanisms for protecting DNA and repairing damage. Certain substances and other agents (eg X-rays) that cause damage to DNA are called *genotoxic* or *mutagenic*. Genotoxic injury of a cell can reveal itself in various ways, particularly as abnormalities in the appearance of the chromosomes, shrinkage of the cell nucleus, and mutation.
- 5.108** Genotoxic injury occurs constantly in our bodies, partly because we are exposed to a variety of natural and artificial mutagens, and partly because it can occur spontaneously through random errors in the replication of DNA during cell division. Most damage is repaired. If it is substantial, the cell can die. However, certain sequences of modest genetic damage can result in mutations that push a cell in a number of steps towards the cancerous state (conventionally described as *initiation*, *promotion* and *progression*). The cells eventually proliferate through rapid cell division (Santini *et al*, 1988; Cohen and Ellwein, 1991; Wu *et al*, 1994).
- 5.109** It is now widely agreed that cancer is initiated by alterations in the genetic material (DNA) in the cell (genotoxic effects), although some non-genotoxic chemicals and processes (called epigenetic carcinogens) have been recognised. After initiation, the cell may progress to full malignancy without any further external stimulus but more often further events are required, which may be further genomic alterations or other cellular events such as a stimulus to divide or the absence of signals required for cell differentiation. An agent which will cause this further progression towards malignancy is often termed a promoting agent.
- 5.110** Studies of possible genotoxic effects of RF radiation, enhanced cell proliferation and inappropriate gene expression have been carried out at the cellular level. In addition, there have

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been a number of long-term studies of cancer induction in animals, including tests of epigenetic interaction with known carcinogens.

Ornithine decarboxylase: does RF exposure, *in vitro* or *in vivo*, affect catalytic action?

- 5.111** Protein kinases, such as ornithine decarboxylase (ODC), are key enzymes that are normally activated as a result of the action of hormones, growth factors and lymphokines on receptors in cell membranes. ODC is the rate-limiting enzyme in the synthesis of substances called polyamines, which can trigger DNA synthesis, cell growth and cell differentiation. Inhibition of ODC activity retards the growth of both normal cells and tumour cells (Marton and Pegg, 1995). ODC activity is modulated by membrane-mediated signalling events, and its activation is associated with the activity of mitogens (substances that cause mutation) and tumour-promoting agents of various types, such as the phorbol ester TPA, during carcinogenesis. Activation of ODC has been related to the late, “promotional” phase of cancer production, which is usually (but not always) correlated with proliferation (an increase in the rate of cell division) in the affected tissue. Most chemical tumour promoters increase the level of ODC in cells (through stimulating expression of the gene that produces ODC). They also increase the activity or enzymatic effectiveness of ODC, leading to an accumulation of polyamines. It is important to note that although all carcinogenic factors stimulate ODC, not all stimuli that increase ODC activity promote cancer.
- 5.112** A report of an Expert Panel of the Royal Society of Canada (1999) has recently reviewed investigations of the effects of electromagnetic radiation on the level and activity of ODC (see Table 5.7). Various cell lines were exposed to RF radiation, including mobile phone radiation, amplitude modulated at frequencies in the ELF range. In general, the studies reported modest increases in ODC activity only at modulation frequencies of about 10–60 Hz. DNA synthesis, which would indicate a proliferative response to raised ODC activity, was not subsequently increased.

Table 5.7 Ornithine decarboxylase (ODC) activity *in vitro*

Model	Exposure conditions	Results	References
Reuber H35 hepatoma; Chinese hamster ovary; 294T human melanoma cells	450 MHz; AM at 5, 10, 16, 20, 60 and 100 Hz; 10 W/m ² ; SAR estimated as 0.08 W/kg; 1 h	Increased ODC activity by up to 100% at 12–20 Hz modulation	Byus <i>et al</i> , 1988 Byus and Hawel, 1997
L929 mouse fibroblasts	915 MHz; AM at 50, 60 or 65 Hz; SAR estimated as 2.5 W/kg; up to 8 h	Increased ODC activity by up to 100%	Litovitz <i>et al</i> , 1993
L929 mouse fibroblasts	835 MHz; AM at 6, 16, 55, 60, 65, or 600 Hz; SAR of 2.5 W/kg	Increased ODC activity by up to 100% at 16–65 Hz modulation	Penafiel <i>et al</i> , 1997

AM = amplitude modulated

- 5.113** Many studies (Royal Society of Canada, 1999) have shown that conventional 50–60 Hz electromagnetic fields (without an RF carrier frequency) can produce a similar increase in ODC activity. Hence, the effect of amplitude-modulated RF fields might be due to the ELF currents within the tissue, although it is difficult to understand how such currents could be generated (see paragraph 5.16). However, the maximum increase in ODC activity produced by amplitude-modulated RF radiation (approximately a doubling) is much less than that elicited by known tumour-promoting substances, which can cause up to 500-fold changes in ODC activity in relevant tissues.

5.114 Although most cancer-producing conditions lead to large rises in the expression of ODC and proliferation of cells (which do not occur with even amplitude-modulated RF fields), promotional changes have been reported despite relatively small rises in ODC activity, and sometimes without cell proliferation (see, for example, Hibshoosh *et al*, 1991; Moshier *et al*, 1993, 1994; Kubota *et al*, 1997).

5.115 *CONCLUSION Pulse-modulated RF fields from mobile phones may cause a slight increase in ODC levels and activity, at non-thermal levels. However, it is very unlikely that these small changes could, on their own, have a tumour-promoting effect. It is also unlikely that such effects act synergistically with other environmental hazards and contribute to tumour promotion.*

Gene expression: does RF exposure initiate changes in the action of genes?

5.116 All the somatic cells (not the eggs or sperm) in the human body contain the same set of genes in their chromosomes. Each gene contains the information to make a particular protein (eg an enzyme or a structural protein). The differences in appearance and function of different types of cells (eg skin cells, liver cells and neurons) are caused by different sets of genes being active in each cell. The activation of genes is known as gene expression. The production of a protein involves two main steps: *transcription* (the synthesis of RNA, which contains the same information as that in the sequence of DNA in the gene) and *translation* (the building of the protein molecule from amino acids, under the control of the RNA). Changes in the characteristics of cells (differentiation), cell growth and programmed cell death can all occur as a result of the modulation of gene expression, which can be initiated by external events, acting through intracellular signalling pathways.

5.117 Certain genes are switched on specifically in response to stressful challenges to the cell. For instance, a set of genes producing *heat shock proteins*, which protect other proteins from damage, are activated by a sudden increase in temperature, and also by other forms of shock, such as toxic challenge. Further, as part of the response to stress, intense sensory stimulation, mitogenic chemicals, etc, other genes called *immediate early genes*, such as *c-fos* and *c-jun*, are turned on. Their proteins activate protective signalling pathways in the cell. The expression of these various genes is, then, a sensitive early marker of the cellular response to stress. The expression of genes called *proto-oncogenes* can be increased by tumour-promoting agents, ultraviolet radiation and X-rays. These genes, including *c-ras*, *c-myc* and *c-abl*, have normal cellular functions but can also contribute to the initiation of cancerous changes.

5.118 Recently, de Pomerai and colleagues have developed an invertebrate model to examine stress-induced gene expression. They used a transgenic soil nematode, *C elegans*, carrying a reporter gene under the control of the genetic mechanism for activation of heat shock genes. Hence the reporter (an enzyme or fluorescent protein that can easily be detected in the worm) is produced whenever the heat shock gene is turned on. Danniells *et al* (1998) and Power *et al* (1998) have shown that exposure of these worms to 750 MHz radiation (continuous or pulsed) for a few hours (0.5 W power), without detectable elevation of temperature, results in elevated expression of heat shock protein genes. Similar results were described after exposure for seven hours to the emission of a conventional digital mobile phone (de Pomerai *et al*, 1999).

5.119 By comparison, results of studies of gene expression in mammals have been variable and generally rather negative (Table 5.8). Studies of changes in the expression of the early response genes *c-fos* and *c-jun* (Mickley *et al*, 1994; Walters *et al*, 1995; Fritze *et al*, 1997b; Morrissey *et al*, 1999) in the brains of rats and mice exposed to RF radiation generally find no effects following exposure at thermally insignificant levels. In any case, *c-fos* expression is known to increase simply as a result of mild stress, such as that associated with immobilisation of an

Table 5.8 Recent studies on gene expression

Model	Exposure conditions	Results	References
<i>In vitro studies</i>			
PC12 rat pheochromocytoma cells	836.55 MHz; TDMA-modulated; 0.5–5 mW/kg; up to 60 min	Expression of <i>c-jun</i> elevated at highest exposure level only; no effect on <i>c-fos</i>	Ivaschuk <i>et al</i> , 1997
Mouse C3H 10 T ½ embryonic fibroblasts	835.62 MHz; FM and 847.74 MHz; CDMA-modulated; 0.6 W/kg; up to 4 days	Slight increase in <i>c-fos</i> expression; no effect on <i>c-jun</i> or <i>c-myc</i>	Goswami <i>et al</i> , 1999
<i>In vivo studies</i>			
Rat brain	600 MHz; whole-body SAR of 9.3 W/kg; 2 h	Increase in <i>c-fos</i> protein levels; brain surface temperature increased by 2 °C	Mickley <i>et al</i> , 1994
Rat brain	0.25–2.5 GHz; high peak power ultra-wide band radiation; 7–8 ns pulses; 60 pps for 2 min; peak <i>E</i> -field of 250 kV/m	No effect on <i>c-fos</i> protein levels; no heating effect	Walters <i>et al</i> , 1995
Mouse brain	1.6 GHz CW or pulsed with 9.2 ms pulses at 11 Hz	Increased <i>c-fos</i> expression in stress-responsive and thermoregulatory regions of brain at an SAR of 2.99 W/kg and above	Morrisey <i>et al</i> , 1999
Rat brain	900 MHz pulsed (GSM); brain SAR 0.3 or 1.5 W/kg OR 7.5 W/kg CW for 4 h	Increased <i>c-fos</i> only at highest SAR; no effect on <i>hsp70</i> or <i>c-jun</i>	Fritze <i>et al</i> , 1997b

CW = continuous wave FM = frequency modulated TDMA = time division multiple access CDMA = code division multiple access

animal (Cullinan *et al*, 1995), and this must be kept in mind when interpreting the results of experiments on awake animals. *In vitro* studies of mammalian cells have produced mixed results (Ivaschuk *et al*, 1997; Goswami *et al*, 1999).

5.120 *CONCLUSION* While there is currently little evidence that exposure to mobile phone radiation causes a stress response in mammalian cells, judged by elevated gene expression, the results on nematode worms are indicative of a non-thermal influence on gene expression. This model and similar model systems, using cultured mammalian cells carrying reporter transgenes linked to important genes, could be valuable in defining genetic responses to RF radiation.

Does RF radiation affect cell growth, survival or proliferation?

5.121 Changes in the kinetics of cell division and in the proliferation of cells play a crucial role in the generation of cancer. Any increase in cell proliferation resulting from RF radiation might indicate a carcinogenic influence. Several studies of the possible effects of exposure to RF radiation are described in Table 5.9.

5.122 Grundler *et al* (1992), pursuing Fröhlich’s suggestion (see, for example, Fröhlich, 1986) that electromagnetic radiation in the microwave range could interact with some sort of resonant process in undefined molecules in living biosystems, studied the influence of very low power RF radiation at 41–42 GHz on the cell cycle and growth rate of yeast cells. Even at extremely low SARs, they found that such radiation could cause small, but reliable changes in growth rates (increases of less than 10% and decreases of almost 20%), with sharp resonant peaks, dependent on frequency. They interpreted these results in terms of some internal “oscillator” in the cells,

capable of coupling with these extremely weak fields to modulate growth rate. These results were not confirmed in several further studies (see paragraph 5.19).

Table 5.9 Recent studies of cell growth, survival and proliferation in the presence of RF fields

Cell line	Exposure conditions	Results	References
Yeast cells	41.650–41.798 GHz; 20 mW; forward power of 20 mW for 4 h	Absence of frequency-dependent effects on growth	Furia <i>et al</i> , 1986
Yeast cells	41–42 GHz	Small changes in growth rates, which were frequency dependent	Grundler <i>et al</i> , 1992
Yeast cells	41.682–41.710 GHz; 0.5 or 50 $\mu\text{W}/\text{m}^2$; up to 1 W/kg; 5.5 h	Absence of frequency-dependent effects on growth	Gos <i>et al</i> , 1997
LN71 glioma cells; human lymphocytes	27 MHz or 2.45 GHz; up to 75 W/kg; 2 h; isothermal conditions	Increased incorporation of radiolabelled nucleic acid at SARs of 50 W/kg or less	Cleary, 1995
C6 glioma and primary glial cells	836.55 MHz; TDMA-modulated; 0.6–60 mW/kg; 24 h	Increased uptake of radiolabelled nucleic acid precursors in glioma cells at 6 mW/kg	Stagg <i>et al</i> , 1997
Human epithelial amnion cells	960 MHz pulsed (GSM); 217 pps; 8.3 pps; 24 h	Decrease in cell growth	Kwee and Raskmark, 1998

TDMA = time division multiple access GSM = global system for mobile telecommunications

5.123 In general, other studies report modest increases in proliferation (see Cleary, 1990a,b; 1995), no effect except at only one low (5.9 mW/kg) SAR level (Stagg *et al*, 1997), or a decrease in cell proliferation (Kwee and Raskmark, 1998). Only the latter two studies investigated possible effects of exposure to mobile phone radiation.

5.124 *CONCLUSION Taken together, these and other experiments on DNA synthesis do not demonstrate convincing, consistent changes in cell proliferation under conditions that mimic emissions from mobile phones or base stations. However, in view of the work by Stagg et al (1997), the effects of RF fields on nucleic acid synthesis deserve further study.*

Genotoxicity: does RF exposure cause DNA damage, mutation or chromosomal aberrations?

5.125 Studies of the genotoxic actions of carcinogenic substances and ionising radiation on cells and experimental animals have been of value in supplementing epidemiological evidence about human disease. For instance, many experiments on the effects of tobacco tars on cells and animals have strengthened the hypothesis that smoking causes cancer.

5.126 Many studies of potential genotoxicity have been carried out, involving the exposure of molecules, cells, isolated explants of tissue and whole animals to RF radiation in and around the frequency band used for mobile telecommunications (recently reviewed by Verschaeve, 1995; Brusick *et al*, 1998; Verschaeve and Maes, 1998; Jokela *et al*, 1999; Moulder *et al*, 1999; Royal Society of Canada, 1999). Some studies, especially the early ones, are difficult to interpret either because the exposure was very intense or because its exact characteristics and physical effects (local electric field, intensity, SAR, etc) were not fully recorded or computed. In particular, the thermal effects of higher intensity stimulation complicate interpretation, since heating alone can

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be genotoxic (Asanami and Shimono, 1999) and can enhance the action of known genotoxic agents (Jorritsma and Konings, 1984; Miura *et al*, 1986).

Mutagenesis

5.127 Experiments on bacteria have shown increased mutation rates, but in general the intensities used in these positive studies were high enough to cause significant heating (see, for example, Averbeck *et al*, 1976; Dutta *et al*, 1979; Blevins *et al*, 1980; Anderstam *et al*, 1983). In contrast, many researchers have reported that low power RF radiation produces no change in the rate of mutation of microbes or mouse lymphoma cells (see, for example, Blackman *et al*, 1976; Dardalhon *et al*, 1981; Hamnerius *et al*, 1985; Phillips *et al*, 1999: Royal Society of Canada, 1999).

5.128 A large number of studies on whole animals, from fruit flies to rats, have consistently failed to demonstrate mutation of either somatic cells or sperm after exposure to RF radiation, even with power densities up to 1000 W/m² and SARs up to 110 W/kg (Royal Society of Canada, 1999). However, Varma *et al* (1976), Varma and Traboulay (1976) and Goud *et al* (1982) reported increased dominant lethal mutations in the offspring of exposed male mice and abnormal sperm (see Table 5.10). The intensities used were very high and the effects were almost certainly due to elevated temperature. Studies carried out at lower intensities found no effect.

