

REVIEW OF HEALTH EFFECTS AND GAPS IN KNOWLEDGE

Dr M H Repacholi

World Health Organization, Geneva, Switzerland
Tel: +41 22 791 34 27, Fax: +41 22 791 41 23, Email: repacholim@who.int

✍ **Abstract**

There have been a number of recent reviews of the health effects of various parts of the electromagnetic spectrum. In addition to the reviews under the International EMF Project in Munich in November 1996 and in Erice, Sicily in 1999 on RF fields and the review of static and ELF fields, held in Bologna in June 1997, there have been substantial reviews held by other organizations. Recent RF field reviews include the Independent Expert Group on Mobile Phones (UK, 2000), while reviews on the health effects of static and ELF electric and magnetic fields have been conducted by IARC (June 2001), by the Health Council of the Netherlands (May 2001), and by an expert Advisory Group of the National Radiological Protection Board in the United Kingdom (AGNIR) (March 2001). The results of these reviews will be summarised here and gaps in knowledge identified.

✍ **Introduction**

Electromagnetic field (EMF) sources to which people may be exposed are predominantly in two frequency ranges are currently the main object of concern among the public for their possible effects on human health :

- ✍* the extremely low frequency (ELF, < 300 Hz) range incorporating the 50 and 60 Hz frequencies of the electric power supply and of electric and magnetic fields generated by electricity power lines and electric/electronic appliances;
- ✍* the radio frequency (RF, microwaves, 10 MHz - 300 GHz) range at which the current wireless communication devices operate, mainly the 900 MHz and 1800 MHz used by GSM mobile phones.

Most research studies devoted to possible biological or health effects of EMF today concern ELF or RF fields. The intermediate range of frequency (300 Hz - 10 MHz) has not yet received enough attention despite the rapid development of appliances such as induction heating devices, anti-theft and remote detection systems. However, a recent WHO review of this area is included.

This review will summarise biological and health effects in the 3 ranges and identify gaps in knowledge that need to receive further research before better health risk assessments can be made.

✍ **Health hazard: definitions and criteria**

Many effects on biological systems exposed to static and ELF fields have been reported. However, the seminar's principal concern was to determine whether these lead to any adverse health consequences. Explicit distinctions were made between the concepts of interaction, biological effect, and health hazard, consistent with the criteria used by international bodies when making health assessments (Repacholi and Cardis, 1997): Biological effects occur when fields interact to produce physiological responses that may or may not be perceived by people. Deciding whether biological or physiological changes have health consequences depends, in part, upon whether they are reversible, are within the range for which the body has effective compensation mechanisms, or are likely, taking into account the variability of response among individuals, to lead to unfavourable changes in health.

WHO defines health as the state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. Not all biological effects are hazardous. Some may be innocuously within the normal range of biological variation and physiological compensation. Others may be beneficial under certain conditions, and the health implications of others may be simply indeterminate. Uncertainty adds to the unacceptableness. Health hazard was generally defined to be a biological effect of field exposure outside the normal range of physiological compensation and adverse to a person's well-being.

✍ **ELF Fields**

Most public exposure to ELF fields comes from electrical appliances, household wiring, and AC transmission and distribution lines. Recent reviews on the health effects of static and ELF electric and magnetic fields conducted by IARC at a working group meeting in June 2001, by the Health Council of the Netherlands (2001), and by an expert Advisory Group of the National Radiological Protection Board in the United Kingdom (AGNIR, 2001).

Interaction mechanisms

A well known mechanism of interaction of ELF fields with biological tissues is the induction of time-varying electric currents and fields. At sufficiently high levels, these can produce direct stimulation of excitable tissues such as nerve and muscle cells. At the cellular level, the interaction induces voltages across the membranes of cells sufficient to stimulate nerves to conduct or muscles to contract. This mechanism accounts for the ability of humans and animals to perceive electric currents in their

bodies and to experience electric shocks. Other mechanisms have been proposed, but there is little evidence to support them.

Electric fields

External ELF electric fields induce time varying electric charges on the surface of the body. The magnitude and distribution of the charges depend on the body shape and its location and orientation relative to the field and ground plane. In addition, electric fields, electrical polarization changes, and currents are induced inside the body as a result of time variation of this surface charge density. Charges fixed on internal molecules polarize and depolarize as the field changes. Since time variation in the ELF range is slow compared to the ability of charges to move, the fields and currents generated inside the body from this source are very small. The induced current density distribution depends on the electrical properties of the tissue and varies inversely with the body cross section. Typically, the strength of the internal electric fields is less than 10^{-6} of the external field.

Magnetic fields

The induced current density is proportional to the rate of change of the magnetic flux density. For sinusoidal applied fields, the induced fields and currents are linearly dependent on frequency. The magnitude of the currents induced by pulsed magnetic fields will depend on the rise and fall time of the pulse. The highest current densities are induced in peripheral tissues, since these have the largest inductive loop radius in the body. However, tissue inhomogeneity and orientation of the body to the field will affect the current path. In general, the electric field induced in peripheral tissues by a horizontal magnetic field is approximately 1.5 times that induced by a vertical magnetic field of similar magnitude. Currents circulating from head to foot due to a horizontal magnetic field will be high in the neck because its small cross section concentrates the flow.

