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SCIENTIFIC COMMITTEE ON EMERGING AND NEWLY IDENTIFIED HEALTH RISKS (SCENIHR)

Preliminary Opinion on

Possible effects of Electromagnetic Fields (EMF) on Human Health

Adopted by the SCENIHR
by written procedure on 19 July 2006

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EXECUTIVE SUMMARY

The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) presented an opinion on "Possible effects of Electromagnetic Fields (EMF), Radio Frequency Fields (RF) and Microwave Radiation on human health" in 2001. The SCENIHR has been asked to update this opinion and also to continuously monitor new information that may influence the assessment of risks to human health. In preparation for this update, scientific data published since the previous opinion has been reviewed and their impact on the conclusions of the previous opinion has been assessed. The main focus of the opinion is whether health effects might occur at exposure levels below those of established biological mechanisms and, in particular, in relation to long term exposure at such low levels. The present opinion is divided according to frequency band. A separate section discusses environmental effects.

Radio Frequency Fields (RF fields)

Since the adoption of the 2001 opinion extensive research has been conducted regarding possible health effects of exposure to low intensity RF fields, including epidemiologic, in vivo, and in vitro research.

The balance of epidemiologic evidence indicates that mobile phone use of less than 10 years does not pose any increased risk of brain tumour or acoustic neuroma. For long-term use, data are sparse, and the following conclusions are therefore uncertain and tentative. However, from the available data it does appear that there is no increased risk for brain tumours in long-term users, with the exception of acoustic neuroma for which there is some evidence of an association. For diseases other than cancer, very little epidemiologic data are available.

A particular consideration is mobile phone use by children. While no specific evidence exists, children or adolescents may be more sensitive to RF field exposure than adults. Children of today will also experience a much higher cumulative exposure than previous generations. To date no epidemiologic studies on children are available.

Observational and provocation studies have failed to provide consistent support for a relation between RF exposure and neurovegetative symptoms (sometimes referred to as electromagnetic hypersensitivity).

Studies on neurological effects and reproductive effects have not indicated any health risks at exposure levels below the ICNIRP-limits established in 1998.

Animal studies have not provided evidence that RF fields could induce cancer, enhance the effects of known carcinogens, or accelerate the development of transplanted tumours. The open questions include adequacy of the experimental models used and scarcity of data at high exposure levels.

There is no consistent indication from in vitro research that RF fields affect cells at the nonthermal exposure level.

The technical development is very fast and sources of RF field exposure become increasingly common. Yet, there is a lack of information on individual RF field exposure and the relative contribution of different sources to the overall exposure.

In conclusion, no health effect has been consistently demonstrated at exposure levels below the ICNIRP-limits established in 1998. However, the data base for this evaluation is limited especially for long-term low-level exposure.

Intermediate Frequency Fields (IF fields)

Experimental and epidemiological data from the IF range are very sparse. Therefore, assessment of acute health risks in the IF range is currently based on known hazards at lower frequencies and higher frequencies. Proper evaluation and assessment of possible health effects from long term exposure to IF fields are important because human exposure to such fields is increasing due to new and emerging technologies.

Extremely low frequency fields (ELF fields)

The previous conclusion that ELF fields are possibly carcinogenic, chiefly based on childhood leukaemia results, is still valid. There is no known mechanism to explain how electromagnetic field exposure may induce leukaemia. The effects have not been replicated in animal studies.

The calculations in the previous opinion of the possible proportion of childhood leukaemia cases that might be attributed to ELF fields still hold.

For breast cancer and cardiovascular disease, recent research has indicated that an association is unlikely. For neurodegenerative diseases and brain tumours, the link to ELF fields remains uncertain. A relation between ELF fields and symptoms (sometimes referred to as electrical hypersensitivity) has not been demonstrated.

Static Fields

Adequate data for proper risk assessment of static magnetic fields are very sparse. Developments of technologies involving static magnetic fields, e.g. with MRI equipment require risk assessments to be made in relation to the exposure of personnel.