Table 5.10 Effects of RF fields on mutation, as indicated by dominant lethal mutations in male rodents

Model	Exposure conditions	Results	References
Swiss mice	2.45 GHz; 500 W/m ² ; 30 min or 100 W/m ² ; 80 min	Increased dominant lethal frequency	Varma <i>et al</i> , 1976
Swiss mice	1.7 GHz; 500 W/m ² ; 30 min or 100 W/m ² ; 80 min	Increased dominant lethal frequency	Varma and Traboulay, 1976
Sprague-Dawley rats	2.45 GHz; either prenatally and postnatally or as young adults; 50 W/m ² ; about 105 days; 100 W/m ² ; 5 days; 280 W/m ² ; 4 weeks	No increase in dominant lethal mutations	Berman <i>et al</i> , 1980
Swiss mice	2.45 GHz; 1.7 kW/m ² ; 70 s	Increased dominant lethal frequency	Goud <i>et al</i> , 1982
C3H mice	2.45 GHz; 43 W/kg to lower half of body; 30 min	No increase in dominant lethal mutations	Saunders <i>et al</i> , 1983
C3H mice	2.45 GHz; 100 W/m ² ; whole-body SAR 4 W/kg; 6 h/day over 8 weeks	No increase in dominant lethal mutations	Saunders <i>et al</i> , 1988

5.129 *CONCLUSION* The balance of evidence suggests that at normal temperatures (consistent with exposures below guidelines), RF fields do not induce mutation of either somatic cells or germ cells.

DNA damage: *in vitro* studies

5.130 Studies on bacteria, plant and animal cells exposed *in vitro*, where thermal effects can be directly observed and/or controlled, have failed to reveal direct evidence of DNA damage or repair, even at power densities up to 100 W/m² and SARs up to 20 W/kg (see, for example, Dutta *et al*, 1979; Meltz *et al*, 1987, 1990; Phillips *et al*, 1998; Verschaeve and Maes, 1998; Royal Society of Canada, 1999; Vasquez *et al*, 1999). The studies of Malyapa *et al* (1997a,b) on human cells are

perhaps the most relevant because they were modelled on experiments by Lai and Singh (1995, 1996) who suggested that exposure of rats *in vivo* to pulsed RF fields produces DNA strand breaks in cells of the brain. In one experiment, Malyapa *et al* (1997a) employed 2.45 GHz continuous-wave RF radiation. In the other (Malyapa *et al*, 1997b), they used 836 MHz frequency-modulated radiation or 848 MHz radiation with CDMA modulation, simulating the transmission characteristics of mobile phones in the USA. In neither case did they find DNA strand breaks.

DNA damage: *in vivo* studies

5.131 Studies of DNA damage *in vivo* are summarised in Table 5.11 (see also Verschaeve *et al*, 1998). In early work, Varma and Traboulay (1976, 1977) reported DNA damage in mice but the intensities used were high enough to cause thermal effects. More recently, three further studies in rodents have suggested that RF fields at lower intensities may affect DNA directly (Sarkar *et al*, 1994; Lai and Singh, 1995, 1996), although the data are, at best, preliminary. Evidence suggesting that the exposure of mice to 2.45 GHz radiation resulted in large-scale structural rearrangement of DNA in cells in the brain and testes was reported by Sarkar *et al* (1994). In this study, DNA was isolated from the brain and testes after exposure and cut into small fragments using a restriction enzyme. The fragments were separated according to size by electrophoresis, and probed for DNA sequences with a simple probe. The appearance or disappearance of bands could be indicative of some form of structural genomic rearrangement, but this technique is very susceptible to variable DNA digestion.

Table 5.11 Effects of RF fields on DNA damage and repair *in vivo*

Model	Exposure conditions	Results	References
Swiss albino mice	2.45 GHz; 10 W/m ² ; whole-body SAR estimated as 0.2 W/kg; 2 h/day for 120, 150, 200 days	Evidence of increased DNA rearrangement in samples from testes and brain	Sarkar <i>et al</i> , 1994
Mice	34 GHz pulsed (Police radar); 200 mW/m ² ; 17 h/day; 5 days/week for 2 weeks	DNA synthesis in cells from irradiated corneas reduced by 25%, but not statistically significantly	Rotkovska <i>et al</i> , 1993
Sprague-Dawley rats: comet assay for DNA damage in cerebral cortex	2.45 GHz CW; whole-body SAR 1.2 W/kg; 2 h	No effect on the frequency of DNA breaks immediately or 4 h after exposure	Malayapa <i>et al</i> , 1998
Sprague-Dawley rats: comet assay for DNA in rat brain	2.45 GHz CW or pulsed; 2 µs pulses; 500 pps; whole-body SAR 0.6 or 1.2 W/kg; SA per pulse = 1.2 or 2.4 mJ/kg; 2 h	Increased single- and double-strand DNA damage; maximum 4 h after exposure	Lai and Singh, 1995, 1996

CW = continuous wave

5.132 An increase in the number of single-strand and double-strand DNA breaks was reported in the brain cells of rats exposed for two hours to pulsed or continuous-wave 2.45 GHz radiation (Lai and Singh, 1995, 1996). Moreover, this effect was blocked by treatment, before or after exposure, with melatonin (see paragraph 5.96) or another free-radical scavenger (Lai and Singh, 1997). The DNA breaks were revealed using a single cell gel electrophoresis (or comet) assay in which the brain cells were isolated, placed on a microscope slide, lysed and eventually electrophoresed. DNA was stained using a fluorescent stain and DNA “fragmentation” assessed from the DNA migration path length. Curiously, in both studies the background levels of DNA breaks in brain cells from the unexposed animals were unusually high compared to values reported in other studies (see, for example, McKelvey-Martin *et al*, 1993). This raises the possibility that there was

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insufficient control of DNA breakage during preparation of the rat brain cells, although this in itself could not explain significant differences between exposed and control groups.

5.133 More rigorous studies by Malyapa *et al* (1997a,b, 1998) were not able to reproduce these findings. In particular, no effect was seen in the brain (hippocampal cells) of rats exposed for two hours to 2.45 GHz radiation, nor in mouse C3H10T $\frac{1}{2}$ fibroblast cells and human glioblastoma U87MG cells exposed *in vitro* (Malyapa *et al*, 1997a,b) to 2.45 GHz radiation or modulated 835 MHz radiation. A number of other studies have also failed to reveal any evidence of DNA damage.

5.134 *CONCLUSION This area deserves further research, but the evidence of Sarkar et al (1994) and Lai and Singh (1995, 1996) for DNA damage in mice is contradicted by a number of other studies in vivo and is not supported by in vitro work.*

DNA damage: indirect indicators

5.135 Various agents (clastogens) induce distortions of chromosomes, visible under the microscope. These chromosomal aberrations are generally thought to be due to damage to DNA or unusual interactions between DNA and protein molecules. Their accumulation is evidence of genotoxicity and is usually associated with cancer, but can also result in developmental abnormalities or miscarriage, if present in the tissue that generates eggs or sperm, or in the developing embryo or fetus.

5.136 Genotoxic substances tend to cause sister chromatid exchanges (switching of DNA from one part of the chromosome to another), which can be quite sensitively detected.

5.137 The occurrence of cells with unusually small nuclei (micronuclei) is also taken as an indicator of DNA damage. The detection of cells with micronuclei is simple, but is relatively unreliable because of the high and variable incidence of cells judged to be micronucleate in healthy tissues (10%–20% false positive rate). Heating is also known to induce micronuclei.

Chromosomal aberrations

5.138 Many studies have not detected obvious chromosomal aberrations in isolated animal cells after exposure to low power RF radiation (see, for example, Alam *et al*, 1978; Lloyd *et al*, 1984, 1986; Wolff *et al*, 1985; Meltz *et al*, 1987, 1989, 1990; Kerbacher *et al*, 1990; Maes *et al*, *in press*). However, a similar number of studies have reported increased chromosomal aberration (Yao and Jiles, 1970; Chen *et al*, 1974; Yao, 1976, 1982; Garaj-Vrhovac *et al*, 1990a, 1991, 1992; Khalil *et al*, 1993; Maes *et al*, 1993, 1995). In those studies with positive results in which the stimulus intensity was properly documented, it was generally rather high and therefore thermal effects cannot be ruled out. The experiments of Garaj-Vrhovac *et al* (1990a, 1991) are a notable exception; they reported an increase in chromosomal aberration after exposure of Chinese hamster V79 cells to 7.7 GHz radiation. Khalil *et al* (1993), in a preliminary report, also described increased chromosomal aberration in human lymphocytes after exposure to 167 MHz RF fields at 55 W/m² for up to 72 h.

5.139 Most experiments on whole animals have shown no increase in chromosomal aberration after exposure to RF fields, even though many of them employed high intensities, which were likely to have caused a rise in body temperature (Table 5.12). There have also been a few reports of aberrations *in vivo*, again with intensities near to or above the thermal limit. Of particular interest is the work by Garaj-Vrhovac *et al* (1990b) on chromosomal aberration in the lymphocytes of people who had experienced occupational exposure to 30–300 GHz at 10–50 W/m², although Maes *et al* (1995) found no such chromosomal aberrations in antenna maintenance workers who had been exposed to various RF fields at least one hour each day for more than a year.

Table 5.12 *In vivo* studies of chromosomal aberrations

Model	Exposure conditions	Results	References
Human lymphocytes from antenna workers	2.45 GHz and 954 MHz	Increased CA frequency	Maes <i>et al</i> , 1993, 1995
Mammalian, C3H mice	2.45 GHz CW; 100 W/m ² ; 4 W/kg; 6 hours/day; 120 hours over 8 weeks	No effect on CA frequency	Saunders <i>et al</i> , 1988
Male germ (sperm-forming) cells of C3H/HeH mice	2.45 GHz CW; 1, 100, 400 W/m ² ; 0.05–20 W/kg; 30 min/day; 6 days per week, for 2 weeks	No effect on CA frequency	Beechey <i>et al</i> , 1986
Male germ (sperm-forming) cells of CBA/CEY mice	2.45 GHz CW; whole-body SAR 0.05–20 W/kg; 30 min per day; 6 days per week for 2 weeks	Increased CA frequency	Manikowska-Czerska <i>et al</i> , 1985
Human lymphocytes (radio-linemen)	0.4 MHz to 20 GHz; occupational exposure	No increase in CA frequency	Garson <i>et al</i> , 1991
Human lymphocytes (antenna workers)	Various frequencies (including 450 and 950 MHz); 1 h/day for at least one year; occupational exposure	No increase in CA frequency	Maes <i>et al</i> , 1995
Human lymphocytes (radar station workers)	30–300 GHz, 1000–5000 W/m ² ; occupational exposure	Increased CA frequency	Garaj-Vrhovac <i>et al</i> , 1990b

CW = continuous-wave

Sister chromatid exchange

5.140 Most observations of sister chromatid exchange *in vitro* (Table 5.13) have failed to detect any effect of RF exposure, even at high intensities (see, for example, Lloyd *et al*, 1984 and 1986, Wolff *et al*, 1985, and Maes *et al*, 1993 and 2000, on human lymphocytes; Wolff *et al*, 1985, Meltz *et al*, 1990, and Ciaravino *et al*, 1991, on hamster ovary cells). Maes *et al* (1997) described a very small increase (statistically significant in two out of four samples) in sister chromatid exchange in human lymphocytes exposed to 935.2 MHz at an SAR of 0.3–0.4 W/kg. Khalil *et al* (1993) observed a clear increase in sister chromatid exchange in isolated human lymphocytes after exposure to 167 MHz at 55 W/m². However, this study was described as preliminary, and may have been compromised by the fact that the control cultures were kept in the stable environment of an incubator while the experimental samples were brought out for exposure.

Micronucleus formation

5.141 In contrast to these generally negative results from observations of chromosomal aberrations and sister chromatid exchange, there have been reports of an increase in the number of cells with micronuclei after exposure to RF radiation (Royal Society of Canada, 1999). Increased micronucleus formation has been seen in *in vitro* studies of various plant and animal cells (Garaj-Vrhovac *et al*, 1991, 1992; Maes *et al*, 1993; Haidler *et al*, 1994; Garaj-Vrhovac, 1999). However, the exposure conditions were generally rather poorly defined or sufficiently intense to have caused thermal effects (Table 5.14). Results of observations *in vivo* have been less clear. For instance, Vijayalaxmi *et al* (1997a,b) saw no effect on blood cells in mice exposed to 2.45 GHz radiation for 18 months at a whole-body SAR of 1 W/kg. However, Antipenko and Koveshinkova (1987) found an increase in the numbers of micronuclei in mouse hepatocytes after exposure to continuous-wave or pulsed RF radiation at an intensity of 5 W/m² for 45 days at 7 hours per day. Garaj-Vrhovac *et al* (1990b) reported no increase in micronuclei in the lymphocytes of human subjects who had had occupational exposure of unknown intensity.

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However, Balode (1996) found significant effects in the blood of cattle on farms close to a major radar installation in Latvia.

Table 5.13 Effects of RF fields on sister chromatid exchange *in vitro*

Model	Exposure conditions	Results	References
Human lymphocytes in hypothermic or mildly hyperthermic conditions	2.45 GHz; up to 200 W/kg; 20 min	No effect on SCE frequency	Lloyd <i>et al</i> , 1984; 1986
Human lymphocytes and Chinese hamster ovary cells during MRI	100 MHz pulsed; 330 μ s pulses; 100 pps; static magnetic field of 2.35 tesla	No effect on SCE frequency	Wolff <i>et al</i> , 1985
Chinese hamster ovary cells with or without chemical mutagen; mildly hyperthermic	2.45 GHz Pulsed; 10 μ s pulses; 25×10^3 pps; 33.8 W/kg; 2 h	No effect of RF on SCE frequency; no effect on mutagen-induced SCE frequency	Ciaravino <i>et al</i> , 1991
Human lymphocytes	167 MHz; 55 W/m ² ; up to 72 h	Increased frequency of SCE	Khalil <i>et al</i> , 1993
Human lymphocytes maintained at 36.1°C	2.45 GHz; 75 W/kg; 30 or 120 min	No effect on SCE frequency	Maes <i>et al</i> , 1993
Human lymphocytes with or without chemical mutagen (Mitomycin C)	935.2 MHz CW; 0.3–0.4 W/kg; 2 h	Little or no effect of RF alone on SCE frequency; slight enhancement of effects of the mutagen	Maes <i>et al</i> , 1997
Human lymphocytes with or without chemical mutagen	900 MHz CW (pseudo-random signal and dummy burst signal); 0.4–10 W/kg; 2 h	No effect on SCE frequency	Maes <i>et al</i> , <i>in press</i>
Human lymphocytes maintained at 17°C with or without chemical mutagen	954 MHz pulsed (GSM); 1.5 W/kg; 2 h	No effect of RF alone on SCE frequency; RF-enhanced effect of chemical mutagen	Maes <i>et al</i> , 1995

Table 5.14 *In vitro* studies on micronucleus formation

Model	Exposure conditions	Results	References
Peripheral blood of Latvian Brown cows (2000 erythrocytes)	Farm close to and in front of the Skruna Radar	Significant differences in the frequency distribution of micronuclei	Balode, 1996
C3H/HeJ mice (prone to mammary tumours); peripheral blood	2.45 GHz; whole-body SAR 1 W/kg; 20 h/day; 7 days/week for 18 months	Small but significant increase in micronuclei in polychromatic erythrocytes in peripheral blood and bone marrow	Vijayalaxmi <i>et al</i> , 1997b (1998 erratum)
CF-1 male mice, peripheral blood and bone marrow	Ultra-wideband radiation; estimated whole-body SAR 37 mW/kg; 15 min;	No effect on micronuclei in polychromatic erythrocytes in peripheral blood and bone marrow	Vijayalaxmi <i>et al</i> , 1999
Mouse hepatocytes	CW or pulsed RF; 5 W/m ² ; 7 h; 45 days	Increase in micronuclei	Antipenko and Koveshinkova, 1987
Lymphocytes from human subjects (radar station workers)	30–300 GHz; 1000–5000 W/m ² ; occupational exposure	Variable increase in micronuclei in lymphocytes	Garaj-Vrhovac <i>et al</i> , 1990b

5.142 Micronucleus formation is thought to reflect DNA damage, and is a sensitive assay (since the aberrant cells tend to accumulate, especially among non-dividing and slowly-dividing cells). However, its implications for health are unclear. In any case, the incidence of micronuclei in normal tissues is rather high and variable, making the assessment of individual experimental results more difficult.