For a human with torso radius of 0.15 m and tissue conductivity of 0.2 S/m, a 50 Hz magnetic field parallel to the long axis of the body will induce a current in the tissue periphery of about 5 A/m² per tesla. Since current density is proportional to body radius, current density values can be used to scale between animal and human exposure. Typical induced currents and fields for 1 μT, 60 Hz uniform magnetic field exposure of mice, rats and humans are in the range of 0.1~0.4, 0.3~1.3, and 1~20 μA/m², respectively.

ELF biological effects

Laboratory studies

Above about 0.1 mT, a variety of studies have demonstrated effects *in vitro* on ornithine decarboxylase (ODC) activity. Not all replication attempts have succeeded, however. Many other biological effects have been reported above about 1 mT. How magnetic field exposure produces such effects is unknown. For most

effects, such as those reported on genotoxicity, intracellular calcium concentrations, or general patterns of gene expression, convincing and reproducible results have not been observed. None of the *in vitro* effects are necessarily indicative of an adverse health effect. Without knowledge of the mechanisms involved, effects observed at high field strengths cannot be extrapolated to lower fields, since the mechanisms may be different.

While there is no convincing evidence that ELF fields cause cancer in animals, only a limited number of studies have been conducted to test this hypothesis. Some recent studies suggest a positive relationship between breast cancer in animals treated with carcinogens and ELF magnetic field exposure at approximately 0.02~0.1 mT. The importance of these findings needs to be investigated further. Currently available data do not provide convincing evidence of adverse effects from exposure to power frequency fields on reproduction or development in mammals. There is evidence of behavioural and neurobehavioural responses in animals, but only following exposure to strong ELF electric fields.

Neuroendocrine changes are associated with exposure to ELF magnetic fields, but these alterations have not been shown to cause adverse effects in animals. Some studies suggest magnetic fields of strength between 0.01 and 5.2 mT might inhibit night time pineal and blood melatonin concentrations in experimental animals. However, such effects have not been demonstrated in humans.

Human laboratory studies

Perception

Exposure to ELF electric fields can result in field perception as a result of alternating electric charge induced on the surface causing body hair to vibrate. Most people can perceive electric fields greater than 20 kV/m, and a small percentage of people perceive field strengths below 5 kV/m. In two well controlled studies, humans were unable to perceive magnetic fields at levels up to 1.5 mT.

During exposure to ELF magnetic fields above 3~5 mT, volunteers experience faint visual flickering sensations or magnetophosphenes. The threshold current density in the retina for induction of magnetophosphenes is about 10 mA/m² at 20 Hz, which is well above typical endogenous current densities in electrically excitable tissues. Higher thresholds have been observed for both lower and higher frequencies.

Cardiovascular

Several reports indicate that ELF fields influence the cardiovascular system. Exposure of human volunteers to combined 60 Hz electric and magnetic fields (9 kV/m, 0.02 mT) resulted in small changes in cardiac function. Resting heart rates were found to be slightly but significantly reduced (about 3~5 beats/minute) during or immediately after exposure. This response did not occur with exposure to stronger (12 kV/m, 0.03 mT) or weaker

(6 kV/m, 0.01 mT) fields and was reduced if the subject was mentally alert. In these double blind studies, subjects were unable to detect the presence of the fields. While continuous exposure to combined electric and magnetic fields at 9 kV/m, 0.02 mT slows the heart, intermittent exposure can result in both slowing and increasing heart rate. None of the effects on heartbeat exceeded the normal range. No obvious acute or long term cardiovascular related hazards have been demonstrated at levels below current exposure standards for ELF or radio frequency fields.

Spectral analysis of electrocardiograms indicated that intermittent exposure to ELF reduced power in the Fourier spectrum at frequencies associated with blood pressure and thermoregulatory control mechanisms, and increased the power associated with respiration. These results were replicated in another sample of volunteers using a different experimental design. In contrast, a third study by the same group failed to show any effects on heart rate variability when subjects were exposed continuously rather than intermittently to the same ELF field. The patterns of heart rate variability observed in the above studies are similar, but not identical to, the pattern found to be predictive of sudden cardiac death.

Hormone and Immune System Effects

No changes in blood chemistry, blood cell count, blood gases, lactate concentration, skin temperature or circulating hormones have been observed. Field related suppression of the hormone melatonin has been proposed as a mechanism for the relationship between exposure to magnetic fields and increased cancer risk reported alterations in melatonin production in people sleeping at home under electric blankets, although all subjects did not show melatonin suppression. Suppression of melatonin has also been reported in studies of Finnish garment workers, electric utility workers, and VDU workers. In contrast, well-controlled laboratory studies report mostly negative results. Some laboratory studies, however, have reported positive results.