Environmental Effects

The continued lack of good quality data in relevant species means that there is insufficient data to identify whether a single exposure standard is appropriate to protect all environmental species from EMF. Similarly the data is inadequate to judge whether the environmental standards should be the same or significantly different from those appropriate to protect human health.

Research Recommendations

Important research needs were identified within all frequency bands.

1. BACKGROUND

For the general public, Council Recommendation of 12 July 1999[1] on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz) fixes basic restrictions and reference levels to electromagnetic fields (EMFs). These restrictions and reference levels are based on the guidelines published by the International Commission on Non Ionising Radiation Protection (ICNIRP)[2]. The ICNIRP guidelines had been endorsed by the Scientific Steering Committee (SSC)[3] in its opinion on health effects of EMFs of 25–26 June 1998[4].

For workers, the Council and the Parliament have adopted Directive 2004/40/EC of 29 April 2004[5] on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (EMFs).

In a questionnaire sent to Member States in 2000, all have notified the Commission that they have implemented the provisions of Council Recommendation on the limitation of exposure of the general public to EMFs. The position of the new member states has not yet been ascertained.

The Commission has announced that it intends to prepare a report to the Council on the implementation of the Recommendation, taking account of an earlier report of 2002 on implementation by the then member states.[6]

The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) was requested to prepare an update of the Scientific Steering Committee's opinion. The request derived from the increasing exposure to EMF consequent to the further growth in the use of electricity, from the continuous development of the telecommunications industry, and to a rapid increase in the installation of transmitter masts used as radiotelephone base stations. In addition to domestic, industrial and medical electrical appliances and devices, the high voltage overhead transmission lines (and to a lesser extent underground cables) are major sources of exposure to Extremely Low Frequencies (ELF) in the environment. The CSTEE opinion "on Possible effects of Electromagnetic Fields (EMF), Radio Frequency Fields (RF) and Microwave Radiation on human health"[7], of 30 October 2001, concluded that the information that had become available since the SSC opinion of June 1999 did not justify revision of the exposure limits recommended by the Council[8].

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[1] (OJ. L 199/59, 30.7.1999)

[2] http://www.icnirp.de/

[3] http://ec.europa.eu/food/fs/sc/ssc/index_en.html

[4] http://ec.europa.eu/food/fs/sc/ssc/out19_en.html

[5] (OJ. L 184/1, 24.5.2004)

[6] http://ec.europa.eu/health/ph_determinants/environment/EMF/implement_rep_en.pdf

[7] http://ec.europa.eu/health/ph_risk/committees/sct/documents/out128_en.pdf

[8] The main frequencies in the ELF frequency range are 50 Hz in Europe and 60 Hz in North America. The RF and lower microwave frequencies are of particular interest for broadcasting, mobile telephony. The 2.45 GHz frequency is mainly used in domestic and industrial microwave ovens.

A substantial number of scientific publications and reviews on the possible health effects of EMF (focusing mostly on mobile telephones) have become available since the CSTEE opinion of 2001, for example the 2002 Dutch report[9], the 2003 AGNIR report[10] and the 2004 British National Radiological Protection Board (NRPB) report on "Mobile phones and health"[11], which is the most recent of them. The NRPB provided a detailed review of the recent literature and useful contribution to the discussions on whether there are health effects related to the use of mobile phones. The report concluded that there is no hard evidence at present that the health of the public is being adversely affected by mobile phone technologies but uncertainties remain and a continued precautionary approach is recommended until the situation is clarified.

Additional results are expected shortly from Community funded research and development (R&D) activities, from national programmes, and from work within the International EMF Project of the World Health Organisation (WHO).

Community funded R&D comprises direct support to the Joint Research Centre and indirect support to competitive projects under the 5th Framework Programme[12] and the 6th Framework Programme (FP6)[13] for Research and Technological Development. Under FP6, the EMF-NET Coordination Action[14] brings together European and national EMF programmes. EMF-NET will start publishing its first interpretation reports at the end of 2005. In total, this project will run another three years.