Other evidence

5.143 Several publications in Russian, two decades ago or more, described a number of changes in cellular appearance and function after exposure to RF radiation. For instance, Zalyubovskaya and Kiselev (1978, in Russian), cited by McRee (1980), reported various pathological effects of 6.5 mm (46 GHz) RF radiation on cultured embryonic human and pig kidney cells, and Hep-2 cells. The cells developed pyknotic or vacuolised nuclei and damaged membranes, and their survival rate was reduced by 30%–50%. Kiselev and Zalyubovskaya (1976, in Russian), cited by McRee (1980), found that exposure of adenovirus to 6.5 mm (46 GHz) RF radiation reduced the capacity of the virus to infect cultured human kidney cells. Unfortunately the exact conditions of stimulation in many of these early studies were either poorly defined or were so intense that they would have produced thermal effects.

5.144 *CONCLUSION Several different assays of genotoxicity have failed to produce clear evidence that RF radiation is genotoxic at non-thermal levels. The most consistent results come from observations of micronucleus formation, but these are not simple to interpret and have uncertain implications for health.*

Long-term studies of cancer induction in animals

5.145 A demonstration that long-term exposure to RF fields increases the incidence of tumours in animals would provide direct evidence that such radiation is carcinogenic. Early studies (Prausnitz and Susskind, 1962; Spalding *et al*, 1971; Skidmore and Baum, 1974; Baum *et al*, 1976) in which biological endpoints relevant to carcinogenesis were examined suffered from insufficient dosimetry, poor histopathology or inadequate follow-up.

Spontaneous tumour incidence

5.146 Later studies (Table 5.15) avoided many of these deficiencies. Chou *et al* (1992) exposed (from 2 to 27 months of age) 100 rats to low level pulsed 2.45 GHz fields. The total number of benign tumours of the adrenal medulla was higher in the exposed group compared to the control group,

Table 5.15 Effect on spontaneous tumour incidence

Model	Exposure conditions	Results	References
Sprague-Dawley rats	2.45 GHz pulsed; 10 µs pulses at 800 pps, pulse modulated at 8 pps; whole body SAR of 0.4–0.15 W/kg for up to 25 months	No increase in individual cancers; four-fold increase in primary malignancies	Chou <i>et al</i> , 1992
Spontaneous mammary tumours in C3H/HeA mice	2.45 GHz; up to 6–8 W/kg; to 12 months of age	Increased tumour development	Szmigielski <i>et al</i> , 1982
Mammary tumour prone C3H/HeA mice	435 MHz pulsed; 1 µs pulses at 1000 pps; whole-body SAR of 0.32 W/kg; 21 months	No effect	Toler <i>et al</i> , 1997
Mammary tumour prone C3H/HeA mice	2.45 GHz; whole-body SAR 0.3 or 1.0 W/kg; 18 months	No effect	Frei <i>et al</i> , 1998a,b

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although not particularly higher than that reported elsewhere for this strain of rat. There was no significant difference between groups in the incidence of all benign neoplasms at death. In addition, no single type of malignant tumour was enhanced by exposure and, overall, the incidence of primary malignancies was similar to the spontaneous rate reported for this strain of rat. However, when the occurrence of primary malignant lesions was pooled without regard to site or mode of death, the exposed group had a significantly higher incidence compared to the control group.

- 5.147** Other authors have reported a lack of effect of RF exposure on cancer incidence in mice prone to mammary tumours. Toler *et al* (1997) found that the long-term exposure of mammary-tumour-prone C3H/HeJ mice to 435 MHz pulsed RF radiation had no effect on survival, nor on the latency, incidence or growth rate of mammary tumours compared to sham-exposed animals, nor were there differences in the numbers of malignant, metastatic or benign tumours. Frei *et al* (1998a,b) used the same animal model to investigate the effects of chronic (18-month) low level 2.45 GHz RF exposure and found no differences compared to sham-exposed animals.

Epigenetic effects: does RF radiation interact with known genotoxic agents to enhance their promotional effects?

- 5.148** Epigenetic factors, although not themselves genotoxic, act synergistically to enhance the carcinogenic effects of other agents (Williams and Whysner, 1996). There are several published studies that suggest that RF radiation can have an epigenetic effect *in vivo*, working to exaggerate the genotoxic influences of ionising radiation or cancer-inducing substances, or to potentiate other epigenetic factors. However, the evidence for an epigenetic effect of RF exposure is equivocal, with several failures to replicate positive results.
- 5.149** Balcer-Kubiczek and Harrison (1985, 1991) reported that 2.45 GHz radiation can induce “latent transformation” of a cultured cell line. This RF radiation potentiated the tumour-transforming effect of X-rays or the carcinogenic substance benzo[a]pyrene, but only in the presence of TPA, a known epigenetic agent. On the other hand, Cain *et al* (1997) found no cell transformation in similar experiments involving 836.55 MHz radiation.
- 5.150** Scarfi *et al* (1996) reported that intense RF fields amplified the genotoxic effects of the mitogenic substance mitomycin-C, as judged by the presence of micronuclei in cultured bovine lymphocytes. Maes *et al* (1997) described a small but statistically significant enhancement of the effects of mitomycin-C on human lymphocytes after exposure to 935.2 MHz radiation for two hours. However, Ciaravino *et al* (1987, 1991) found no epigenetic influence of RF radiation on the production of chromosomal aberrations by mitomycin-C or another mitogen, adriamycin. A number of other studies have failed to demonstrate enhancement of the mutagenic action of chemical carcinogens (Meltz *et al*, 1989, 1990; Kerbacher *et al*, 1990).
- 5.151** Heating alone can enhance the action of genotoxic agents (Jorritsma and Konings, 1984; Miura *et al*, 1986) and it is possible that some of the epigenetic influences reported for RF could be due to thermal effects. Indeed, this was one of the conclusions of Pakhomova *et al* (1997), who found that higher frequency RF radiation (61 GHz) did enhance DNA recombination (but not mutagenesis) in yeast cells exposed to ultraviolet radiation.
- 5.152** Chemical tumour-inducing agents have been used to examine possible epigenetic, promotional effects of RF radiation in animals (Table 5.16). Early studies were carried out by Szmigielski and colleagues (Szmigielski *et al*, 1982; Szudinski *et al*, 1982) who reported that the chronic RF exposure of mice resulted in a SAR-dependent increase in the development of spontaneous mammary tumours or skin tumours induced by the repeated application of benzo(a)pyrene. Body temperatures were not raised but the authors suggested a possibility of localised heating at the

highest level of exposure. A further experiment (Szmigielski *et al*, 1988) showed that exposure followed by the application of a “subcarcinogenic” dose of the same carcinogen to the skin, a procedure repeated daily, eventually resulted in a three-fold increase in the numbers of skin tumours appearing. The authors noted that these results needed confirmation but suggested that long-term exposure to RF fields might promote the development of neoplasms that would not normally reach a clinically identifiable stage.

Table 5.16 Promotional studies *in vivo*

Model	Exposure conditions	Results	Reference
Chemically induced skin tumours in BALB/c mice	2.45 GHz; whole-body SAR 2–3 or 6–8 W/kg; 1–3 months	Increased incidence of skin tumours	Szmigielski <i>et al</i> , 1982; Szudinski <i>et al</i> , 1982
Chemically induced hepatomas and sarcomas in mice	2.45 GHz; whole-body SAR up to 4–5 W/kg; several months	Increased incidence of tumours	Szmigielski <i>et al</i> , 1988
Chemically induced colon cancers in BALB/c mice	2.45 GHz; whole-body SAR 10–12 W/kg; 5 months	No effect	Wu <i>et al</i> , 1994
Lymphoma-prone Eμ- <i>Pim1</i> transgenic mice	900 MHz pulsed (GSM); 600 μs pulses; 217 pps; whole-body SAR; 0.008–4.2 W/kg; 1 h per day; 18 months	Two-fold increase in lymphoma incidence	Repacholi <i>et al</i> , 1997
Medium term rat liver tumour promotion model	1.439 GHz pulsed; 6.7 ms at 50 pps; whole-body SAR 0.4–0.7 W/kg; 6 weeks	No effect	Imaida <i>et al</i> , 1998a
Medium term rat liver tumour promotion model	929.2 MHz pulsed; 6.7 ms pulses; 50 pps; whole-body SAR 0.6–0.8 W/kg	No effect	Imaida <i>et al</i> , 1998b
Lymphoma incidence in CBA/S mice exposed to 4 Gy ionising radiation	902 MHz CW; 1.5 W/kg or 902 MHz pulsed (GSM); 0.35 W/kg; 1.5 h/day; 5 days/week	No effect on survival or incidence of lymphoma	Juutilainen <i>et al</i> , 1998; <i>in press</i>
Spontaneous and chemically induced CNS tumours in Fischer rats	836.55 MHz pulsed; 6.7 ms pulses; 50 pps; brain SAR 0.3–0.5 W/kg; perinatally and for 24 months	Fewer CNS glial tumours in exposed group	Adey <i>et al</i> , 1999
Chemically induced sarcomas in female Sprague-Dawley rats	900 MHz pulsed (GSM); whole-body SAR 75 or 270 MW/kg; 2 weeks; 20, 40 or 75 days after carcinogen	No effect on tumour appearance or survival	Chagnaud <i>et al</i> , 1999
Chemically induced brain tumours in Sprague-Dawley rats	860 MHz bipolar RF pulses (MIRS: 11.1 Hz frame rate unipolar wave form) or 860 MHz CW; head SAR 0.4–1.0 W/kg; 6 h/day; 5 days/week; 2–24 months of age	No effect on incidence, multiplicity, volume, malignancy or fatal outcome of neural tumours	Zook, 1998; 1999

CW = continuous wave MIRS = Motorola integrated radio service GSM = global system for mobile telecommunications

5.153 The most positive evidence, as yet unreplicated, of an effect of exposure to RF radiation similar to that used by digital mobile phones was reported by Repacholi *et al* (1997), using Eμ-*Pim1* transgenic mice. Experimental transgenic animals have genetic material added to their DNA to predispose them to the endpoint being investigated. Such animals that are prone to cancer can be

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used to test the carcinogenic influence of chemical agents in a short time (generally six months). This not only provides a sensitive animal model to test for cancer, but tests can be conducted in a time much less than the animal's lifetime. E μ -*Pim1* mice, which are moderately susceptible to the development of lymphoblastic lymphomas, were exposed or sham-exposed for one hour per day for eighteen months to pulse-modulated 900 MHz RF radiation. The authors reported an increase in the incidence of all lymphomas (lymphoblastic and non-lymphoblastic) in the exposed mice (43% compared to 22% in the controls), the most significant effect resulting from increased non-lymphoblastic lymphomas. However, lymphoma incidence was rapidly increasing in both exposed and sham-exposed animals when the study was terminated; in addition, only moribund animals were examined histopathologically. Replication of this study and extension with more complete follow-up and improved dosimetry would be useful and is currently under way in Australia. Another replication study is commencing in Europe in 2000. These replication studies will expose the mice to different levels of RF radiation to determine if there is a dose-response relationship. Even if replicated, there will need to be further assessment of the relevance of these findings for human health (Repacholi, 1998).

5.154 Other recent studies investigating a possible promoting effect on chemically induced cancers have generally found tumour incidence to be unaffected by RF exposure. Wu *et al* (1994) reported that the chronic exposure to 2.45 GHz RF radiation had no effect on the incidence or size of colon cancers induced in mice by dimethylhydrazine. Imaida *et al* (1998a) found no effect of exposure at the Japanese cellular phone frequency of 1.439 GHz for six weeks using the standard medium-term rat liver tumour promotion model, in which neoplastic foci are induced in the liver by diethylnitrosamine and partial hepatectomy. Similar results for 929.2 MHz radiation had been reported previously (Imaida *et al*, 1998b). In contrast to these reports, Adey *et al* (1999) found that exposure to 836.55 MHz radiation with North American Digital Cellular Modulation (at SAR levels reported to simulate the localised peak brain exposures experienced by a cell phone user) over a 24-month period had a slight inhibitory effect on both spontaneous and chemically induced brain tumour incidence in rats, the latter resulting from treatment *in utero* with the carcinogen ethylnitrosourea. There was, however, no evidence of any tumorigenic effect.

5.155 *CONCLUSION* Although thermal effects may account for the positive reports that RF radiation enhances the actions of genotoxic agents, the evidence for epigenetic effects must be taken seriously. Further research is needed in this area to clarify the position.

Tumour transplantation: does RF radiation enhance the progression of transplanted tumours?

5.156 The effect on tumour progression of exposure to continuous-wave or pulse-modulated RF radiation following the transplantation of tumour cells into mice and rats has been examined in several studies. Szmigielski *et al* (1982) reported a SAR-dependent increase in the number of neoplastic colonies on the lung surfaces of mice injected intravenously with suspensions of mouse sarcoma cells and exposed to 2.45 GHz radiation. In contrast, other studies (Santini *et al*, 1988; Salford *et al*, 1993; Higashikubo *et al*, 1999) have found no effect of RF exposure (see Table 5.17).

General conclusions from studies of cancer

5.157 *Some individual experimental studies have suggested that RF radiation can initiate tumour formation, enhance the effects of known carcinogens or promote the growth of transplanted tumours. However, in some of these the intensity was high enough to produce thermal effects. The balance of evidence, from both in vitro and in vivo experiments, indicates that neither acute*

Table 5.17 Tumour transplantation studies

Model	Exposure conditions	Results	References
BALB/c mice injected with L1 mouse sarcoma cells	2.45 GHz; whole-body SAR 2–3 or 6–8 W/kg; 3 months	Increased incidence of tumour colonies on lung surface	Szmigielski <i>et al</i> , 1982
Mice injected with mouse B16 melanoma cells after exposure	2.45 GHz CW or pulsed; whole-body SAR 1.2 W/kg	No effect on survival	Santini <i>et al</i> , 1988
RG2 glioma cells injected into rat brains	915 MHz CW or pulsed; whole-body SAR 0.01–2 W/kg; 2–3 weeks	No effect on tumour growth	Salford <i>et al</i> , 1993
9L gliosarcoma cells injected into rat brains	835.62 MHz; FM or 847.74 MHz CDMA; brain SARs estimated as around 0.75 W/kg; 21 weeks after treatment;	No effect on tumour growth	Higashikubo <i>et al</i> , 1999

CW = continuous wave FM = frequency modulated CDMA = code division multiple access

nor chronic exposure to RF fields increases mutation or chromosomal aberration frequencies when temperatures are maintained within physiological limits (UNEP/WHO/IRPA, 1993). This suggests that RF exposure is unlikely to act as a tumour initiator. Further, a variety of cancer studies using animals have sought evidence of an effect of RF exposure on spontaneous or natural cancer rates, the enhancement of the effects of known carcinogens or effects on the growth of implanted tumours. However, they have provided equivocal evidence for an effect on tumour incidence (ICNIRP, 1996; Repacholi, 1998; Moulder et al, 1999; Royal Society of Canada, 1999).

Haematopoietic system, immune system and longevity

- 5.158** Changes in the haematopoietic system (tissues related to the formation of blood cells) can have a direct effect on health. Information about any effects of RF exposure on this system is fundamentally important, then, for the assessment of possible risks to health and well-being.
- 5.159** No consistent effects of low level RF exposure have been reported on the blood-forming and circulating blood cells (eg changes in numbers of bone marrow cells, lymphocytes or erythrocytes, or in the amount of haematocrit) (UNEP/WHO/IRPA, 1993; Jauchem, 1998). Most of the earlier studies used continuous-wave fields, but a well-conducted lifetime study in rats exposed to low level, pulsed RF fields also found no effect on haematology or serum chemistry parameters (Chou *et al*, 1992).
- 5.160** The immune system defends against micro-organisms, viruses, and some cancer cells. Thus any effects of RF exposure on this system could have significant implications for health. Thermal levels of RF exposure elicit both stimulatory and inhibitory responses in components of the immune system (UNEP/WHO/IRPA, 1993). However, these effects (eg changes in lymphocyte activity and responsiveness) were generally found to be transitory, returning to normal levels following termination of RF exposure. Studies using low level RF exposure have given inconsistent results, making it difficult to attribute any effects to the exposure. Several acute and chronic *in vivo* studies, using low RF exposure levels, have indicated positive effects that were transient and similar to those resulting from thermal stress or physiological changes occurring during thermoregulation (Smialowicz *et al*, 1983; Yang *et al*, 1983). However, Fesenko *et al* (1999) have recently shown that exposure of mice to 10 GHz radiation, or radiation with a frequency swept between 8.15 and 18 GHz, at very low intensity (probable SAR 2–5 mW/kg), increases the production by macrophages of tumour necrosis factor, which is

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involved in immune attack on viruses, foreign proteins and damaged tissues. Novoselova *et al* (1999) showed that this effect is enhanced by a diet rich in antioxidants. These authors suggest that “the activation of cellular immunity by RF irradiation and antioxidant treatment may provide therapeutic strategies for interfering with acute immunodeficiency processes”.