Two recent French reports indicate that acute exposure for one night to a linearly polarized magnetic field at 10 μ T has no effect on hormonal or immune parameters in healthy male volunteers. No published reports have examined possible differential effects in women, possible influence of longer exposure or of altering field polarization.

Epidemiological studies

The following are the concluding remarks from the report of a Working Group formed by the National Institute of Environmental Health Sciences (NIEHS, 1998) to evaluate the health effects from exposure to ELF. The Working Group concluded that ELF fields are a *possible human carcinogen*. The evidence in support of this decision resulted from studies on childhood leukemia in residential environments and on chronic lymphocytic leukaemia (CLL) in adults in occupational settings. "The fact that limited evidence was seen for

CLL in adults should not be construed as providing support for the finding with regard to leukemia in children. Childhood leukemia and adult CLL are very different diseases with different etiologies. Also, the inadequacy of the evidence for an effect on the risk for CLL in adults in the studies of residential exposure neither supports nor refutes the findings in the studies of occupational exposure. The *in vitro* and mechanistic data provide, at best, marginal support for the conclusion that ELF fields are possibly carcinogenic to humans. While ELF magnetic fields at intensities greater than 100 μ T provide moderate support for effects *in vitro*, there was little evidence of effects at intensities below this limit, which cover most of the range of exposure in the studies of residential childhood exposure and adult occupational exposure. Relatively few of the studies of occupational exposure addressed exposure to electric fields. Finally, the inadequate evidence from long term bioassays for carcinogenicity in rodents is driven more by lingering concerns about single findings in two separate studies than by an overall concern that something has been missed in these studies or that there is a trend toward a positive effect in poorly conducted studies."

Pooled analyses (Ahlbom et al, 2000; Greenland et al 2000) of the epidemiological studies on exposure to ELF magnetic fields suggest that residence in homes near external power lines is associated with an approximate 1.5-2.0 fold relative risk of childhood leukaemia. These data were influential for a working group of the International Agency for Research on Cancer (IARC) concluding that ELF magnetic fields were a "possible human carcinogen" for childhood leukaemia. "Possibly carcinogenic to humans" is a classification used to denote an agent for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence for carcinogenicity in experimental animals.

This classification is the weakest of three categories ("is carcinogenic to humans", "probably carcinogenic to humans" and "possibly carcinogenic to humans") used by IARC to classify potential carcinogens based on published scientific evidence. Some examples of well known agents that have been classified by IARC are listed in the table.

ELF fields are known to interact with tissues by inducing electric fields and currents in them. This is the only established mechanism of action of these fields. However, the electric currents induced by ELF fields commonly found in our environment are normally much lower than the strongest electric currents naturally occurring in the body such as those that control the beating of the heart.

Since 1979 when epidemiological studies first raised a concern about exposures to power line frequency magnetic fields and childhood leukaemia, a large number of studies have been conducted to determine if measured ELF exposure can influence cancer development, especially in children.

| Classification | Examples of Agents |
|--|-------------------------|
| Carcinogenic to humans (usually based on strong | Asbestos Mustard gas |

| | |
|---|--|
| evidence of carcinogenicity in humans) | Tobacco (smoked and smokeless) Gamma radiation |
| Probably carcinogenic to humans (usually based on strong evidence of carcinogenicity in animals) | Diesel engine exhaust Sun lamps UV radiation Formaldehyde |
| Possibly carcinogenic to humans (usually based on evidence in humans which is considered credible, but for which other explanations could not be ruled out) | Coffee Styrene Gasoline engine exhaust Welding fumes ELF magnetic fields |

There is no consistent evidence that exposure to ELF fields experienced in our living environment causes direct damage to biological molecules, including DNA. Since it seems unlikely that ELF fields could initiate cancer, a large number of investigations have been conducted to determine if ELF exposure can influence cancer promotion or co promotion. Results from animal studies conducted so far suggest that ELF fields do not promote cancer.

However, two recent pooled analyses of epidemiological studies provide insight into the epidemiological evidence that played a pivotal role in the IARC evaluation. These studies suggest that, in a population exposed to average magnetic fields in excess of 0.3 to 0.4 μT , twice as many children might develop leukaemia compared to a population with lower exposures. In spite of the large number data base, some uncertainty remains as to whether magnetic field exposure or some other factor(s) might have accounted for the increased leukaemia incidence.

These uncertainties occur for a number of reasons. Childhood leukaemia is a rare disease with 4 out of 100,000 children between the age of 0 to 14 diagnosed every year. Also average magnetic field exposures above 0.3 or 0.4 μT in residences are rare. Less than 1% of populations using 240 volt power supplies are exposed to these levels, although this may be higher in countries using 120 volt supplies.

Occupational studies have generally used job titles, sometimes in combination with workplace ELF field measurements, to determine if any association exists between exposure to these fields and cancer. Elevated risks of various cancers have been reported, especially leukaemia, nervous system tumours and breast cancer; but the lack of uniformity of the results has been a major concern. Any excess cancer risk among electrical workers, compared to other occupations, is small and difficult to detect using epidemiological methods. Studies so far have been complicated by the lack of adequate exposure assessment in the workplace and possible confounding factors.