As part of its mission to protect public health and in response to public concern over health effects of EMF exposure, WHO established the International EMF Project[15] in 1996 to assess the scientific evidence of possible health effects of EMF in the frequency range from 0 to 300 GHz. The EMF Project encourages focused research to fill important gaps in knowledge and to facilitate the development of internationally acceptable standards limiting EMF exposure.

In view of the amount of scientific evidence that has become available since the publication of the CSTEE of 30 October 2001 and of the Commission's intention to prepare a report to the Council and the frequency of new scientific publications on the health effects on EMF which require rapid assessment, the SCENIHR is asked to both update the previous opinion of the CSTEE and to continuously monitor new information that may influence the assessment of risks to human health in this area.

[9] Mobile telephones – evaluation of health effects, Report of the Health Council of the Netherlands, 28.1.2002, http://www.gr.nl

[10] AGNIR (2003). *Health effects from radiofrequency electromagnetic fields.* Report of an Advisory Group on Non-ionising Radiation. Doc NRPB, 14(29, 1-177.Available at http://www.nrpb.org

[11] IEGMP (2000) *Mobile Phones and Health.* Report of the Independent Expert Group on Mobile Phones, Chairman: Sir. William Stewart, Chilton, NRPB. Available at http://www.iegmp.org.uk

[12] http://ec.europa.eu/research/fp5.html and http://cordis.europa.eu/fp5/home.html.

[13] http://ec.europa.eu/research/fp6/index_en.cfm and http://cordis.europa.eu/fp6/dc/index.cfm?fuseaction=UserSite.FP6HomePage .

[14] http://www.jrc.ec.europa.eu/eis-emf/emfnet.cfm

[15] http://www.who.int/peh-emf/project/en/

2. TERMS OF REFERENCE

The Committee is requested:

(1) to update the CSTEE opinion of 30 October 2001 by summer 2006 in the light of newly available information;

(2) to monitor the scientific literature concerning the health effects of EMF;

(3) to draw the Commission's attention to significant new scientific findings;

(4) to provide the Commission with an annual review of the opinion in the light of significant new evidence;

(5) to take full advantage of the periodic reviews undertaken under the auspices of EMF-NET.

In reviewing and evaluating the studies on the potential health effects of EMF, the Committee is asked to pay particular attention to

- the nature of EMF studies, i.e., epidemiology, laboratory biology (in vivo vs. in vitro), clinical examinations (heart function, sleep electrophysiology, immune system, blood chemistry, hormones including melatonin, etc.), and theory;

- the methodology of EMF studies, in particular, epidemiology (e.g., "background health condition", "odds ratio", and the problem of ubiquitous technologies), measurement (cf., spot measurement, time-weighted average, personal monitor, calculated historical fields, laboratory measurement, etc.), and combined exposures (from different EMF sources as well as from simultaneous exposure to EMF and other factors such as chemicals, noise, stress, etc.);

- the characterization of risks, in particular, nature and magnitude of damage, likelihood of occurrence (expressed preferably in terms of natural frequencies rather than probabilities), uncertainty, geographical distribution, persistence over time, reversibility, delay, possible violation of equity, potential for public mobilization etc.; and

- the identification and physical characterization of existing and foreseeable sources of exposure to EMF, e.g., electromagnetic vs. magnetic including magnetic resonance imagery (MRI), from AC vs. DC current, new frequency ranges, higher transmission power, etc.

3. SCIENTIFIC RATIONALE

3.1. Introduction

The objective of this section is to establish the scientific rationale that is necessary in order to provide an opinion in response to the request to the Committee, in particular to update the CSTEE opinion of 30 October 2001. This section therefore summarizes what was known at the time of the 2001 Opinion, reviews the scientific data that have been published after 2001, and assesses to what extent these new data affect previous conclusions. Following the Committee's general principles, only studies published in peer reviewed journals have been considered.