- 5.161** In general, studies conducted to determine if RF exposure affects longevity have revealed no influence on lifespan in experimental animals. Indeed, the most convincing changes reported are very slight increases in lifespan, perhaps because of a subtle, thermally-mediated effect on food intake. Summaries of typical studies are given in Table 5.18.

Table 5.18 Longevity and general physiological condition

Model	Exposure conditions	Results	References
Mice	0.80 GHz; 43 W/m ² ; 2 hours/day; 5 days/week; 35 weeks	No effect on lifespan	Spalding <i>et al</i> , 1971
CFW mice (<i>in utero</i> exposure to RF and implantation of tumour cells)	2.45 GHz; 35 W/kg (leading to an increase in body temperature of 2.24 °C); 20 min/day; 3 days; 11-14 th day of gestation	Increased lifespan in tumour-bearing and tumour-free animals	Preskorn <i>et al</i> , 1978
Sprague-Dawley rats	2.45 GHz pulsed; 10 µs pulses; 800 pps; pulse modulated at 8 pps; whole-body SAR of 0.15–0.4 W/kg; up to 25 months	No effect on lifespan	Chou <i>et al</i> , 1992
CD1 mice	2.45 GHz; 30–100 W/m ² ; whole-body SAR 2 or 6.8 W/kg; 1 h/day; 5 days/week throughout their life	Significantly shortened lifespan of mice exposed to 100 W/m ² and slight but not significantly longer average lifespan of mice exposed to 30 W/m ²	Liddle <i>et al</i> , 1994
New Zealand rabbits	2.45 GHz; head SAR of 0.55 or 5.5 W/kg; 7 h per day; 13 weeks	No effect on haematology, cataract incidence or histopathology; slight drop in food consumption in high exposure group	Chou <i>et al</i> , 1983

Reproduction and development

- 5.162** Many of the processes associated with reproduction are especially sensitive to toxic influences. Meiosis (the division of cells to produce sperm and eggs), fertilisation and implantation of the embryo can all be disturbed by toxic insults. The high rates of cell division and differentiation in the developing fetus make it particularly vulnerable. It is well known that some drugs and environmental hazards have damaging (teratogenic) effects on the developing embryo or fetus at exposure levels that pose little or no risk to the adult animal. It is therefore important to assess the possible effects of RF fields on fertility and development.
- 5.163** Extensive research on a wide range of species (from beetles to guinea pigs) has failed to reveal any convincing effects of low level RF fields on developing animals (reviewed by UNEP/WHO/IRPA, 1993; Jauchem, 1998; O’Connor, 1999). For instance, exposure of pregnant Holtzman rats for 20 minutes at SARs of 14 or 28 W/kg, sufficient to raise the rectal temperature to an average of 42°C, produced no observable effects on the offspring (O’Connor, 1980). Only if the field strength was so high that the rectal temperature of the dam reached near-lethal levels

(43°C) was there an increase in fetal absorption, a decrease in fetal body mass and excessive occurrence of birth defects (Chernovetz *et al*, 1977; O'Connor, 1980). The survival of fetuses was inversely correlated with the temperature to which the dam was raised, and similar effects were produced by raising the dam's body temperature by infrared heating (Chernovetz *et al*, 1977).

- 5.164** Jensch (1997) described extensive studies on the effects of prenatal RF exposure at non-thermal levels on development in rats. Female rats were exposed for six hours each day throughout pregnancy to continuous-wave radiation at 915 MHz (100 W/m²), 2.45 GHz (200 W/m²) or 6 GHz (350 W/m²) and many physiological and behavioural parameters were assessed in both mothers and offspring. Some of the offspring from RF-exposed pregnancies were later bred and the second generation offspring were also assessed. Exposure to 915 MHz radiation (in the range of mobile phone signals) had no detectable effect. For 2.45 GHz radiation, the only positive result was a very slight increase of activity in the offspring. Exposure to 6 GHz radiation at 350 W/m² did have some just statistically significant effects. The number of monocytes (a class of white blood cells) in the mothers' blood was slightly but significantly reduced. The weight of the offspring at term and during the first five postnatal weeks was slightly lower than that for control litters and there were small differences in the relative weights of kidney and liver. The exposed offspring opened their eyes slightly earlier than did control pups. The offspring from exposed litters tended to be more active in an "open field" test of spontaneous activity, and the females were slightly more active on an activity wheel, in a swimming test and in a water T-maze. Their actual performance on the water maze was slightly worse than that of control animals. In subsequent pregnancies from matings of animals derived from exposed mothers, the weight gain of the pregnant females and the size of their litters was slightly reduced. Jensch (1997) concluded that, since all these effects were so minor, and almost all were associated only with 6 GHz radiation, the fields associated with mobile phones do not "produce a significant increase in reproductive risk".
- 5.165** From other experiments on rats and mice, Berman *et al* (1978) and Lary *et al* (1982, 1983) concluded that the threshold for teratogenic effects corresponds to an elevation of temperature of the fetus to 40°C for some considerable time. Prolonged exposure of pregnant rats at thermal levels can lead to behavioural deficits in the offspring, including poorer performance in a water T-maze and an open-field activity test (Jensch *et al*, 1983a,b; Jensch, 1984a,b), and altered thermoregulatory behaviour (O'Connor, 1988).
- 5.166** Exposure to relatively high level RF radiation (but not high enough to be teratogenic on its own) enhances the effects of chemical teratogens (see, for example, Marcickiewicz *et al*, 1986; Nelson *et al*, 1991), but this is almost certainly due to the rise in fetal temperature.
- 5.167** There were early reports of decreased fertility in male rats exposed to RF fields (Varma and Traboulay, 1976, 1977). However, it is likely that these effects were due to heating. Saunders and Kowalczyk (1981) found no abnormality of testis cells or sperm count even in adult male rats that had been exposed to quite strong RF fields (66 W/kg for 10 minutes or 7 W/kg for 260 minutes). Very prolonged exposure to 200 MHz fields, amplitude modulated at 16 Hz, at an SAR of about 2 W/kg, has been reported to decrease male fertility, judged by the number of offspring per litter and by histological changes in the seminiferous tubules (Khillare and Behari, 1998). These effects could well have been caused by modest warming integrated over the long exposure period.
- 5.168** Magras and Xenos (1997) have reported an apparently dramatic decrease in the fertility of mice exposed to extremely low level RF fields near the "antenna park of Thessaloniki" (almost 100 TV and FM-radio antennas on the Chortiatis mountain in Greece). The mice, which were

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kept in, and moved between, various locations (including a school) in a nearby village, were exposed to a broad spectrum of RF radiation with an integrated intensity between about only 1.7 and 10 mW/cm². Within three to five matings, the number of pups per litter had fallen literally to zero. Unfortunately there was no matched control group and no account was taken of the possibility that the result was due to noise, smells or other stressful factors in the environment of the experimental mice.

- 5.169** *CONCLUSION* *There is no convincing evidence from studies of rodents that exposure to RF fields at levels associated with mobile telecommunications poses any risk for the fetus or for male fertility. While there are good reasons to doubt whether the decline in female fertility described by Magras and Xenos (1997) was actually due to the very low level exposure, it is important to repeat this study under better controlled conditions.*

Influences on the cardiovascular system

- 5.170** Radiofrequency radiation might affect the heart and circulation through a number of routes. There could be direct effects on the heart and blood vessels. There might be influences on the cardiovascular centres in the medulla of the brainstem, which regulate the heart and circulation via the outflow in the sympathetic and parasympathetic systems. Exposure to RF fields might conceivably affect the receptors in the carotid body, which normally detect blood pressure and blood gases and which initiate reflex influences on the heart and blood vessels. Finally, the cardiovascular system is known to be affected by a variety of circulating substances, especially catecholamine hormones, whose release might possibly be changed by exposure to RF fields.
- 5.171** Exposure of animals to high levels of RF radiation, sufficient to raise body temperature, certainly results in a variety of direct and indirect effects on the cardiovascular system. However, there is no evidence that they differ qualitatively or quantitatively from effects triggered by similar rises in body temperature produced by other means (Jauchem and Frei, 1992). High peak-power pulsed RF fields or broad-spectrum pulses of electromagnetic radiation (which would result in *total* absorbed energy in people well below guidelines) do not cause detectable changes in heart rate or blood pressure in animals (Erwin and Hurt, 1993; Jauchem and Frei, 1995; Jauchem, 1997).
- 5.172** *CONCLUSION* *Studies on animals do not justify any concern about the influence of RF radiation at levels associated with mobile phones on the heart or circulation. Effects at high intensities appear to be due to heating of the body.*

Summary and conclusions on animal and cellular experimental studies

- 5.173** *The thermal consequences of acute RF exposure in animals appear to account for many of the reported effects on the cardiovascular, endocrine and immune system and on behaviour (UNEP/WHO/IRPA, 1993). Rectal temperature increases of at least 1–2°C are needed to produce these effects. Developmental effects, similar to those known to be induced by heat, have been reported in rodents following large (3–4°C) temperature increases in the fetus during prenatal RF exposure (Lary and Conover, 1987).*
- 5.174** *Other effects remain somewhat controversial. The question of whether low level RF exposure might increase the risk of cancer is of particular concern, although, since the radiation lacks sufficient energy to disrupt molecular bonds directly, there appears to be no theoretical basis to suggest that it could adversely affect DNA.*
- 5.175** *It has been reported that exposure to low level pulsed (and sometimes continuous-wave) RF fields can damage ocular tissues in primates and produce non-specific stress-like changes in the*

rat brain. If such effects occur in people they could have implications for health. There is also a body of evidence describing biological responses to amplitude-modulated RF fields at SARs too low to involve any response to heating. This literature is, however, inconsistent, and the effects that are reported are typically small and close to the level of statistical noise. It is thus very difficult to interpret, in terms of either its biological significance or its implications for human health.

Laboratory Studies of the Effects of RF Radiation on People

Brain function

- 5.176** Among the concerns expressed over the use of mobile phones is the possibility that mobile phone signals have deleterious effects on cognitive functions such as memory, attention and concentration. Despite these concerns, relatively few laboratory studies have addressed this issue in people and, of those that have, all have investigated short-term effects of exposure. Further, with three exceptions, studies investigating exposure to low levels of RF radiation in the mobile phone frequency range have focussed not on indices of cognitive performance *per se*, but on physiological measures of brain function such as the electroencephalogram (EEG).

Studies of cognitive performance

- 5.177** Investigation of short-term effects of exposure to electromagnetic fields is, in principle, relatively easy. A wide range of tasks have been developed by experimental psychologists to assess specific aspects of cognitive function (eg short-term and long-term memory, selective attention, speed of decision-making), and the experimental designs required to determine whether electromagnetic field exposure affects performance on such tasks are unproblematic. To date, however, the effects of mobile phone signals on cognitive performance have been assessed in only three published studies (Preece *et al*, 1999; Koivisto *et al*, 2000, *in press*).
- 5.178** Preece *et al* (1999) investigated the performance of 36 volunteers on a wide range of tasks, including short-term and long-term memory, simple and choice reaction time (RT), and sustained attention, which, together, yielded a total of 15 dependent variables. These variables were grouped for combined analysis by multivariate analysis of variance into four sets: RT on attentional tasks (simple, choice and vigilance RT), speed on memory tasks, accuracy on memory tasks and accuracy on attentional tasks. Using a counterbalanced, crossover design, two exposure conditions – continuous and pulsed (217 Hz) 1 W, 915 MHz signals (simulating analogue and GSM mobile phone signals with mean power levels of 1 W and 0.125 W, respectively) – were compared to a no-exposure control condition. The signals were delivered through a simulated headset placed over the left ear with the antenna extending over the temporo-parietal scalp. Initial statistical analyses revealed a significant effect of exposure for RT on the attentional tasks. Follow-up analyses revealed a single statistically significant effect of exposure, which took the form of a shortening of RT (by 14 ms) during exposure to the analogue signal in the choice RT task, which required speeded discrimination between visual presentations of the words “yes” and “no”. The effect was not accompanied by a reduction in the accuracy of responding, suggesting that it did not reflect a “speed–accuracy tradeoff”. Exposure effects on RT in the two other attentional tasks showed trends in the same direction, but were of trivial magnitude (< 3 ms). Exposure effects for the three other groupings of dependent variables were far from statistical significance (minimum $p = 0.144$). However, non-significant trends towards shortened RT during exposure to the analogue signal were observed to varying degrees in all four of the memory tasks. The Expert Group reanalysed the most important parts of the data from Preece *et al* (1999). The reanalysis, in general, confirmed and indeed slightly strengthened the conclusions of Preece *et al*.

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- 5.179** Preece *et al* (1999) conjectured that their findings were thermal in origin, and reflected the facilitatory effect of heating on synaptic transmission in cerebral cortex directly underlying the simulated headset. They argued that this explanation was consistent with their finding of an effect for the analogue but not the digital signal (the two signals differed in mean power by a factor of eight, and any heating effect would be proportional to power). They further argued that a local cortical effect was consistent with the task-specificity of their findings, as any effects on behaviour would be greatest for those tasks that depended most heavily on cognitive operations supported by the affected region of cortex.
- 5.180** Koivisto *et al* (2000) studied 48 volunteers, also with a wide range of cognitive tests (12 in total, providing 14 measures of RT and a similar number of accuracy measures). Their test battery included a two-choice RT task very similar to that employed by Preece *et al* (1999). A counterbalanced, crossover design was used to compare performance under conditions of no-exposure with performance during exposure to a 902 MHz GSM signal (modulated at 217 Hz) of 0.25 W mean power. The phone was positioned over the left ear with the antenna located over the posterior temporal scalp. Koivisto *et al* reported that three measures of RT – simple RT, the estimated time taken to perform a mental subtraction of two digits, and the average time taken to detect rarely occurring “targets” in a stream of visually presented letters (a “vigilance” task) – were shortened (by 9, 29 and 25 ms, respectively) to a statistically significant extent when the tasks were performed during exposure to the mobile phone signal. Accuracy scores did not indicate the presence of a speed–accuracy tradeoff; indeed, in the vigilance task errors of commission showed a small but statistically significant reduction during exposure. The effect of exposure on the choice RT task analogous to that employed by Preece *et al* (1999) was far from significant. Koivisto *et al* nonetheless considered their findings to be consistent with those of Preece *et al* (1999), noting that they too had failed to find an effect of GSM signals on a two-choice RT task. Koivisto *et al* argued that their own results suggested that exposure to the mobile phone signals had affected cortical regions, such as the inferior parietal cortex, that support sustained visual attention. Similarly to Preece *et al* (1999), they proposed that the mechanism underlying this effect may be thermal.
- 5.181** The Koivisto *et al* (2000) study can be criticised on the grounds that the data were subjected to an inappropriate form of statistical analysis. Fourteen measures of RT were considered, and the effect of exposure on each measure was assessed by a separate pairwise statistical test performed in the absence of any initial multivariate analysis that demonstrated a general exposure effect. Thus, across all the tests, the chance probability of obtaining a significant effect of exposure was considerably greater than the significance level ($p < 0.05$) that was employed to evaluate the outcome of each test. Indeed, according to the Bonferroni criterion (a standard method of correcting significance levels when multiple tests are performed), of the four “significant” findings reported, only RT in the vigilance task demonstrated a statistically significant exposure effect. That said, it is noteworthy that RT on 11 of the 14 measures was numerically, if not significantly, shorter during exposure. These trends offer some reassurance that a genuine exposure effect was operating, which would be strengthened if it was known that the 14 measures were not intercorrelated to any great extent; the relevant data were not, however, reported.
- 5.182** In a second study, Koivisto *et al* (*in press*) employed a very similar experimental design to investigate the effects of mobile phone signals (dosimetry as in their previous study) on the performance of 48 subjects in an “n-back” “working memory” task. In this task, subjects are presented with a sequence of characters (letters in the present case) and must respond discriminatively according to whether a letter is a “target” or “non-target”. Targets comprise items repeated after a designated number of trials. In the easiest case, targets are designated as items that repeat on the immediately succeeding trial (“1-back” condition). The load on working memory is manipulated by increasing the number of trials that intervene between the first and

second presentations. In Koivisto *et al (in press)*, 1-back, 2-back and 3-back conditions were employed. Accuracy and RT measures were obtained for both target and non-targets and analysed with analysis of variance. No exposure effects were found for accuracy. For target RT only, a reliable interaction effect was obtained between load (1-back, 2-back, or 3-back) and exposure condition. Pairwise comparisons revealed a significant ($p < 0.05$) RT reduction of 36 ms in the 3-back condition during exposure. Non-significant *increases* in RT were observed during exposure for the 1-back and 2-back conditions (11 ms and 21 ms, respectively).