The basic problem with all epidemiological studies so far has been the lack of any concept of dose or an exposure metric established from laboratory

studies. Metrics used have generally been cumulative exposure or time-weighted average field strength. Very little information has been obtained about exposure from appliances, ground currents or devices that may be associated with transient fields. Brief exposures to high amplitude magnetic field transients or to high frequency harmonics have not been assessed in published studies. Personal dosimeters do not exist that can capture this information.

ELF Research needs

Independent replication of some key studies is a high priority. When effects are robust, replication should be straightforward and can be used as a basis for extending observations. It is important to characterize the dose-response relationship (field strength, threshold and exposure duration) of any effect, particularly at environmentally relevant field strengths.

Where possible, *in vivo* studies should consider exposures that include intermittency, transients, and duration as important variables. In addition, it would be valuable to consider the interactions of ELF fields with other agents, such as ionizing radiation and chemicals. These interactions should test the hypothesis that ELF fields may act as a co promoter for cancer, but other end points suggested by the *in vitro* literature should also be examined. Wherever possible, exposures should be relevant to those experienced by humans in occupational and residential settings. Some cancer related studies using various animal models are currently under way. Research gaps for which additional results are needed, are as follows:

1. Confirmation and extension of animal studies reporting increased tumour incidence when magnetic fields are applied in combination with chemical carcinogens. These experiments should focus on dose-response relationships and the relationship between different exposure conditions.
2. Confirmation and extension of studies suggesting that magnetic field exposure influences mammary cancer development. Possible changes in relevant hormonal factors in magnetic field-exposed animals and controls should be investigated to examine potential mechanisms.
3. Neurophysiology neurobehavioural studies using models of neurodegenerative diseases are indicated because of recent reports of possible ELF field influence on human neurodegenerative diseases, such as Alzheimer disease.
4. While most studies of ELF field effects on various end points in reproduction and development have been negative, new studies should provide information on long-term neurobehavioural consequences following *in utero* exposure to magnetic fields. These studies should address whether ELF fields can produce effects on early

brain development as measured in functional behaviour in adult animals.

ELF epidemiology research needs

The most important prerequisite for future epidemiological studies is a clearer understanding of what metric should be used to characterize ELF field exposure. This may come from laboratory work or from additional hypothesis-generating epidemiological studies, each of which has advantages and disadvantages in cost, time, and precision. Project designs for new epidemiological research should, within the limits of what is possible, increase the role of measured past and present exposures. Dependence on surrogates, such as wire codes and job classifications, should decrease, particularly if data do not exist that establish how well the surrogates select for historical exposure. The *a priori* estimates of the power of future studies must be strong enough to predict useful information, given the outcomes of past research.

Because many, but not all studies show a small but significant excess in childhood leukaemia associated with residence in high wire code homes in the US (the only country where this surrogate has been used) a concerted effort is needed to explain this association. While efforts have been made to define the relationship between wire codes and average magnetic field exposure or socio-economic confounding factors, little evidence is available about the relationship between wire codes and high amplitude transient fields or high frequency harmonics. Future studies should include these and ground currents in the exposure assessments. Another aspect to be seriously pursued in future studies is the inclusion of non occupational exposure.

With the above caveats, needed future epidemiological studies include:

1. Studies of the relationship between exposure and cancer incidence that properly assess both residential and occupational exposure over long periods, including transient magnetic field exposure and high-frequency harmonics.
2. Studies to determine if correlates of wire codes, such as traffic density, age of home and sociodemographic characteristics of home occupants, can explain the statistical relationship between wire codes and childhood leukaemia.
3. Studies of the relationship between breast cancer and field exposure, including evaluation of both average field levels and of transients and high frequency components and taking into account both occupational and non-occupational exposures.
4. Studies of the relationship between neurodegenerative disorders and field exposure, including evaluation of the role of average fields levels, transients and high-frequency components. Both occupational and non occupational exposures should be considered.

5. Studies of the relationship between heart disease end points and exposure to ELF fields, including evaluation of the role of transient and high frequency components and taking into account both occupational and non-occupational exposures.

Volunteer studies

Further studies are needed, especially using transient and high frequency components typical of environmental ELF fields, to determine:

1. Whether any component of the human melatonin hormone system is susceptible to ELF field exposure and, if so, the likely health consequence of this susceptibility.
2. Whether sleep disruption, changes in neurotransmitter metabolism, and learning and memory are associated with ELF field exposure.
3. The relationship between field exposure and slowing and variability in heart rate.
4. Whether electrophysiological indices of central nervous system activity and function are affected by ELF fields.

Subjective effects

Given the limited evidence, but widespread concern about subjective effects, more research is needed to determine:

1. Whether these health effects can be substantiated and can be related to EMF exposure.
2. Why people experiencing apparent hypersensitivity and attributing it to EMF exposure, cannot determine reliably whether the fields are on or off in laboratory tests. The current laboratory results should be extended, and their relevance clarified.