The section is divided in four sub-sections according to frequency (f) range: radio frequency (RF) (100 kHz < f ≤ 300 GHz), intermediate frequency (IF) (300 Hz < f≤100 kHz), extremely low frequency (ELF) (0< f ≤ 300 Hz), and static (0 Hz) (only static magnetic fields are considered in this opinion). These frequency ranges are discussed in order of decreasing frequency, RF, IF, ELF, and static. For each frequency range the review begins with a description of sources and exposure to the population. This is followed, for each frequency range, by a discussion that is organized according to outcome. For each outcome relevant human, in vivo, and in vitro data are covered.

It is well recognized that there are established biophysical mechanisms that can lead to health effects as a consequence of exposure to sufficiently strong fields. For frequencies up to, say, 100 kHz the mechanism is stimulation of nerve and muscle cells due to induced currents and, for higher frequencies, tissue heating is the main mechanism. These mechanisms lead to acute effects. Existing exposure guidelines, such as those issued by ICNIRP, protect against these effects. The current issue is the possibility that health effects occur at exposure levels below those where the established mechanisms play a role and in particular as effects of long term exposure at low level.

Table 1 below illustrates some typical sources of electromagnetic fields with frequency and intensity. Note, however, that big variations occur. For an explanation of some of the terminology used please be referred to the next chapter.

Table 1. Typical sources of electromagnetic fields.

Frequency range	Frequencies	Field source	Examples of maximal intensities
Static	0 Hz	Natural VDU (video displays) MRI and other diagnostic / scientific instrumentation Industrial electrolysis	70 μT 1 T in the tunnel; 200 mT at the gate; < 0.5 mT outside the device room 10-30 mT at the level of the feet
ELF	0-300 Hz 50 Hz	Powerlines Domestic distribution Electric engines in cars, train and tramway	10-20 μT under the line, or 10 kV/m < 0.1-0.2 μT (microteslas) in the room 50 μT and 300 V/m
Intermediate frequencies	300 Hz – 100 kHz	Typical examples are: VDU, anti theft devices in shops, hands free access control systems, card readers and metal detectors	30 to max 700 nT 10 V/m
RF	100 kHz – 300 GHz	Broadcasting and TV; mobile telephony microwave oven Radar, portable and stationary radio transceivers, personal mobile radio.	0.1 W/m² 0.5 W/m² 0.2 W/m²

The Committee has been made aware of the military use of certain radiofrequency devices. Further consideration of this is outside the scope of this opinion.

3.2. Terms and definitions

This section includes technical terms and definitions used within the document. The definitions are given in alphabetical order.

Conductivity: A property of materials that determines the magnitude of the electric current density when an electric field is impressed on the material.

Dielectric properties: In the context of this document the properties of materials conductivity and permeability.

Electric field strength (E): The magnitude of a field vector at a point that represents the force (F) on a charge (q). E is defined as E = F/q and is expressed in units of Volt per meter (V/m).

Electromagnetic field: Electromagnetic phenomena expressed in vector functions of space and time.

Electromagnetic radiation: The propagation of energy in the form of electromagnetic waves through space.

EMF: Electromagnetic field.

Exposure: Exposure occurs wherever a person is subjected to electric, magnetic or electromagnetic fields or contact currents other than those originating from physiological processes in the body.

Extremely low frequency (ELF): Extremely low frequency fields include, in this document, electromagnetic fields from 1 to 300 Hz.

Frequency modulation (FM): Frequency Modulation is a type of modulation representing information as variations in the frequency of a carrier wave. FM is often used at VHF frequencies (30 to 300 MHz) for broadcasting music and speech.

Frequency (Hz): The number of cycles of a repetitive waveform per second.

Intermediate frequencies (IF): Intermediate frequencies are, in the frame of this report, defined as frequencies between 300 Hz and 100 kHz.

Magnetic flux density (B): the magnitude of a field vector at a point that results in a force (F) on a charge (q) moving with the velocity (v). The force F is defined by F = q*(v x B) and is expressed in units of Tesla (T).