- 5.183** These findings are consistent with those of Preece *et al (1999)* and Koivisto *et al (2000)* in suggesting that exposure to mobile phone signals facilitates RT during some cognitive tests. The findings further suggest that these facilitatory effects increase along with the cognitive demands of the test. Two aspects of the Koivisto *et al (in press)* study suggest, however, that the findings should be interpreted with a degree of caution. First, it is puzzling why exposure should have tended (albeit non-significantly) to increase RT in the 1-back and 2-back conditions. Second, the exposure effect in the 3-back condition was of only modest statistical significance.
- 5.184** Together, the findings of Preece *et al (1999)* and Koivisto *et al (2000, in press)* suggest that exposure to mobile phone signals at power levels within existing exposure guidelines has biological effects that are of sufficient magnitude to influence behaviour. Both groups conjectured that their findings reflected the effect of small temperature increases on synaptic transmission in the region of cerebral cortex directly under the headset antenna. An easily testable prediction of this account is that the tasks most sensitive to exposure to mobile phone signals should vary according to the position of the headset, and thus the cortical locus of the heating effect.
- 5.185** Considerably more work along the lines of the Preece *et al (1999)* and Koivisto *et al (1999)* studies is needed before it will be possible to evaluate fully the generality and significance of their findings. For example, it is currently unclear why Preece *et al* found effects only for analogue signals, whereas Koivisto *et al* were able to find effects with GSM signals. It is also unclear why the effects found in the studies of Preece *et al* and Koivisto *et al (2000)* involved different tasks. It is plausible that these disparities reflect differences in the signal powers and antenna positions employed in the two studies, and these variables should be among those investigated in future studies. As already noted, the reliability of some of the above findings is questionable because they were obtained from analysis of datasets containing numerous dependent variables. Future research conducted in light of these findings should, as much as is practical, employ a more hypothesis-driven approach to investigate exposure effects on relatively small numbers of variables.
- 5.186** Two further points should be made about the three studies described in this section. First, it should not be concluded that the findings of these studies indicate that the acute effects of exposure to mobile phone signals, when they are found, will invariably be beneficial to cognitive performance. This may be true for simple tasks of the kind on which Preece *et al (1999)* and Koivisto *et al (2000, in press)* were able to find exposure effects, although this result may not extend to more complex tasks which require co-ordination between several concurrently active cognitive operations (eg driving). In such cases, any change in the function of a single component operation may be detrimental for the functioning of the system as a whole.
- 5.187** Second, while further studies along the lines discussed above will be important in establishing whether the biological effects of mobile phone signals are indeed sufficient to cause short-term changes in cognitive performance, these studies will not directly address the question of whether long-term changes in cognitive function follow sustained exposure of the kind experienced by

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mobile phone users. The relevance of such studies to the question of whether mobile phone use is detrimental to health is therefore limited.

Electroencephalogram (EEG)

- 5.188** The scalp-recorded EEG is a reflection of synchronous activity in relatively large populations of cortical neurons. The “spontaneous” EEG is conventionally divided into a number of frequency bands, the relative amounts of activity which depend upon the psychological state of the subject, and the nature of the cognitive function in which he or she is engaged. The functional significance of these different components of the normal, waking EEG is poorly understood. Thus, while a demonstration that mobile phone signals influenced these components would be indicative of a biological effect of such signals, interpretation of the effect would be uncertain. This is less so in the case of EEG patterns associated with sleep, which are well characterised and routinely used as indices of the different sleep stages that a typical healthy individual will move between during the night. There would also be little uncertainty in the interpretation of a change from a normal to a frankly pathological pattern of EEG activity, such as might be observed in epilepsy.
- 5.189** A measure of brain function closely related to the EEG is the “evoked” or “event-related” potential (ERP). ERPs are obtained by sampling the EEG time-locked to a reference event such as the presentation of a stimulus or the onset of a motor response, and averaging the samples together so as to obtain an electrical waveform that represents brain activity associated specifically with that class of event. ERPs are commonly used to study the timing and functional integrity of neural systems supporting sensory, cognitive and motor processing.
- 5.190** Laboratory studies investigating the effects of mobile phone signals on the spontaneous EEG in awake subjects have produced somewhat mixed results. For example, Reiser *et al* (1995) reported that exposure to GSM signals was associated with increases some 15 minutes later in the power of EEG frequencies of about 10 Hz and above (although this finding is of questionable statistical validity). Roschke and Mann (1997), however, were unable to detect any differences in EEG spectra related to exposure to GSM signals. A similar inconsistency appears to hold for the study of sleep EEG. Mann and Roschke (1996) reported that exposure to GSM-like signals reduced latency to sleep onset, and altered the abundance and spectral characteristics of REM sleep, although a subsequent study by the same group (Wagner *et al*, 1998) failed to replicate these findings. In a more recent study, however (Borbely *et al*, 1999), exposure to a “pseudo-GSM signal” (15 minute on/off cycles, 900 MHz, duty cycle of 87.5% rather than the 12.5% used in phone signals, and an estimated whole-body SAR of 1 W/kg) was associated with reduced waking after sleep onset and changes in EEG power spectra during the first of the night’s episodes of non-REM sleep.
- 5.191** Krause *et al* (2000) studied the effects of GSM signals (dosimetry and general experimental design as in the studies of Koivisto *et al* (2000, *in press*) see paragraph 5.180) on “event-related” changes in the EEG recorded during the performance of a “memory scanning” task. Each trial involved the auditory presentation of four words (the “memory set”), followed after two seconds by the presentation of a “probe” word which matched an item from the memory set on 50% of trials; subjects were required to indicate whether or not the probe was a match. The principal finding was that the pattern of EEG changes (as indexed by changes in the power of four frequency bands between 4 Hz and 12 Hz) elicited by the probe word differed between exposure and no-exposure conditions. These differences were considered by Krause *et al* to be possible physiological correlates of the short-term effects of GSM signals on behaviour described by Koivisto *et al* (2000, *in press*). Unfortunately, Krause *et al* (2000) did not report measures of task performance. Thus it not possible to determine whether exposure facilitated RT in the memory

scanning task, as would be expected if the reported EEG changes are indeed a correlate of this effect.

- 5.192** In three studies, ERPs were investigated during exposure to GSM-like signals. In the first (Urban *et al*, 1998), visual sensory responses to checkerboard reversal were found to be unaffected during exposure. In two other studies (Eulitz *et al*, 1998; Freude *et al*, 1998) positive effects were reported. In the study of Eulitz *et al*, these took the form of the suppression of high frequency (18–30 Hz approximately) spectral power in ERP waveforms elicited by infrequent auditory “oddball” stimuli interspersed among a more frequent class of auditory stimulus. In Freude *et al*, the effect was a small reduction in the amplitude of response-related potentials in a visual monitoring task; no such effect was found in the potentials preceding spontaneous movements, nor were there any exposure effects on task performance.
- 5.193** Together, the findings from electrophysiological studies suggest that exposure to mobile phone signals influences brain function. The evidence is sufficiently substantial to warrant further investigation, notably with respect to the influence of GSM-like signals on sleep and on event-related EEG changes during the performance of cognitive tasks. It should be emphasised, however, that neither the biological nor the clinical significance of the findings described above is clear at present, and the relevance of the findings to the question of the safety of mobile phone technology is uncertain.

Conclusions from studies on brain function

- 5.194** *Together, the findings of Preece et al (1999) and Koivisto et al (2000, in press) from human laboratory studies of the acute effects of exposure to mobile phone signals suggest that exposure to mobile phone signals at exposure levels that fall within existing exposure guidelines have biological effects that are of sufficient magnitude to influence behaviour. The causal mechanism is unclear, but could include a small, localised heating effect.*
- 5.195** Human studies of cognitive performance and EEG have, however, yet to provide evidence directly relevant to the question of the safety of mobile phones in the long term. As already noted, the experimental designs employed thus far are not appropriate for this purpose, as they focus on the consequences of short-term exposure. To address the question of whether mobile phone use has long-lasting effects on measures of human brain activity or cognitive performance, it will be necessary to conduct laboratory-based studies on carefully matched groups of subjects who differ with respect to their history of exposure to mobile phone signals. A complementary approach would be to follow a group of new phone users over time so as to identify any changes in brain or cognitive function associated with cumulative exposure. Studies such as these should be a priority for future research.

Effects on the heart and blood pressure

- 5.196** As explained above (paragraphs 5.170–5.172), RF fields could, in principle, affect the cardiovascular system via a number of mechanisms. With normal use of a mobile phone, placed against the side of the head, direct influences on the human heart seem very unlikely. However, influences on the cardiovascular centres of the brainstem or the carotid body receptors are more conceivable.
- 5.197** Early reports from the former Soviet Union (see, for example, Drogichina *et al*, 1966; Sadčikova, 1974) implied that occupational exposure to RF radiation can directly or indirectly alter cardiovascular function. The most common observation was a reduction in blood pressure associated with either bradycardia or tachycardia (slowing or speeding of the heart). However, the general conclusion of a number of reviews of this literature is that most of the early studies

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were poorly controlled and that the results may have reflected chance variation (Kaplan *et al*, 1971; Resnekov, 1981; Kristensen, 1989; Jauchem, 1997).

- 5.198** More recently, Braune *et al* (1998a) have reported acute effects on blood pressure in human volunteers exposed to a conventional GSM digital mobile phone positioned close to the right side of the head. After 35 minutes of exposure, heart rate, blood pressure and capillary perfusion were measured with the subject either supine or standing for 60 seconds. They found that the heart rate during these tests was slightly lower after exposure to RF radiation than following non-exposed control sessions, and both systolic and diastolic blood pressure were elevated by 5–10 mm of mercury. Since capillary perfusion (blood flow through capillaries of the hand) was decreased, the authors concluded that the effects on blood pressure were due to excessive vasoconstriction, caused, perhaps, by an increase in sympathetic activity originating in the brainstem.
- 5.199** This study has been criticised on the basis of both its design and the statistical analysis (Reid and Gettinby, 1998). In particular, the “placebo” (non-exposed) session preceded the test session for all subjects, and therefore the small cardiovascular changes might have resulted simply from the lengthy period of the experiment. Braune *et al* (1998b) argued that they chose not to randomise the sequences because of other evidence that effects of RF exposure could persist for some time. However, they should, then, have included a true control group in which testing was carried out during a *second* non-exposed session following the first placebo period.

Conclusions on heart and blood pressure studies

- 5.200** *There is, on the basis of published evidence, no basis for concern about effects of mobile phone use on the heart and circulation. However, this is a subject that merits more experimental work on human volunteers. In particular, we advise that a study similar to that of Braune et al (1998a) is carried out with larger numbers of subjects and appropriate control conditions.*

Mobile Phones and Driving

- 5.201** Mobile phones could have a detrimental effect on public health not only through the direct effects of exposure to electromagnetic radiation, but also indirectly by interfering with the phone user’s ability to perform a concurrent task. Perhaps the most important, and certainly the most well-publicised, example of such interference involves the use of mobile phones while driving. These effects are considered by the Department of the Environment, Transport and the Regions to be sufficiently serious to warrant a major publicity campaign (DETR, 2000) aimed at dissuading drivers from using a mobile phone, especially one that is hand-held, when in control of a vehicle.
- 5.202** While it may seem obvious that using a hand-held mobile phone while driving will have negative consequences for road safety, it is perhaps less obvious that similar consequences may follow from the use of hands-free equipment. Experimental psychologists have, however, produced a wealth of evidence indicating that when mental (cognitive) tasks are performed concurrently, performance is often worse than when each task is performed alone. These “dual task” effects arise for a variety of reasons, chief among which are the need to switch or divide attention between the two tasks, and the interference that occurs when tasks compete for the same cognitive processes or mental representations.
- 5.203** In light of the psychological findings, it is likely that, in addition to the purely “peripheral” interference arising when a driver attempts both to operate a vehicle and to manipulate a

hand-held phone, there will also be sources of “central” interference that arise when the cognitive demands of a mobile phone conversation compete with those required for driving. In assessing the possible impact of mobile phones on road safety, it is important, therefore, to understand the relative magnitudes of these two sources of interference; there is little point in stressing the inadvisability of using a hand-held phone if the greater part of the associated risk is also present when hands-free equipment is used.

- 5.204** Evidence concerning the impact of mobile phones on driving ability is reviewed below in two sections. First, experimental studies are discussed in which the effects of phone use on driving have been assessed. Such studies allow the mechanisms by which phones interfere with driving to be elucidated, and the effects of different kinds of phone use to be compared. They provide, however, only indirect information about the actual impact of phone use on road safety. This issue is taken up in the second section, which discusses epidemiological studies that attempted to quantify the increased risk associated with the use of a mobile phone while driving. Finally, the implications of this evidence are discussed in relation to policy regarding the use of different kinds of phones in vehicles.

Experimental evidence for effects on driving

- 5.205** The impact of phone use on various aspects of driving performance has been investigated in a sizeable number of studies. Some studies investigated performance on laboratory tasks analogous to driving, such as a visuospatial tracking task (Strayer *et al*, 1999) or in a driving simulator (McKnight and McKnight, 1993; Alm and Nilsson, 1994, 1995; Haigney, 2000); others employed real cars and road situations (Brown *et al*, 1969; Brookhuis *et al*, 1991; Lamble *et al*, 1999). Some studies limited their investigations to the effects of mobile phone conversations in a hands-free setting, sometimes employing phone tasks that differed with respect to “mental workload”, eg “shadowing” (repeating back) words *versus* “generation” (producing a new word beginning with the last letter of the one just heard). Other studies directly contrasted the effects of using hand-held *versus* a hands-free sets (Brookhuis *et al*, 1991; Strayer *et al*, 1999; Haigney, 2000); or compared the use of hands-free phone to a task requiring some manual control of some other device, eg entering numbers on a keypad (Lamble *et al*, 1999) or a keypad task and tuning a radio (McKnight and McKnight, 1993).
- 5.206** The results of these experimental studies are consistent and easily summarised. Relative to either a “no-conversation” condition (or, in the case of Strayer *et al*, 1999, listening to a car radio), engaging in a mobile phone conversation had a detrimental effect on driving performance as measured by such indices as the time taken to react to an imperative stimulus (Alm and Nilsson, 1994; Strayer *et al*, 1999) or a change in the speed of a leading car (Brookhuis *et al*, 1991; Lamble *et al*, 1991; Alm and Nilsson, 1995); failure to react to a potentially dangerous road situation (McKnight and McKnight, 1993); speed adaptation (Haigney, 2000; interestingly, this measure was found to exhibit a “carry-over” effect, in that adaptation continued to be affected during a 2.5 minute period after the call was terminated); maintaining a safe distance from a leading car (Haigney, 2000); and the ability to control a car in “non-routine” situations (Brown *et al*, 1969). Although the detrimental effect of mobile phone use increased with the mental workload imposed by the conversation (McKnight and McKnight, 1993; Strayer *et al*, 1999), an effect was evident nonetheless with “casual” conversations (McKnight and McKnight, 1993), even when the control condition consisted of listening to a car radio (Strayer *et al*, 1999). Furthermore, in one simulator study (Alm and Nilsson, 1994) it was found that the detrimental effects of a phone conversation on reaction time were greater when driving conditions were relatively undemanding as opposed to when they were taxing. The findings of two studies (McKnight and McKnight, 1993; Alm and Nilsson, 1995) suggest that the negative effects of a phone conversation on driving increase with age. This finding is not unexpected given evidence

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of a general age-related decline in ability to divide attention (see, for example, Gottlob and Madden, 1999).