Intermediate frequencies (IF)

Compared to the extremely low frequency (ELF) and radiofrequency (RF) range, few biological effects studies have been conducted and few reviews have been published that focus on health risks. International EMF exposure guidelines (ICNIRP, 1998) at IFs have been established by extrapolating limits from the ELF and RF frequency ranges, based on principles of coupling of external fields with the body and assumptions about the frequency dependence of bioeffects. Because applications of EMF in this frequency range are increasing rapidly, it is important to properly evaluate the significance of any effects on human health.

A wide range of equipment produces electric or magnetic fields in the IF range. In most cases the exposures to humans from these devices are within recommended limits, although the guidelines may be exceeded in some cases. Workers in a few occupational groups (operators of heat sealers and induction heaters, some military personnel, technicians working near high

powered broadcast equipment) are undoubtedly exposed to considerably higher levels of IF fields than the general population.

Mechanisms of Interaction

Understanding the mechanisms of interaction between EMF and biological systems is important for several reasons. First, determining the thresholds for hazard at IFs currently requires extrapolation of biological data from lower and higher frequency ranges, which requires assumptions about the frequency dependence of the effect. For this, an understanding of the mechanisms for effects is important. More generally, hypotheses about mechanisms of interaction can help to clarify biological phenomena and guide further experimentation.

Several mechanisms, both thermal and nonthermal, by which electromagnetic (primarily, electric) fields can interact with biological systems are well established. Each mechanism is characterised by a strength of interaction and a response time. The first determines the threshold for producing observable effects in the presence of random thermal agitation (noise). The second determines the frequency response of the effect, which is typically characterised by a cut off frequency (above which the threshold increases with frequency). In addition, EMF can heat tissue, resulting in a variety of thermal effects. The limiting hazard will arise from the adverse effect (thermal or nonthermal) that has the lowest threshold under given exposure conditions.

IF biological and health effects

Most biological effects studies in the IF range have employed field levels far above exposure guidelines, and above realistic exposure levels for humans. However, in some cases the exposure levels have been below recommended limits. Virtually none of the effects described below have any apparent explanation in terms of accepted biophysical mechanisms of interaction. The results and conclusions here are from the recent review by Litvak et al (in press)

Most studies have used field levels above international guidelines for human exposure or otherwise have unclear significance to health risk. As with other EMF ranges, few reported effects of IF fields have been subject to independent confirmation, and in some cases investigators have suggested the presence of confounding effects that may have led to previously reported effects of IF. Most epidemiological studies on human exposure to IFs concern possible reproductive effects and were motivated by health concerns from exposure to fields emitted by VDUs. Other studies have been reported on workers occupationally exposed to fields in the IF range. However, because of the weak associations in these studies, the use of multiple comparisons in the data analysis, and other uncertainties, they provide no strong evidence for health hazards.

The working group formed during the WHO meeting on the IF, held in Maastricht in June 1999, felt that the

health implications of these findings are difficult to assess. A detailed review of the IF range is shortly to be published in *Bioelectromagnetics* (Litvak et al., in press). The general consensus of the working groups was that current scientific evidence does not show the presence of health hazards from IFs at exposures below recommended guidelines. However, the biological data is sparse, particularly related to effects of low level exposure. A few epidemiology studies have suggested links between IF exposure and health effects, but they are compromised by technical problems and cannot be reliably interpreted. Even for established hazards, there is a need to better determine thresholds, particularly for fields with complex waveform or pulsed fields. Any epidemiological studies at IFs should be preceded by pilot studies demonstrating their feasibility.

Radiofrequency Fields

Common sources of RF fields include: monitors and video display units (3 - 30 kHz), AM radio (30 kHz - 3 MHz), industrial induction heaters (0.3 - 3 MHz), RF heat sealers, medical diathermy (3 - 30 MHz), FM radio (30 - 300 MHz), mobile telephones, television broadcast, microwave ovens, medical diathermy (0.3 - 3 GHz), radar, satellite links, microwave communications (3 - 30 GHz) and the sun (3 - 300 GHz).

Hazards of exposure to high levels of RF fields, which result in tissue heating, are basically understood, although there are still a number of unresolved issues. Thermal hazards are associated with acute exposures and are thought to be characterized by thresholds, below which they are not present. However, many studies have suggested that RF exposure at low levels may have biological effects, but they have either not been consistently replicated or else their significance for human health cannot be adequately assessed using information currently available. Scientific research into possible health effects has been unable to keep pace with the rapid advances in the applications of RF fields in our working and living environment. This delay has led to widespread concerns among the general public and workforce that there are unresolved health issues that need to be addressed as a matter of urgency.

Although many reports in the scientific literature claim effects in biological systems exposed to low levels of RF, of principal concern is to determine if these exposures produce any adverse health effects. In this respect, one of the major challenges is to better understand or establish the effects reported at low RF levels. Are there mechanisms by which hazards to humans at these low exposure levels might be produced?