Magnetic field strength (H): the magnitude of a field vector that is equal to the magnetic flux density (B) divided by the permeability (μ) of the medium. H is defined as H = B/μ and is expressed in units of Ampere per metre (A/m).

Microwaves: Microwaves are defined in the frame of this expertise as electromagnetic waves with wavelengths of approximately 30 cm (1 GHz) to 1 mm (300 GHz).

Milliwatt (mW): A unit of power equal to 10^{-3} Watt.

Nanowatt (nW): A unit of power equal to 10^{-9} Watt.

Non – thermal effects (or athermal effects): An effect which can only be explained in terms of mechanisms other than increased molecular motion (i.e. heating), or occurs at absorbed power levels so low, that a thermal mechanism seems unlikely, or displays so unexpected a dependence upon some experimental variable that it is difficult to see how heating could be the cause (see also Bernhardt et al. (1997)).

Permeability: A property of materials that indicates how much polarisation occurs when an electric field is applied.

Power density (S): Power per unit area normal to the direction of propagation, usually expressed in watts per meter squared (W/m²).

Radio frequency (RF): The frequencies between 100 kHz and 300 GHz of the electromagnetic spectrum.

Specific absorption rate (SAR): A measure of the rate of power absorbed by or dissipated in an incremental mass contained in a volume element of dielectric materials such as biological tissues. SAR is usually expressed in terms of watts per kilogram (W/kg).

S**tatic electric field:** Static fields produced by fixed potential differences.

Static magnetic fields: Static fields established by permanent magnets and by steady currents.

VDU: Video display units for computers, videos, TV and some measurement devices using cathode ray tubes.

3.3. Radio Frequency Fields (RF fields)

3.3.1. Sources and distribution of exposure in the population

Nowadays the use of RF sources is widespread in our society. Prominent examples are mobile communication, broadcasting or medical and industrial applications. Information on emissions arising from RF sources is often available and can be used for compliance assessment or similar applications such as in-situ measurements. It has to be taken into account that information on the exposure of individual persons is scarce; there is a need to optimize methodology to assess individual exposure, e.g. by using and further developing existing dosimeters. The existing RF sources are operated in different frequency bands and can be subdivided in several categories:

Sources operated close to the human body

Many devices of this type are mobile RF transmitters. One of the examples is mobile phones; more than 1.5 billion people are using mobile phones worldwide. The most common mobile communication technologies in Europe are the digital technologies GSM 900, GSM 1800 and UMTS, analogue technologies are nowadays almost not in use any longer in Europe. Mobile phone use is common in Europe and the proportion of users can reach values of 80 % or more. Before mobile phones can be brought into the European market they have to show compliance with the requirements of European directives, i.e., it has to be shown that the limits for the amount of power absorbed in the human body are not exceeded. The limit for mobile phone use is the specific absorption rate (SAR) of 2 W/kg for the human head. Mobile phones are tested

under worst case conditions, i.e. at the highest power level, e.g., 2 W peak power. Maximum local SAR values averaged over 10 gram of tissue range typically between 0.2 and 1.5 W/kg, depending on the type of mobile phone. It has to be taken into account that the emitted power is often orders of magnitude lower than the maximum power leading to much lower exposure due to power control and discontinuous transmission mode for GSM phones. The power control of a GSM phone automatically reduces the emitted power by a factor of 1,000 if the intensity is not needed for stable transmission. No exposure occurs from a mobile phone being switched off. Phones operated in the standby mode cause typically much lower exposure compared to mobile phones operated with maximum power, but an accurate figure for this lower exposure depends on the exact details of the reachability of transponders and on the traffic requested by the communication protocol and by incoming / outgoing SMS.