- 5.207** Importantly, the foregoing studies suggest that the “central” effects of mobile phone use on driving are equivalent for hands-free and hand-held operation. Two studies that directly compared these modes of operation (Strayer *et al*, 1999; Haigney, 2000) reported no difference, albeit, in the case of Strayer *et al*, with a laboratory “tracking” task somewhat removed from driving (it is noteworthy that the Haigney study also failed to find any difference between hand-held and hands-free operation even when gear changes were made manually rather than automatically). In a third study (Brookhuis *et al*, 1991) the effects of the two modes of phone operation were compared during real driving (although with only six subjects in each group), and were found to have equally detrimental effects on speed of reaction to the slowing of a leading car. However, dialling with a hand-held set was associated with poor control over steering, especially when driving in city traffic. In the studies of McKnight and McKnight (1993) and Lamble *et al* (1999) the effects of conversation via a hand-held set were compared with those from tasks involving a combined cognitive and manual component (tuning a radio or keying in numbers); in both cases, merely engaging in a demanding conversation had effects equivalent to those of the combined task. According to Lamble *et al* (1999), the effect they observed on braking time was approximately three times that found for drivers with a blood alcohol level of 0.05% (the limit for many European countries; the UK limit is 0.08%).

Conclusions on experimental evidence for effects on driving

- 5.208** *There is strong experimental evidence that engaging in a mobile phone conversation impairs drivers’ ability to react to potentially hazardous road situations. The impairment appears to be greater than that associated with merely listening to a radio or engaging in a relatively “automatic” task such as repeating back words heard over the phone; is evident during a “casual” conversation; increases along with the mental workload imposed by the conversation; is greater in elderly drivers; and is unaffected by mode of phone use (hand-held versus hands-free). There is less evidence as to whether aspects of driving other than speed or accuracy of reaction to changing road circumstances differ according to mode of phone operation. Consistent with what might be expected on the basis of common experience, one study found that placing a call on a hand-held set is associated with a transient impairment in the basic control of the vehicle. The extent to which this “peripheral” effect adds to the risk posed by the more sustained “central” effects that are shared by hand-held and hands-free operation appears to be unknown at present. It should be noted that none of the studies reviewed above compared the effects on driving performance of phone use to the effects caused by conversing with a passenger. Thus it remains to be established whether an in-car conversation that places a cognitive load on the driver equivalent to that imposed by a mobile phone call has similarly detrimental effects on performance. There are, however, good reasons to suppose that the effects of an in-car conversation will be less than those associated with the use of a phone. In contrast to the individual on the other end of a phone call, a passenger can monitor the road situation and “pace” the interaction according to circumstances (for example, suspending conversation during an overtaking manoeuvre). In addition, a passenger can act as a second “pair of eyes”, alerting the driver to potential hazards.*

Epidemiological evidence for effects on driving

- 5.209** There are few systematic studies of the effects of mobile phone use on road traffic accident rates. Violanti and Marshall (1996) conducted a questionnaire survey of 100 randomly selected drivers who had been involved in a “reportable” road traffic accident during a 12 month period, and 100 geographically matched control drivers who had been accident-free for at least ten years.

Fourteen of the drivers who consented to participate were mobile phone users. After controlling for factors such as years of driving experience, Violanti and Marshall reported that there was a significant association between the likelihood of involvement in an accident and the use of a mobile phone for more than 50 minutes per month. These findings are, however, of questionable significance with respect to whether in-car phone use is detrimental to road safety; not only was the number of cases available for analysis very small, but the critical variable – monthly use of a mobile phone – provides, at most, a highly indirect index of in-car usage. The latter criticism also holds for the study of Dreyer *et al* (1999), who reported an association between the amount of mobile phone usage and road accident mortality.

- 5.210** Violanti (1997, 1998) examined accident records from the state of Oklahoma in the USA, where traffic police routinely record whether a mobile phone was present in a car involved in an accident, as well as whether the phone was reported to be in use when the accident occurred. In the first study (Violanti, 1997) rate-ratios were assessed for phone use and presence with respect to a number of accident characteristics. Use and presence were associated with a significantly elevated risk for accidents when these involved, among other things, “driver inattention”, driving in cities, running off the road, overturned vehicles, and injuries and fatalities. Phone users most at risk from fatalities were young males, but otherwise there was a trend for phone-related risks to increase with age. No steps were taken in the analyses as presented to remove the effects of any potential confounding variables that might have acted to exaggerate differences between phone users and non-users. The second study (Violanti, 1998) focussed exclusively on fatal accidents, addressing the question of whether, among drivers who had experienced an accident, the probability of a fatal outcome was influenced by the use or presence in the car of a mobile phone. Logistic regression was used in an attempt to remove the confounding effects of such variables as age and involvement with alcohol or drugs, as well as, puzzlingly, accident characteristics such as “unsafe speed”, and “driver inattention”. It was estimated that the likelihood of a fatality, given involvement in an accident, increased by a factor of about nine if a phone was in use, and was doubled if a phone was merely present in the car.
- 5.211** These two studies suggest there is a strong statistical association between the presence and use of mobile phones in cars and the likelihood of a serious traffic accident. There are, however, possible reasons for this association other than a detrimental effect of phone use on driving. It might be, for example, that drivers who carry or use a mobile phone differ from those who do not in ways that make them more likely to be involved in an accident. The finding that the mere presence of a phone in a car was associated with elevated risk is consistent with this possibility, although the finding could also reflect an underestimation of the proportion of accidents in which the phone was actually in use.
- 5.212** Redelmeir and Tibshirani (1997) employed a “case–crossover” design, in which each participant served as his or her own control. They investigated a group of 699 drivers who had reported involvement in a minor traffic accident, addressing the question whether these individuals were more likely to have been using a phone in the period leading up to their accident than they were during a comparable “control” period in the recent past. A correction factor was employed to allow for the fact that participants may not have driven during a control period. Redelmeir and Tibshirani found that *relative risk* increased with the proximity of phone use to the time of the accident. For example, use of a phone within 10 minutes of the accident was associated with an approximate quadrupling of risk, whereas phone use more than 15 minutes before the accident did not carry a significant risk. These findings were robust with respect to the choice of control period (eg day before, same day a week previously, etc) and were similar for a subgroup of drivers who reported (when questioned some two years afterwards) that they had definitely driven during the control period, and therefore for whom no correction for “driving intermittency” was required. Although numbers were small ($N = 129$ for hand-held;

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41 for hands-free), there was no evidence that risk differed according to mode of phone operation; indeed, there was a non-significant trend for hands-free operation to carry the greater risk.

- 5.213** The findings of Redelmeir and Tibshirani (1997) converge with those of Violanti (1997, 1998) to suggest that the use of a mobile phone while driving is associated with an increased risk of an accident. While the study does not suffer from the problems inherent to comparisons involving different groups of individuals, it nonetheless has a number of limitations, as indeed discussed by the investigators. Chief among these is that the findings do not permit the conclusion that the association between phone use and traffic accidents is causal. For example, it might be that the critical variable is the level of stress or time-pressure experienced by the driver, which is associated with an increased probability of making a phone call while on the move and an increased probability of an accident. Among other limitations of the study are its use of a self-selected group of drivers (of 1000 or so candidates, about 300 refused to participate), its focus on minor accidents, and the need, in the overall analysis, to rely upon a correction factor to allow for “driving intermittency” during control periods. These limitations notwithstanding, the study provides persuasive evidence that the use of a mobile phone while driving has a detrimental effect on road safety.

Conclusions on epidemiological evidence for effects on driving

- 5.214** *Experimental studies provide compelling evidence that engaging in a mobile phone conversation impairs driving performance. Consistent with this evidence, epidemiological research points to an association between mobile phone use while driving and an increased risk of involvement in an accident. Together, these two sources of evidence indicate that current concerns about the impact of mobile phones on road safety are well founded. As already noted, however, current experimental evidence suggests there is little or no justification for the assumption that the detrimental effects of phone use on driving are ameliorated by hands-free operation, a conclusion supported by the limited epidemiological evidence relevant to this question (Redelmeir and Tibshirani, 1997). There is therefore no strong empirical justification at present for the enactment of a policy or legislation that differentiates between the use of hand-held and hands-free phone sets in motor vehicles. While an argument might be made for focussing legislation on the more detectable of these two modes of use – it is of course much easier to detect the use of a hand-held set than a hands-free set – such an approach runs the risk of seeming to condone, or at least to tolerate, the use of hands-free phones.*

Epidemiological Studies on General Health Effects

- 5.215** Epidemiology is the branch of science that is concerned with the distribution and determinants of disease in human populations. As such, it provides the most direct evidence on whether and to what extent suspected environmental hazards cause disease. This evidence comes mainly from investigations that compare risks of disease in different groups of people according to their exposure to a suspected hazard. Usually, the results are expressed in terms of an estimate of relative risk, ie the multiplier by which risk is higher in people exposed to the hazard than in others who are unexposed or exposed at a lower level. For example, a relative risk of two for brain cancer in exposed compared with unexposed people would imply that the rate of brain cancer was twice as high in the former as in the latter group. It should be noted that the impact of a raised relative risk will depend on the underlying incidence of the disease to which it applies. A doubling in the frequency of a very rare disease represents a much smaller absolute increase in risk than a doubling of a common disorder.

- 5.216** The practical and ethical constraints on research in human populations mean that all epidemiological studies have limitations that must be taken into account in the interpretation of their findings. There may be deficiencies in their design or execution, often unavoidable, which tend spuriously to inflate or diminish estimates of risk – an effect known as “bias”. Practical restrictions on the numbers of people who can be studied mean that epidemiological studies are subject to statistical uncertainty, and may produce misleading results simply by chance (statistical techniques can be used to quantify the extent of this uncertainty). Even where risk is genuinely elevated, this does not necessarily indicate a causal relationship between the hazard and the disease. There may be one or more “confounding factors” that are associated with exposure to the hazard and that independently influence the chance of occurrence of a disease. For example, an increased risk of lung cancer in people living near to a radio mast might reflect the fact that on average they smoke more than people living elsewhere, rather than an effect of radiation emitted by the mast. In general, the closer the relative risk is to unity, the more difficult it is to rule out bias and confounding as explanations for an association between exposure and disease.
- 5.217** The scope for bias, chance effects and confounding is such that generally little weight can be given to a single epidemiological study in isolation and, when evaluating epidemiological evidence, it is important to base conclusions on the totality of all relevant studies. Sometimes, several studies that address the same problem can produce quite different estimates of risk. As well as differences in the impact of bias, chance and confounding, such discrepancies may reflect differences in the extent or pattern of exposure that was examined or the presence of other factors that modify the body’s response to a hazard.
- 5.218** To date, few epidemiological studies have directly examined the relationship of mobile phones to morbidity or mortality, and none has explored the effects of exposure to RF radiation from base stations. However, rather more information is available regarding exposure to other types of RF radiation – for example, in radar mechanics and radio operators, and from residence near broadcasting towers and masts. These exposures differ in frequency, dose and other characteristics from those produced by mobile phones and base stations, so they give only an indirect indication of the possible risks from mobile phone technology. Nevertheless, they are relevant and worth consideration.
- 5.219** Four main types of study have been used in this area of research – cohort studies, case-control studies, cross-sectional surveys of morbidity, and cross-sectional, “ecological” comparisons of mortality or cancer incidence between populations. In a cohort study, individuals who have been exposed to a known or suspected hazard are identified and their subsequent disease incidence or mortality is assessed over a period of follow-up. This is then compared with the corresponding rate of disease or death in a control group who have been unexposed or only exposed at a lower level. A case-control study starts with patients who have developed a disease (cases) and compares their past exposure to known or suspected causes with that of suitably chosen controls who do not have the disease. Cross-sectional surveys of morbidity focus on a representative sample of a population (eg residents of a specified area), and collect information from individuals in the sample about their disease experience and about current and past exposures to known or suspected causes of disease. The statistical association between exposure and disease is then examined. Ecological analyses of mortality and cancer incidence assess the frequency of death or of new cases of cancer in different populations (eg in occupational groups or residents of defined geographical areas) over a period (say a few years), and relate this to differences in the levels of exposure of the whole population to known and suspected hazards. For example, death rates might be compared in people living close to and further away from a television mast. It should be noted that the first three methods assess disease and exposure in individuals, whereas the ecological method relates to populations. Even where disease rates are consistently high in heavily exposed populations, it does not necessarily follow that the individuals within those

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populations who suffer the disease have themselves been exposed. In general, the ecological method, because of the lack of individual data, is the least robust of the four study designs, and often, although by no means always, the cohort method is the most rigorous.

Studies of people using mobile phones

- 5.220** Widespread use of mobile phones is a recent phenomenon, and as yet few epidemiological studies have looked directly at whether there are associated risks of illness or death.

Mortality and cancer incidence

- 5.221** One investigation has examined mortality among customers of a large mobile phone operator in the USA (Rothman *et al*, 1996). It covered some 250,000 phone users, who were followed for one year. During this time, the overall death rate was similar in people using hand-held phones and in users of other mobile phones that did not have an antenna in the handset, and therefore gave lower exposures to RF radiation. For those customers who had been listed as continuous users for at least three years, overall mortality was slightly lower in the hand-held phone users than the other mobile phone users, but the difference was not statistically significant (relative risk = 0.86). Numbers of brain tumour and leukaemia deaths were small and showed no substantial indication of increasing risk with number of minutes of hand-held phone use per day, or with years of hand-held phone use (Dreyer *et al*, 1999). No data were reported on whether phones used analogue or digital signals (at this time, in the USA most mobile phone networks used analogue signals). If mobile phones do affect mortality, the impact is likely to be on only certain specific causes of death. Also, any increase in diseases such as cancer may not be manifest until many years after people are first exposed to a hazard. *Therefore, although no significant differences in mortality were demonstrated between the two exposure groups, the conclusions that can be drawn from this report are limited, and it does not rule out important effects.*

- 5.222** In a case-control study in Sweden, patients with brain tumours were asked about various aspects of their life including their use of mobile phones, and the findings were compared with those in controls selected from the general population (Hardell *et al*, 1999). Overall, the risk of brain tumours did not appear to be elevated in people who used mobile phones, either analogue or digital, even if their use was relatively heavy. In a series of subsidiary analyses, an association was observed between tumours in the temporal and occipital lobes of the brain and reported use of analogue phones on the same side of the head (regardless of whether that was to the left or right). However, this was not statistically significant, and could easily have occurred by chance. Interpretation of this study is complicated because it failed to identify a substantial number of brain tumour patients who were eligible for inclusion according to the reported entry criteria (Ahlbom and Feychting, 1999), and in the absence of an explanation for this under-ascertainment, it is unclear whether important bias could have resulted. Also, as in the study by Rothman *et al*, an effect of exposure that was delayed for ten or more years would not have been apparent.

Other health effects

- 5.223** In an attempt to identify other, more immediate, adverse health effects that might be associated with the use of mobile phones, Hocking (1998) placed a notice in a medical journal in Australia. From this and subsequent publicity, he recruited 40 individuals with symptoms which they related to using mobile phones. These symptoms were mainly in the head, and included pain, unpleasant warmth or heating, blurring of vision and deafness or vertigo. Most started within five minutes of beginning a call, but some built up over the course of the day. A perceived temporal association between use of a phone and the development of symptoms does not necessarily imply that RF radiation is responsible. Rather, the findings of Hocking's study should be regarded as an

indication of the types of symptom that users claim, and which might merit more rigorous investigation to determine whether there is any causal relationship to mobile phone use. It is notable, however, that there were no reports of epileptic seizures triggered by phone use, although this has been alleged to occur in relation to exposures from base stations.

- 5.224** Larger-scale data on self-reported, subjective symptoms are available from a cross-sectional survey of some 11,000 mobile phone users in Sweden and Norway (Hansson Mild *et al*, 1998). A postal questionnaire was used to collect information about various symptoms including fatigue, headache and warmth behind and on the ear. Of the participants, 13% in Sweden and 30% in Norway reported the occurrence of at least one symptom, which they themselves related to mobile phone use. For both analogue and digital phones, the prevalence of reported symptoms increased with minutes per day of phone use. The proportion of GSM phone users reporting a symptom was rather lower than in other groups. The marked difference in the prevalence of complaints between Sweden and Norway has a number of possible explanations. It is well known that somatic complaints can be influenced by psychosocial circumstances. For example, back pain is more likely to be reported by people who are depressed or dissatisfied in their work. Furthermore, at the time of the survey there had been much publicity in Scandinavia about possible adverse health effects of electromagnetic fields. In these circumstances, it would not be surprising if people who used mobile phones extensively were more aware of and troubled by minor symptoms, and more likely to report them when questioned. Thus as in the Australian study, the various symptoms reported by the users of mobile phones cannot necessarily be attributed to RF radiation. To address this question, further research is needed with a different study design (see paragraphs 5.258–5.260).