Mechanisms of interaction

RF fields induce torques on molecules, which can result in displacement of ions from unperturbed positions, vibrations in bound charges (both electrons and ions), and rotation and reorientation of dipolar molecules such as water. These mechanisms, which can be described by classical electrodynamic theory, are not

capable of producing observable effects from exposure to low level RF fields, because they are overwhelmed by random thermal agitation. Moreover, the response time of the system must be fast enough to allow it to respond within the time period of the interaction. Both considerations imply that there should be a threshold (below which no observable response occurs) and a cut off frequency (above which no response is observed). These thresholds would be expected to be present even in more refined models if they correctly take into account thermal noise and the kinetics of the system.

Exposure to electromagnetic fields at frequencies above about 100 kHz can lead to significant absorption of energy and temperature increases. In general, exposure to a uniform (plane wave) electromagnetic field results in a highly non uniform deposition and distribution of energy within the body, which must be assessed by dosimetric measurement and calculation. For absorption of energy by the human body, electromagnetic fields can be divided into four ranges:

- ?? frequencies from about 100 kHz to less than about 20 MHz, where absorption in the trunk decreases rapidly with decreasing frequency, and significant absorption may occur in the neck and legs;
- ?? frequencies in the range from about 20 MHz to 300 MHz, at which relatively high absorption can occur in the whole body, and to even higher values if partial body (e.g., head) resonances are considered;
- ?? frequencies in the range from about 300 MHz to several GHz, at which significant local, non-uniform absorption occurs;
- ?? frequencies above about 10 GHz, at which energy absorption occurs primarily at the body surface.

In tissue, SAR is proportional to the square of the internal electric field strength. Average SAR and SAR distribution can be computed or estimated from laboratory measurements. Values of SAR depend on the following factors:

- ?? the incident field parameters, i.e. the frequency, intensity, polarization, and source object configuration (near field or far field);
- ?? the characteristics of the exposed body, i.e. its size, internal and external geometry, and the dielectric properties of the various tissues;
- ?? reflection, absorption and scattering effects associated with the ground or other objects in the field near the exposed body.

When the long axis of the human body is parallel to the electric field vector, and under plane wave exposure conditions (i.e. far field exposure), whole body SAR reaches maximal values. The amount of energy absorbed depends on a number of factors, including the size of the exposed body. "Standard Reference Man", if not grounded, has a resonant absorption frequency close to 70 MHz. For taller individuals the resonant absorption

frequency is somewhat lower, and for shorter adults, children, babies, and seated individuals it may exceed 100 MHz. The values of electric field reference levels are based on the frequency-dependence of human absorption. In grounded individuals, resonant frequencies are lower by a factor of about 2 (ICNIRP, 1998).

~~RF~~ RF biological effects

In Vitro

Reports from *in vitro* research indicate that low level RF fields may alter membrane structural and functional properties that trigger cellular responses. It has been hypothesized that the cell membrane may be susceptible to low level RF fields, especially when these fields are amplitude-modulated at ELF frequencies. At high frequencies, however, low level RF fields do not induce appreciable membrane potentials. They can penetrate the cell membrane and possibly influence cytoplasmic structure and function. These RF field induced alterations, if they occur, could be anticipated to cause a wide variety of physiological changes in living cells that are only poorly understood at the present time.

A lack of effects of RF exposure on mutation frequency has been reported in a number of test samples including yeast and mouse lymphoid cells. No effect of RF field exposure on chromosome aberration frequency in human cells has been confirmed.

Animal studies

In contrast to the evidence given above, several rodent studies indicate that RF fields may affect DNA directly. These papers report quantitative data subject to sources of inter-trial variation and experimental error such as incomplete DNA digestion or unusually high levels of background DNA fragmentation. These experiments need to be replicated before the results can be used in any health-risk assessment, especially given the weight of evidence that RF fields are not genotoxic. Further, in animal studies, most well conducted investigations report a lack of clastogenic effect in the somatic or germ cells of exposed animals (ICNIRP, 1998). Other investigations that require further attention relate to possible synergistic action of RF exposures with chemical or physical mutagens or carcinogens.

Most cancer studies of animals have sought evidence of changes in spontaneous or natural cancer rates, enhancement by known carcinogens, or alterations in growth of implanted tumours (ICNIRP, 1998). However, they have provided only equivocal evidence for changes in tumour incidence. Chronic RF field exposure of mice at 2-8 W/kg resulted in an SAR dependent increase in the progression or development of spontaneous mammary or chemically induced skin tumours. In a further study, exposure at 4-5 W/kg, followed by application of a sub carcinogenic dose of a chemical carcinogen to the skin, a procedure repeated daily, eventually resulted in a three fold increase in skin

tumours. However, at these high exposures, temperature-mediated effects cannot be excluded.

Studies in which cancer cells were injected into animals have reported a lack of effect of exposure to CW and pulsed RF fields on tumour progression. Progression of melanoma in mice was unaffected by daily exposure to pulsed or CW RF fields following subcutaneous implantation, and progression of brain tumours in rats was not affected by CW or pulsed RF fields following the injection of tumour cells into the brain.