In addition to mobile phones, other wireless applications like cordless phones, e.g. DECT, or WLAN systems are very common. Due to the fact that they are usually operated with lower output power compared to mobile phones the exposure is below the level of typical mobile phones. The maximum peak power level of a DECT system is 250 mW, of a WLAN system 200 mW. It has to be taken into account also in this case that the average power is much lower than the peak value. The exposure from such systems is therefore below that of mobile phones. For example, close to a WLAN system exposure is typically below 0.5 mW/m². Anti-theft devices have become more and more common during recent years. They are typically operated at the exits of shops or similar areas to prevent theft of goods. Some of the existing systems are operated in the RF range; the exposure depends on the type of system and is, as long as the systems are operated according to the manufacturer's requirements, below the exposure limits. Several industrial appliances are operated in the RF and microwave range, for example for heating. The exposure of the worker operating such systems can reach values close or even above the limits.

Sources operated far away from the human body

Such sources are typically fixed installed RF transmitters. An example is base stations that are an essential part of mobile communication networks necessary to establish the link between the mobile telephone and the rest of the network. In most European countries, base stations have became ubiquitous to guarantee connectivity in large areas of the respective countries; e.g., 18,000 base stations are operated in Austria. The so called reference level for the exposure of the general population at 900 MHz given in the European recommendation 1999/519/EC is 4.5 W/m². The range of exposure of the general population due to GSM signals is typically between some hundred nW/m² and some tens of mW/m². The reasons for this large variation are both technical and environmental factors including distance. For UMTS, the available measurements are limited and so far the traffic is rather low compared to GSM. Values slightly over 1 mW/m² have been measured in a few cases, while minimum levels are a few hundred nW/m². Other important RF sources are broadcasting systems (AM and FM). The maximum values measured in areas accessible for the public are typically below 10 mW/m². Close to the fences of very powerful transmitters, exposure of about 300 mW/m² can be expected in some cases. Looking at the new digital TV technology (DVB-T), exposures between around 40 mW/m² and 0.003 mW/m² were registered in an Austrian study. The range of exposure is similar compared to analogue TV systems. However, the digital systems require more transmitters than the older analogue systems; therefore somewhat higher average exposure levels can be expected. In some countries digital audio broadcasting systems are already in operation. Other examples of sources relevant for far field exposure of the general population are civil and military radar systems, private mobile radio systems, or new technologies like WiMax.

Medical applications

Several medical applications use electromagnetic fields in the RF range. Therapeutic applications such as soft tissue healing appliances, hyperthermia for cancer treatment, or diathermy expose the patient well above the recommended limit values to achieve the intended biological effects. These include heating of tissue (analgetic applications) or burning cells (to kill cancer cells). In these cases exposure of therapists or other medical personnel needs to be controlled to avoid that their exposure exceeds the exposure limit values foreseen by Directive 2004/40/EC for occupational exposure. Diagnostic applications, like magnetic resonance imaging (MRI), are allowed to exceed the basic restrictions of Council Recommendation 1999/519/EC as there is a benefit for the patient. Usual frequencies are those allowed for industrial, scientific, and medical applications similar to most industrial sources: 27 MHz, 433 MHz and 2.45 GHz. At this time, there is no evidence for cumulative effect of exposures below recommended levels which could give rise to a health hazard. Magnetic resonance imaging devices in medical diagnostics use RF fields in addition to static and variable fields. Most actual clinical MRI devices work at 63 MHz.

3.3.2. Cancer

Studies on cancer in relation to mobile telephony have focused on intracranial tumours because deposition of energy from RF fields from a mobile phone is mainly within a small area of the skull near the handset. When whole body exposure is considered, as in some occupational and environmental studies, also other forms of cancer have been investigated.

3.3.2.1. Epidemiology

What was already known on this subject?

At the time of the previous CSTEE opinion of 2001, most epidemiological studies on exposure to RF fields had examined exposures at the workplace. The overall evidence did not suggest consistent cancer excesses. With regard to mobile phones, only few studies were available at the time of the previous opinion and the short exposure period in these studies did not allow any firm conclusions. The few studies on residential exposure to RF fields from transmitters had serious methodological limitations.

What has been achieved since then?