Exposure to RF radiation through work and hobbies

- 5.225** A number of epidemiological investigations have examined the risk of illness or death in people potentially exposed to RF radiation through their work or hobbies, and these have been the subject of several previous reviews (EC, 1996; Elwood, 1999; Moulder *et al*, 1999; Royal Society of Canada, 1999). The diseases most often studied have been lymphatic and haematopoietic cancers (including lymphoma and leukaemia) and brain cancer.

Cancer

- 5.226** Table 5.19 summarises the investigations that provide information about lymphatic and haematopoietic cancers. The study by Szmigielski (1996) stands out in suggesting a more than six-fold elevation in the risk of these diseases among Polish military personnel with occupational exposure to RF radiation. However, Szmigielski's report is unsatisfactory, and can be given little, if any, weight. In particular, it appears that the exposures of cancer cases were ascertained from a different source (medical records) from those of the study population as a whole (provided by safety staff), and this could seriously have biased risk estimates. Also, the statistical methods are not adequately described, and certain important data are missing from the report.
- 5.227** If this investigation is discounted, only one study shows a statistically significant increase in risk – of leukaemia in Norwegian electrical workers (Tynes *et al*, 1992). In some of the other studies, risks were also elevated, although not to the point of statistical significance. These elevations of risk were either for leukaemia or for lymphatic and haematopoietic cancers as a group. (This grouping is often used in epidemiological studies, partly because misclassification of cases may occur when more specific diagnostic categories are employed. However, no carcinogen has yet been identified that causes all of the cancers in the group.) In most of the studies, the index of exposure to radiation was relatively crude and non-specific, and the workers may have experienced other confounding exposures. Thus, the observed increases in risk could have been due to chance or to factors other than RF radiation. At the same time, however, because of their low statistical power and the heterogeneity of the exposures examined, the absence of a clear and

Table 5.19 Epidemiological studies of lymphatic and haematopoietic cancer in people potentially exposed to RF radiation through work or hobbies

Type of study	Study population	Exposure condition	Disease outcome	Number of exposed cases	Estimated relative risk (with 95% CI)*	References
Cohort	Radar technicians in US Navy	Occupations with higher exposure to RF radiation (radar)	Death from lymphatic or haematopoietic cancer	26	1.18	Robinette <i>et al</i> , 1980
Cross-sectional analysis of proportional mortality	Men age 20+ years in Washington State, USA	Radio and telegraph operators	Death from lymphatic or haematopoietic cancer	15	1.37	Milham, 1985
		Radio and television repairmen		12	1.27	
Cohort	Amateur radio operators in California and Washington State, USA	Amateur radio operators	Death from lymphatic or haematopoietic cancer	89	1.23 (0.99–1.52)	Milham, 1988
Cohort	White male enlisted men in US Navy	Radiomen	Non-Hodgkin's lymphoma	2	0.6 (0.1–2.0)	Garland <i>et al</i> , 1988
		Aviation electronics technician		1	0.4 (0.0–2.2)	
Case-control	Men aged 20+ years in New Zealand	Radio and television repairmen	Leukaemia	2	7.9 (2.2–28.0)	Pearce and Fraser, 1989
Cohort	White male enlisted men in US Navy	Radiomen	Leukaemia	4	1.1 (0.3–2.8)	Garland <i>et al</i> , 1990
		Electronics technician		5	1.1 (0.4–2.6)	
Cohort	Norwegian electrical workers	Occupations with potential exposure to RF radiation	Leukaemia	9	2.85 (1.30–5.41)	Tynes <i>et al</i> , 1992
Cohort	Norwegian female radio and telegraph operators	Radio and telegraph operators	Leukaemia	2	1.1 (0.1–4.1)	Tynes <i>et al</i> , 1996
			Lymphoma	5	1.3 (0.4–2.9)	
Cohort	Polish military personnel aged 20–59 years	Occupational exposure to RF radiation	Lymphatic and haematopoietic cancer	Not given	6.31 (3.12–14.32)	Szmigielski, 1996
Cohort	Female employees in an Italian plastics factory	Exposure to RF radiation through work in a dielectric heat sealing department	Death from leukaemia	1	5.0	Lagorio <i>et al</i> , 1997
Cohort	Men and women employed in the design, manufacture and testing of wireless devices	Work in occupations with moderate or high peak exposures to RF radiation	Death from lymphatic or haematopoietic cancer	20	0.54 (0.33–0.83)	Morgan <i>et al</i> , 2000

*Confidence intervals, where shown, are as calculated by the authors

Table 5.20 Epidemiological studies of brain cancer in people partially exposed to RF radiation through work or hobbies

Type of study	Study population	Exposure condition	Disease outcome	Number of exposed cases	Estimated relative risk (with 95% CI)*	References
Cross-sectional analysis of proportional mortality	Man aged 20+ years in Washington State, USA	Radio and telegraph operators Radio and television repairmen	Death from brain cancer	1 2	0.38 0.59	Milham, 1985
Case-control	White men aged 30+ years from three areas of USA	Ever worked in a job with likely exposure to RF radiation	Death from brain cancer	69	1.6 (1.0–2.4)	Thomas <i>et al</i> , 1987
Cohort	Amateur radio operators in California and Washington State, USA	Amateur radio operators	Death from brain cancer	29	1.39 (0.93–2.00)	Milham, 1988
Cohort	Norwegian electrical workers	Occupations with potential exposure to RF radiation	Brain tumours	3	0.61 (0.13–1.78)	Tynes <i>et al</i> , 1992
Cohort	Norwegian female radio and telegraph operators	Radio and telegraph operators	Brain tumours	5	1.0 (0.3–2.3)	Tynes <i>et al</i> , 1996
Cohort	Polish military personnel aged 20–59 years	Occupational exposure to RF radiation	Tumours of the nervous system and brain	Not given	1.91 (1.08–3.47)	Szmigielski, 1996
Case-control	Male personnel in US Air Force	Potential exposure to RF radiation	Brain tumours	94	1.39 (1.01–1.90)	Grayson, 1996
Cohort	Female employees in an Italian plastics factory	Exposure to RF radiation through work in a dielectric heat sealing department	Death from brain cancer	1	10.0	Lagorio <i>et al</i> , 1997
Cohort	Men and women employed in the design, manufacture and testing of wireless devices	Work in occupations with moderate or high peak exposure to RF radiation	Deaths from cancers of the nervous system and brain	7	0.53 (0.21–1.09)	Morgan <i>et al</i> , 2000

*Confidence intervals, where shown, are as calculated by the authors

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consistent elevation of risk in these studies cannot be taken as strong evidence against an association with specific types of RF radiation.

- 5.228** Where several epidemiological studies have addressed the same question, each individually with low statistical power, it is sometimes possible to draw firmer conclusions by combining their findings in a formal statistical “meta-analysis”. However, this approach is not appropriate for the studies listed in Table 5.19 because they are too disparate.
- 5.229** Table 5.20 lists the studies that give information on the risk of brain tumours. Again, for reasons already stated, little weight can be given to the report by Szmigielski (1996). Apart from this, two investigations have found a statistically significant elevation of risk, both of them case-control studies.
- 5.230** The first (Thomas *et al*, 1987) recruited cases from the general population of three areas of the USA, and classified exposure on the basis of job titles as reported by the subjects’ next of kin. The association with exposure to RF radiation was confined to jobs involving the design, manufacture, installation and maintenance of electrical and electronic equipment, leading the authors to suggest that some aspect of work other than RF radiation might be responsible. The aetiology of brain tumours, however, is largely unknown, so it is uncertain whether these occupations have relevant exposures in common.
- 5.231** The second study (Grayson, 1996) focussed on male personnel in the US Air Force, with exposures assessed from occupational histories. Although risk was significantly higher in men exposed to RF radiation than in those classed as unexposed, the elevation was modest even in those thought to have the heaviest exposures.
- 5.232** Other studies of brain cancer have given inconsistent results. As for haematopoietic and lymphatic cancer, the results overall do not indicate an increased risk of brain tumours from RF radiation, but because of various limitations neither do they provide strong reassurance that there is no hazard. These limitations include poor, often highly indirect, assessment of RF exposure and low statistical power.
- 5.233** Data on other types of cancer are more sparse and although some have suggested increased risks from RF exposure, their limitations are such that these findings should not be a cause for concern.
- 5.234** In a cohort study of Norwegian female radio and telegraph operators, Tynes *et al* (1996) found a relative risk of 1.5 for breast cancer (95% confidence interval 1.1–2.0). However, no relationship to RF radiation was apparent in a large case-control study of female breast cancer in the USA that used occupational information obtained from death certificates (Cantor *et al*, 1995), or in a cohort study of workers employed in the design, manufacture and testing of wireless devices in the USA (Morgan *et al*, 2000). However, this study does not give information directly on mobile phone use or exposures occurring from such use (Owen, 2000).
- 5.235** A cluster of six men with testicular cancer has been reported in a population of US police officers who used hand-held radar guns (Davis and Mostofi, 1993). However, in the only epidemiological study to examine the relationship between testicular cancer and work with radar equipment (Hayes *et al*, 1990), results were inconclusive: the risk of testicular cancer was significantly elevated in men who reported occupational exposure to RF radiation, but not when the radiation exposures were inferred from job titles by an occupational hygienist. This inconsistency between the results from the two methods of assessment raises the possibility that cases recalled their

exposures more completely than controls, or overestimated their exposures, leading to a biased risk estimate.

5.236 In a study in the USA, a raised risk of uveal melanoma was found in men with self-reported exposure to RF or radar (Holly *et al*, 1996), but RF radiation has not been examined in other published studies of this tumour.

5.237 *In summary, the overall balance of evidence from epidemiological occupational studies does not indicate that RF radiation affects the risk of cancer in people. However, the types of exposure investigated have varied between studies and are not identical to those associated with mobile phone technology. Also, many of the studies have had low statistical power and some have suffered from methodological deficiencies. Therefore, the absence of consistently positive findings does not establish firmly that RF radiation from mobile phones carries no important risk of cancer.*

Health outcomes other than cancer

5.238 Although cancer has been the main health outcome studied in relation to work with RF radiation, several cohort studies of occupational groups exposed to RF radiation have also examined non-cancer mortality and in some instances morbidity (see, for example, Robinette *et al*, 1980; Muhm, 1992). These do not provide any overall evidence of hazard.

5.239 In addition, several case–control studies have explored the risk of adverse outcomes of pregnancy in physiotherapists using microwaves in the RF range to treat their patients. One such study found a significantly raised risk of spontaneous abortion (miscarriage) in physiotherapists who reported exposure during the six months before and three months after becoming pregnant (relative risk 1.28, 95% confidence interval 1.02–1.59), and a higher risk in those with more frequent exposure (Ouellet-Hellstrom and Stewart, 1993), although with a relatively low response rate to the questionnaire that was used to collect information. No corresponding association was found with use of short-wave diathermy. Overall, however, studies of pregnancy in physiotherapists have not supported a relation of microwave exposure with miscarriage or other adverse outcomes (Kallén *et al*, 1982; Taskinen *et al*, 1990; Royal Society of Canada, 1999).

5.240 Despite this lack of evidence for health risks resulting from the exposure of workers to RF radiation, it would be sensible to set in place a long-term follow-up of workers who are occupationally exposed to RF radiation at relatively high levels. **We recommend that a register of occupationally exposed workers be established and that cancer risks and mortality be examined to determine whether there are any harmful effects. If any adverse effects of exposure to RF radiation are identified then the Health and Safety Executive should establish a system of health surveillance.**

Residence near radio and television transmitters

5.241 The incidence of cancer in people living near to radio or television transmitters has been examined in studies from the USA, Britain and Australia.

5.242 Selvin *et al* (1992) looked for clustering of childhood leukaemia, lymphoma and brain cancer within 3.5 km of a microwave tower in San Francisco. The main purpose of their investigation was to compare methods of statistical analysis, and they did not adjust closely for potential confounding factors. However, they found no evidence of any excess incidence in the study area.

5.243 In contrast, a case–control study in Hawaii suggested an approximate doubling in the occurrence of childhood leukaemia within 4.2 km of a group of radio masts (Maskarinec *et al*, 1994). The

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number of exposed cases was small, however, and the excess was far from statistically significant. Furthermore, the investigation had been prompted by a perceived local excess of the disease, and in this circumstance it is more difficult to rule out the play of chance. In the same way that some communities can have a disproportionate excess of lottery winners purely by chance, a cancer can occur more frequently in a small geographical area (and will then be noticed to be common there) without there being a local cause for the phenomenon.

- 5.244** Concerns about an apparent excess of leukaemia and lymphoma were also the trigger for a geographical analysis of cancer incidence in the neighbourhood of a television and radio transmitter in Sutton Coldfield, England (Dolk *et al*, 1997a). The investigation confirmed that there had been an increased incidence of leukaemia within 2 km of the transmitter, the relative risk being approximately 1.8 in comparison with the regional population. None of the other cancers analysed apart from bladder cancer (relative risk 1.5), showed a statistically significant excess near to the transmitter. The authors recognised that despite their statistical significance, these findings could easily have occurred by chance, and therefore carried out a similar analysis for people living close to other high power radio and television transmitters in Britain (Dolk *et al*, 1997b). This showed no excess of leukaemia within 2 km of the transmitters. Rates of bladder cancer were marginally elevated within a 10 km radius (relative risk 1.09), but did not decline progressively with distance from the transmitters as might be expected if RF radiation were responsible.
- 5.245** In Australia, Hocking *et al* (1996) compared rates of leukaemia and brain tumours in three municipalities of Sydney surrounding television masts and six others at a further distance from the masts. The findings for brain tumours were unremarkable, but there was an approximate 60% excess of leukaemia among children from the three areas close to the towers. Subsequently, McKenzie *et al* (1998) explored this pattern of leukaemia incidence further with an expanded control area. The excess incidence was found to be limited to only one of the three municipalities surrounding the masts, suggesting that chance or some local factor other than RF radiation was responsible.
- 5.246** In addition to these investigations published in scientific journals, some reviews refer to studies of people living near a military microwave generator–detector system in Latvia, and of staff and their dependants in American embassies in Eastern Europe who may have been exposed to microwave radiation beamed into the embassies (Goldsmith, 1995; Repacholi, 1998). However, these have not been published in the peer-reviewed literature, and we have not been able to obtain sufficiently detailed descriptions of these investigations to evaluate them.
- 5.247** The studies to date that have looked at cancer incidence in relation to residence near broadcasting facilities have major limitations, which weaken the conclusions that can be drawn from them. The analyses have not been based on measured levels of radiation. Distance from a broadcasting tower has been taken as a proxy for exposure, but no account has been taken of ground reflections and signal reductions by buildings, vegetation and undulations, which may alter actual exposure considerably. The studies have been based on cancer and exposure data for populations not individuals, with the associated weaknesses of “ecological” studies (see paragraph 5.219). Personal exposures will vary according to how much time people spend at home, whether they are indoors or outdoors, the other sources of RF radiation in and near to their homes, and their levels of exposure at work, when travelling, and from mobile phone use. None of these has been taken into account. Furthermore, the studies have analysed risks in relation to place of residence at the time of cancer incidence or death, but if RF radiation does cause cancer, the relevant exposure may well be years or even decades before the disease becomes manifest. Thus while the balance of evidence from such studies does not indicate a hazard – and where increased rates of

disease have been found they could have occurred by chance or as a consequence of unrecognised confounding factors – the findings do not provide strong evidence against a hazard.

Conclusions from epidemiological studies

- 5.248** *Apart from the risks associated with the use of mobile phones while driving, which are discussed in paragraphs 5.201–5.214, there is no persuasive epidemiological evidence that exposure to RF radiation in general – or to the limited extent that it has been investigated, mobile-phone-related exposures in particular – causes disease in people. Although the epidemiological research that has been carried out to date does not give cause for concern, it has too many limitations to give reassurance that there is no hazard. A substantial number of people report symptoms such as fatigue, headache and feelings of warmth behind the ear that occur during or shortly after the use of mobile phones. However, it is unclear to what extent, if any, these symptoms are caused by RF radiation.*

Proposals for further research

- 5.249** In view of the widespread use of mobile phone technology, any adverse effects on health could affect large numbers of people. This is clearly a source of anxiety among some members of the public. We therefore identify the following epidemiological research to try to resolve the current uncertainty. Details of the methodological considerations needed to conduct these studies with high quality are given by EC (1996), Swerdlow (1997), and Repacholi and Cardis (1997).