Moderately lymphoma-prone $E\mu$ -*Pim1* oncogene-transgenic mice were exposed or sham-exposed to radiofrequency fields for 1 h/day for up to 18 months using pulse modulations similar to that used for digital mobile telephones. Exposure was associated with a statistically significant, 2.4-fold increase in the risk of developing lymphoma (Repacholi *et al.* 1997). This long-term study needs replication and extension to other exposure levels and animal models before it can be used for health-risk assessments. Further research is also needed to determine the significance of effects in this transgenic model for human health risk.

Although weak evidence exists, it fails to support an effect of RF exposure on mutagenesis or cancer initiation. There is scant evidence for a co-carcinogenic effect or an effect on tumour promotion or progression. However, only a few studies have been published and these are sufficiently indicative of an effect on carcinogenesis to merit further investigation.

Effects on other systems

Early signs of neurotoxicity are often behavioural rather than anatomical. While many studies have been conducted at high-levels of RF exposure few relevant studies have used low-levels. Some of the more important studies are described below. The blood-brain barrier (BBB) is a specialised neurovascular complex that functions as a differential filter permitting selective passage of material from the blood into the brain. It maintains the physiological environment of the brain within certain limits that are essential for life. Although extensive previous research has been unable to reliably identify permeability changes at low levels of RF exposure, in recent studies, increased BBB permeability was reported for RF exposures at SARs as low as 0.016 W/kg. These studies need replication and extension to allow a better determination of any possible health consequence.

Exposure to very low levels of amplitude modulated RF fields were reported to alter electrical activity in the brain of cats and rabbits. These experiments need replication and extension.

Pulsed radiation

Exposure to low-level pulsed and CW RF fields has been reported to affect brain neurochemistry in a manner consistent with responses to stress. Effects on behaviour and drug interaction have been obtained with the same exposure parameters. Replication studies are needed to

establish and provide further information on these effects.

Exposure to very intense pulsed RF fields suppresses the startle response and evokes body movements in conscious mice (ICNIRP, 1998). The mechanism for these effects is not well established, and is clearly associated with heating at higher absorbed energies.

People having normal hearing perceive pulse-modulated RF fields with carrier frequencies between about 200 MHz and 6.5 GHz; the so-called *microwave hearing* effect. The sound has been variously described as a buzzing, clicking, hissing or popping sound, depending on modulation characteristics. Prolonged or repeated exposure may be stressful.

Exposure to low levels of pulsed or CW RF fields may affect neurotransmitter metabolism and the concentration of receptors involved in stress and anxiety responses in different parts of the brain.

The retina, iris and corneal endothelium of the primate eye were reported to be susceptible to low-level RF fields, particularly when pulsed. Various degenerative changes in light sensitive cells in the retina, were reported at specific energies per pulse (10- μ s pulses at 100 pps), as low as 2.6 mJ/kg after the application of a drug used in glaucoma treatment. However, these results could not be replicated for CW fields. Further replication studies are needed.

Epidemiological and human volunteer studies

Cancer: By far the greatest public concern has been that exposure to low-level RF fields may cause cancer. Of the epidemiological studies addressing possible links between RF exposure and excess risk of cancer, some positive findings were reported for leukaemia and brain tumours. Overall, the results are inconclusive and do not support the hypothesis that exposure to RF fields causes or influences cancer.

Review groups that evaluated possible links between RF exposure and excess risk of cancer have concluded that there is no consistent evidence of a carcinogenic hazard. In some studies there are significant difficulties in assessing disease incidence with respect to RF exposure and with potential confounding factors such as ELF and chemical exposure. Overall the epidemiological studies suffer from inadequate assessment of exposure and confounding, and poor methodology. Further studies are underway to evaluate potential carcinogenic effects of chronic exposure to low-level RF fields and more are needed.

Other outcomes

Other health outcomes investigated following RF exposure, include headaches, general malaise, short-term memory loss, nausea, changes in EEG and other central nervous system functions, and sleep disturbances. There have also been anecdotal reports from several countries of subjective disorders such as headaches associated with the use of mobile telephones. Whether exposure to RF fields at very low-levels can cause such subjective

effects has not been substantiated from current evidence, but further research is indicated.

Individuals have claimed to be *hypersensitive* to electromagnetic fields. The most common symptoms are headaches, insomnia, tingling and rashes of the skin, difficulty in concentrating and dizziness. Given the limited evidence and widespread concerns that the above effects have provoked, more research is needed to determine if these health effects can be substantiated.

Adverse maternal health outcomes, particularly spontaneous abortions and haematological or chromosome changes, have been reported to occur in certain populations exposed to RF fields. Some of these changes have also been reported in users of video display units. Taken overall, the studies in this area have not substantiated these effects.

RF Field Research Needs

Since the EMF Research Agenda was first published by WHO in 1996, many national and international agencies have funded research that contributes substantially towards the studies needed to make better health risk assessments. Most of the *in vivo* and *in vitro* studies have now been completed or are underway. A major epidemiological study being conducted under IARC supervision to determine if there is a relationship between mobile telephone use and head or neck cancers has been funded and commenced.

By far the most important deficiency in the RF research underway is in the area of effects on human volunteers. There is still a basic need to studies on human volunteers under laboratory conditions to determine basic physiological responses to pulsed, non-thermal levels of RF similar to those emitted by mobile telephones. It is anticipated that following the recommendations of the Stewart report, a further \$10 million will be devoted to this research, with emphasis on human laboratory studies.

Thus it is important that details of WHO's research needs are clearly known to provide guidance on studies that will provide necessary health risk information.

Human laboratory studies

By far the greatest need is for basic studies, using established batteries of tests to investigate:

- ?? Psychological effects related to the use of mobile phones (blood pressure, brain and cognitive function (including memory or learning), any other effects likely to effect the CNS, reaction times, auditory evoked potentials, EEG, ECG, EKG etc (others)
- ?? Studies to determine if human brain function is affected by different RF pulsing regimens (test to Hyland-Frölich hypothesis)
- ?? Effects on children to determine if they are more sensitive to RF effects

- ?? People who claim to show a greater sensitivity to RF fields; hypersensitivity reactions, sleep disturbance, other subjective effects.

There should be part of the research program that is devoted to standard test and part to the encouragement of innovative ideas that investigate RF effects on human CNS function.

Animal studies

- ?? Need to address long-term memory and behavioural studies in animals (Lai) since this cannot be done effectively in humans.
- ?? Follow-up study on cancer promotion using DMBA.

In vitro studies

As a lower priority, there is a need to conduct:

- ?? *In vitro* investigation of ODC and cell signalling molecules. The ODC results need to be resolved, as well as the ongoing debate about calcium efflux.
- ?? Hippocampal slice preparation (Wood et al, 2000) study showing transient changes in evoked and spontaneous activity should be investigated further
- ?? More complete study of the possibility that pulsed RF fields can initiate gene expression.

Further Reading

AGNIR (2001) Advisory Group on Non-Ionising Radiation, Power Frequency Electromagnetic Fields and the Risk of Cancer. National Radiological Protection Board (UK) 2001. See <http://www.nprb.org.uk/>

Ahlbom A, Day N, Feychting M, et al, A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer*; 83:692-8, 2000.

Greenland S, Sheppard A R, Kaune W T, et al, A pooled analysis of magnetic fields, wire codes, and childhood leukemia. *Childhood Leukemia-EMF Study Group. Epidemiology* 1: 624-34, 2000.

Health Council of the Netherlands (2001). *Electromagnetic fields: Annual Update 2001*. See <http://www.gr.nl/engels/welcome/>

Matthes R, van Rongen E and Repacholi M H (eds), *Health Effects of Electromagnetic Fields in the Frequency Range 300 Hz to 10 MHz*. Proceedings of International Meeting, Maastricht, The Netherlands 7-8 June 1999. ICNIRP Pub 8/99. From: ICNIRP C/- Bundesamt für Strahlenschutz, Institut für Strahlenhygiene, Ingolstädter Landstraße 1, D-85764 Oberschleißheim, Germany. Tel: +49 89 31603288, Fax +49 89 316 03289, E-mail RMatthes@bfs.de

ICNIRP, Guidelines on limits of exposure to time-varying electric, magnetic and electromagnetic fields (up

to 300 GHz). International Commission on Non-Ionizing Radiation Protection. Health Physics 74: 494-522, 1998.

Independent Expert Group on Mobile Phones, Mobile phones and health, 2000.

See: <http://www.iegmp.org.uk/>

Litvak E, Foster K R and Repacholi M H, Health consequences of exposure to electromagnetic fields in the frequency range 300 Hz to 10 MHz. Bioelectromagnetics, in press.

NIEHS, Assessment of health effects from exposure to power-line frequency electric and magnetic fields. Portier CJ and Wolfe MS (eds) NIEHS Working Group Report, National Institute of Environmental Health Sciences of the National Institute of Health, Research Triangle Park, NC, USA, pp 523, 1998.

NRC, Possible health effects of exposure to residential electric and magnetic fields. National Research Council, Washington: National Academy Press, 1996.

Repacholi M H and Cardis E, Criteria for EMF Health Risk Assessment. Radiat Prot Dosim 72: 305-312, 1997.

Repacholi M H, Basten A, Gebiski V, Noonan D, Finni J, Harris AW, Lymphomas in $E\mu$ -*Pim1* transgenic mice exposed to pulsed 900 MHz electromagnetic fields. Rad. Res 147: 631-640, 1997.

Repacholi M H, Low-level exposure to radiofrequency electromagnetic fields: Health effects and research needs. Bioelectromagnetics 19: 1-19, 1998.

Repacholi M H and Greenebaum B (eds), Interaction of Static and Extremely Low Frequency Electric and Magnetic Fields with Living Systems: Health Effects and Research Needs. Bioelectromagnetics 20: 133-160, 1999.