Case–control studies of cancer risk in relation to the use of mobile phones

- 5.250** There is a pressing need for case–control studies to examine whether leukaemia and cancers of the brain, acoustic nerve and salivary gland are caused by mobile phone use.
- 5.251** A large case–control study of the risk of brain tumours in relation to the use of mobile phones is close to publication in the USA (Inskip *et al*, 1999), but its results are not yet available to us. An international case–control study of brain cancer, acoustic neuroma, salivary gland tumours and leukaemia co-ordinated by the International Agency for Research on Cancer (IARC), and including components in Britain, has received partial funding from the European Commission. At the time of our review, however, funding is incomplete and it is unclear how much of the study will be undertaken. The IARC study also includes important methodological work to assess the validity of subjects' recall of mobile phone use in comparison with information from billing records.
- 5.252** In view of the possibility that mobile phones might cause malignancies after a long induction period, such case–control studies may need to be repeated in the future when the technology has been in place for a longer time, and also in order to cover the possibility that changes in technology might be material to risk.
- 5.253** *We propose that large case–control studies of brain cancer, acoustic neuroma, salivary gland cancer, and leukaemia should be funded.*

Cohort study of users of mobile phones

- 5.254** The case–control method has several limitations. These include difficulties in the selection of appropriate controls and the possibility that cases recall and report exposures more completely than controls. Also, case–control studies usually focus on only one or two diseases, whereas in a single cohort study many different health outcomes can be examined. In the case of RF radiation from mobile phones, concerns have been expressed about a possible risk of leukaemia or tumours of the head and neck, but there is also uncertainty about the risks of other diseases.

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- 5.255** Therefore, despite its cost, we believe that a large cohort study following up individuals according to their use of mobile phones would be desirable, and would complement the case-control studies discussed in paragraphs 5.250–5.253. Such a study would start to produce results within a few years, but because of the need to monitor possible long-term effects, it would need to continue for many years in the future. It could provide information on risks of all cancers and causes of death, rather than the few specific diseases currently being investigated by the case-control method, and would eventually allow examination of effects that might occur with longer induction periods. It would also offer scope for studies of morbidity in subsets of individuals (eg of neuropsychological disorders) if these were required.
- 5.256** We are aware of three existing cohort studies worldwide: one of 250,000 mobile phone users in the USA that we understand is currently in abeyance (Rothman *et al*, 1996; Dreyer *et al*, 1999), one of 550,000 users in Denmark (Johansen and Olsen, 1999), and one of 50,000 users in the UK (Beral, 2000). The US and Danish studies were based on individuals identified from operators' records, and were planned as mobile phone cohorts, whereas the British subjects, who are from a national cohort of women attending breast screening clinics, were not chosen on the basis of mobile phone use and include few long-term users. Although these studies should provide useful information, we think that there would be benefits from a further cohort study in the UK focussing specifically on long-term use of mobile phones.
- 5.257** In order to have statistical power to examine risks of specific cancers and non-cancer outcomes, a cohort study would need to be very large, including tens or even hundreds of thousands of individuals. For this reason, it would be expensive. In order to maximise the information that could usefully be gained within the next few years, it would be essential that it included large numbers of long-term users of mobile phones. There is usually an interval of some years between first exposure to a cause of cancer and the manifestation of an increased risk of the disease. Also, any risks from the use of early models of mobile phone are of particular importance since these early models had greater power outputs than those used more recently. As mobile phone use in the UK started particularly early by international standards, but covered only a small proportion of the population (120,000 in 1986; 500,000 in 1988), there is the potential to conduct a study of international importance, provided that it focusses on this early-user population. The study will therefore need to concentrate on populations where intensive use began earliest; we understand that this was in the London area. It is also desirable that the study should collect information not just on phone use, but also on potentially confounding variables, as far as practical. Early users of mobile phones may have very different characteristics from the general population with regard to, for instance, reproductive history, socioeconomic factors and other factors related to risk of disease.
- 5.258** *We propose that in addition to already ongoing cohort studies, a large cohort study of long-term mobile phone users be undertaken in the UK, which focusses particularly on people who started use in the 1980s and that, given the considerable design difficulties and potential costs entailed, a pilot study should be undertaken before a full-scale investigation.*

Symptoms in mobile phone users

- 5.259** The Expert Group heard several reports of mobile phone users who claimed symptoms relating to phone use, and the evidence from studies enquiring about this has indicated a substantial prevalence of symptoms thought by users to be related to phone use. To determine whether such symptoms are a consequence of RF radiation from phone use, a "double-blind" trial is needed, ie an experimental study of the occurrence of symptoms in circumstances where neither the user nor the observer knows whether a phone device is switched on or not. The Group also heard reports

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of “highly sensitive” individuals; these individuals particularly need testing as to whether or not they truly have symptoms that relate to phone use under double-blind conditions.

5.260 Although the main focus of research on this question needs to be on trials in volunteers rather than on epidemiology, there would nevertheless be value in conducting a survey in the UK to discover the nature and prevalence of reported symptoms in the British context.

5.261 *We propose that double-blind trials be undertaken to assess the relation of mobile phone use to symptoms such as headache that have been reported by users, and that a cross-sectional survey of symptoms be conducted in relation to mobile phone use in the UK.*

Mobile phone use and motor vehicle accidents

5.262 As reviewed above, the available data suggest that mobile phone use can be a factor causing road traffic accidents, but they do not show greater risk in relation to hand-held as compared with hands-free phones nor whether mobile phones increase risk more than other causes of inattention such as the use of radios or conversations with passengers. The relationship of mobile phone use to the occurrence of accidents has major implications for public health policy, and it is therefore important to gain evidence on which to base this policy, especially on the comparative risks from hand-held and hands-free devices.

5.263 *We propose that further epidemiological studies should be undertaken to clarify the relation of mobile phone use to the risk of motor vehicle accidents, and in particular whether the risk differs between hand-held and hands-free phones, and whether the risk of hands-free use exceeds that of other forms of driver distraction, notably conversation with passengers.*

Effect of mobile phone base stations on well-being

5.264 Whilst we have focussed on the information available in the published literature, the Group was struck by the concerns expressed by many who attended the public meetings and who wrote to us about adverse effects on their well-being which they attributed to the presence of mobile phone base stations near to residences, schools, etc (see paragraphs 3.5 and 3.6). The social impact of mobile phone technologies needs to be fully considered. In addition to the improvements in planning which we consider to be essential (paragraphs 6.55–6.62) *there is a need for a significant research programme to be initiated so that the impact of mobile phone technologies on well-being in its broadest sense is properly addressed and understood through epidemiological or other approaches.* This should be brought to the attention of funding agencies such as the Economic and Social Research Council, the Medical Research Council, the European Commission and other bodies.

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5.265 We conclude that there is one substantial established risk to health from mobile phone technology, namely through the increased incidence of motor vehicle accidents when drivers use mobile phones. Since the chance of an accident appears to be equally elevated for hands-free and hand-held use, this effect is almost certainly due to the distracting effect of the conversation, rather than to interference with steering the vehicle or to a direct influence of RF radiation on the brain.

5.266 There is also good evidence that exposure to mobile phone signals at intensities within existing ICNIRP guidelines has direct, short-term effects on the electrical activity of the human brain and

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on cognitive function. These could have their origin in a variety of biological phenomena, for which there is some evidence from experiments on isolated cells and animals. There is an urgent need to establish whether these direct effects on the brain have consequences for health, because, if so, and if a threshold can be defined, exposure guidelines will have to be reconsidered. It is also important to determine whether these effects are caused by local elevation of temperature or, as seems possible, by some other, “non-thermal”, mechanism.

- 5.267** The epidemiological evidence currently available does not suggest that RF exposure causes cancer. This conclusion is compatible with the balance of biological evidence, which suggests that RF fields below guidelines do not cause mutation, or initiate or promote tumour formation. However, mobile phones have not been in use for long enough to allow comprehensive epidemiological assessment of their impact on health, and we cannot, at this stage, exclude the possibility of some association between mobile phone technology and cancer. In view of widespread concern about this issue, continued research is essential.
- 5.268** Experimental studies on cells and animals do not suggest that mobile phone emissions below guidelines have damaging effects on the heart, on blood, on the immune system or on reproduction and development. Moreover, even prolonged exposure does not appear to affect longevity. The limited epidemiological evidence currently available also gives no cause for concern about these questions.
- 5.269** The balance of evidence indicates that there is no general risk to the health of people living near to base stations where the exposures are only small fractions of guidelines.

Overall Recommendations for Future Research

- 5.270** On the basis of the current state of knowledge **we recommend that priority be given to a number of areas of research related particularly to signals from handsets.** These should include the following:
- effects on brain function,
 - consequences of exposures to pulsed signals,
 - improvements in dosimetry,
 - the possible impact on health of subcellular and cellular changes induced by RF radiation,
 - psychological and sociological studies related to the use of mobile phones,
 - epidemiological and human volunteer studies (paragraphs 5.249–5.264), including the study of children, and individuals who might be more susceptible to RF radiation (paragraphs 4.37, 6.29 and 6.30).
- 5.271** **We recommend that a substantial research programme should operate under the aegis of a demonstrably independent panel.** The aim should be to develop a programme of research related to health aspects of mobile phones and associated technologies. This should complement work sponsored by the EU and in other countries (paragraphs 5.274–5.285). In developing a research agenda the peer-reviewed scientific literature, non-peer-reviewed papers and anecdotal evidence should be taken into account.

Overall Recommendations for Future Research

- 5.272** We further recommend that this programme be financed by the mobile phone companies and the public sector (industry departments, health departments and the research councils), possibly on a 50 : 50 basis. The contribution from industry could be made on a voluntary basis or by a continuing levy reviewable every five years.
- 5.273** It will be essential for further research in this area to be kept under review. **We recommend that the issue of possible health effects of mobile phone technology should be the subject of a further review in three years time, or earlier if circumstances demand it.** We note the World Health Organization (WHO) has an established formal process of risk assessment relating to RF fields within this time frame.

ANNEX

Current Research Funding

- 5.274** Funding for research on health effects arising from exposure to RF radiation progressively increased through the 1990s, although it has not been straightforward to raise sufficient funds for a comprehensive programme. This has resulted from a number of reasons. In particular, funding from Government has been limited, as has support from industry and in the latter case there continues to be a problem of potential conflicts of interest, which needs to be addressed in any future funding arrangements.
- 5.275** In the early 1990s, the emphasis of research on possible health effects associated with exposure to electromagnetic fields and radiations (EMFs) was principally driven by concerns about exposure to extremely low frequency (ELF) electromagnetic fields. Substantial funding was made available in the USA for both epidemiological and experimental studies through the RAPID programme, sponsored jointly by the Department of Energy (DOE) and the National Institute of Environmental Health Sciences (NIEHS) with support from industry. This was also the main emphasis for funding in Europe and around the world.
- 5.276** In the mid-1990s, however, in the early days of mass marketing of mobile telecommunications, issues about possible health effects began to arise. A turning point in the debate was a discussion of the issue on the CNN programme, *Larry King Live*, in the early 1990s, which focussed on a brain tumour in a man who had been occupationally exposed to RF radiation from mobile phones. The suggestion on the programme was that this cancer could have been caused as a result of his exposure. This TV programme was probably instrumental in establishing a programme of research in the USA, funded principally by industry, and finally called the Wireless Technology Research programme. It had a budget in the range from about \$20M to \$30M and supported a programme of experimental and epidemiological studies. It came to a close at the end of the 1990s and much of the work that was carried out under the programme is presently being prepared for publication. There are no indications of a further substantial research effort being mounted in the USA at present.
- 5.277** In Europe, concerns about possible health effects of exposure to RF radiation from mobile phones followed those in North America but with a delay of about two years. In 1996, the European Commission contracted an EC Expert Group to make recommendations for a programme of scientific research on personal telecommunications and human health. The EC Expert Group reported in September 1996 but it has taken until the beginning of 2000 for the programme to get under way. The EC Expert Group recommended a number of areas for research including:
- *in vitro* studies;
 - experimental studies in laboratory animals covering
 - genotoxicity,
 - cancer studies,
 - effects on the immune system,
 - nervous system related studies;
 - human laboratory research on possible neurophysiological effects;

- provocation studies involving the acute exposure of people claiming neurological systems, changes in sleep pattern and effects on the immune system;
 - epidemiological studies related to the possible risk of brain cancer;
 - cancers of other exposed tissues.
- 5.278** Although specific details of the programme to be funded by the EC have not been published, many of the proposals have been supported including experimental studies in laboratory animals and epidemiological investigations. Human volunteer studies do not appear to have been supported at present. The telecommunications industry is supporting the EC programme with input on the design and development of exposure facilities and exposure assessment.
- 5.279** Within the EC, a COST Action Plan has also been developed on possible health effects related to the use of mobile phones. The plan contains an update of the report and recommendations of the 1996 EC Expert Group report and the published proceedings of a forum on future European research on mobile telecommunications and health, held at the University of Bordeaux, 19–20 April 1999. The research recommendations are generally in line with those in the 1996 Expert Group report, updated where appropriate.
- 5.280** Within the UK, NRPB has a programme of research related to possible health effects of RF radiation. Its total budget is about £300k per year and covers the development of the application of anatomically realistic phantoms, based on medical imaging data, to assess exposure; experimental studies on cells in culture; and studies on the possible behavioural effects of RF exposure using experimental animals.
- 5.281** NRPB is providing substantial support on exposure assessment protocols and measuring equipment calibration for a national study to investigate occupational exposure to RF electromagnetic fields and radiation from various sources, including broadcast transmitters and telecommunications. The study started on 1 November 1998 and is being carried out in collaboration with the Institute of Occupational Health, University of Birmingham, with support from industry. It aims to determine the feasibility of undertaking an industry-wide epidemiological study and seeks to develop an appropriate exposure metric.
- 5.282** Over the last three years the Department of Health and the Health and Safety Executive have funded two studies in the UK covering human volunteer investigations and experimental studies on the effects of RF radiation on brain tissue *in vitro*. The total budget has been £117k. In addition, £20k per year is contributed to the WHO EMF programme. Presently Government is in discussion with industry about funding a collaborative UK-based research programme to which public funds could be allocated. This is in response to the Third Report of the Science and Technology Committee (1999).
- 5.283** Internationally, a number of other programmes are under way. The WHO Research Agenda is of particular importance in this context. The Agenda was set out by WHO following an evaluation of research priorities based on the recommendations of the EC Expert Group and conclusions from relevant workshops and reviews.
- 5.284** The items on the WHO Research Agenda relevant to mobile phone technology and human health follow.
- Large-scale standard two-year animal bioassays such as those typically conducted by the US National Toxicology Program. These studies should be carried out using normal animals and animals initiated with chemical carcinogens. The exposures should use RF radiation in the

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mobile phone frequency range and one of the common mobile phone pulsing patterns for two to six hours daily. Each study should use a range of different intensities (normally 4 SARs).

- At least two large follow-up studies on transgenic mice using study designs similar to the Repacholi study on Eμ-*PIMI* mice. Follow-up research is also needed that provides information on the health implications of effects found in transgenic animals.
- Studies to test the reproducibility of reported changes on hormone levels, effects on the eye, inner ear and cochlea, memory loss, neurodegenerative diseases and neurophysiological effects. Studies to be performed on people where possible and on animals as appropriate.
- At least two large-scale epidemiological studies with well-characterised higher level RF exposures to investigate cancers, particularly in the head and neck, and any disorders associated with the eye or inner ear. These studies should preferably be on mobile phone users or on workers in industries giving high RF exposures provided valid exposure assessments can be developed.
- Well-controlled studies to test people reporting specific symptoms such as headache, sleep disorders or auditory effects, and who attribute these symptoms to RF exposure. Several more studies to investigate neurological, neuroendocrine and immunological effects.
- *In vitro* studies relevant to possible *in vivo* effects and addressing the issues of RF exposure, thresholds and reproducibility for reported positive effects on cell cycle kinetics, proliferation, gene expression, signal transduction pathways and membrane changes.

5.285 WHO also provides advice and information on experimental design criteria, experimental systems and dosimetry, data collection and quality assurance, data analysis, reporting results, independent research review and administration and coordination of research.