In total, about 30 papers of original studies on mobile phone use and cancer were published in the last five years. Results are summarized in Table 2 for brain tumours and in Table 3 for acoustic neuroma. All but one study were case-control studies, mostly on brain tumours, some on salivary gland tumours or uveal melanoma. One was a large cohort study of all Danish mobile phone subscribers between 1982 and 1995 who were followed up for a variety of cancers; no increased risk for any cancer was observed but follow up time was short (Johansen et al. 2001).

The Interphone study is a multinational case-control study coordinated by the International Agency for Research on Cancer (IARC). It is a population-based study with prospective ascertainment of incident cases and face-to-face interviews for exposure assessment. With regard to brain tumours, results from the first four components of the Interphone study suggest no risk increase for meningioma or glioma. This is consistently so among subjects with less than 10 years of use. For regular mobile phone users of 10 years or more, no indications of risk increases

were seen in three out of four components, namely in Sweden (Lönn et al. 2005), Denmark (Christensen et al. 2005) and the UK (Hepworth et al. 2006), but the German component does see a somewhat raised relative risk estimate for glioma (Schüz et al. 2006). This increase, however, is based on small numbers and due to the wide confidence interval the result is not in contradiction with the other Interphone components.

In contrast, a Swedish group not participating in the Interphone-study, conducting several case-control studies using self-administered questionnaires for exposure assessment, has repeatedly observed increased relative risk estimates for brain tumours and is the only group that observed such an increase already after few years of use of a mobile phone (Hardell et al. 2005a, Hardell et al. 2005b).

Acoustic neuromas, benign tumours that develop very slowly, arise from the Schwann cells, which enfold the vestibulocochlear nerve (VIII. cranial nerve). They are of particular interest because of their location. The Hardell-group from Sweden has in several studies reported raised relative risk estimates for acoustic neuroma and also with very short induction periods (Hardell et al. 2005b). Two of the Interphone components, Denmark and Sweden, have reported their country specific acoustic neuroma results (Christensen et al. 2004, Lönn et al. 2004). Lönn et al. reported a doubling of the relative risk estimate after ten years of regular mobile phone use compared to subjects who never used a mobile phone regularly. This association became stronger when the analysis was restricted to preferred phone use at the same side as the tumour. Christensen's result did not support this, but it was based on fewer long-term users. Six of thirteen components of Interphone (including Sweden and Denmark) were pooled for a joint analysis to examine the association between mobile phone use and risk of acoustic neuroma (Schoemaker et al. 2005). While no overall association was seen among all long-term users (see Table 3), the data suggest that there may be an increased risk when the preferred side of the head of use is considered in the analysis. For 10+ years of use of mobile phones, the relative risk for acoustic neuroma at the preferred side of use was 1.8 (1.1-3-1). Because of methodological inter-study differences it would have been of considerable interest to compare the results across the six studies, but small numbers in most of the centres preclude that analysis. However, in an attempt to separate the effect in the four additional studies, the Danish and the Swedish studies were excluded from the pooling, which resulted in an increase of the pooled relative risk estimate. This indicates that the association seen by Schoemaker was not only driven by the Swedish data.

All those studies are facing limitations in their exposure assessment, which was either a list of subscribers from the operators or self-reported mobile phone use. While the first method is an objective measure, it has limitations because subscription predicts use of a mobile phone only to some extent. Recent validation studies in volunteers comparing current self-reported use with traffic records from network operators show a moderate agreement, but it cannot be excluded that agreement is worse with respect to past mobile phone use or among patients with brain tumours (Vrijheid et al. 2006). Especially patients with high stage glioma showed some memory performance problems in the Danish Interphone study (Christensen et al. 2005). What seems to be reassuring despite these shortcomings is, that once the amount of mobile phone use is estimated with some validity, this is a satisfactory proxy for RF field exposure from these devices, as was shown in studies recording output power of mobile phones during operation (Berg et al. 2005). Laterality of use is not easy to obtain in a retrospective study, as early symptoms may affect the side of use. Although some results are now available for long-term users, their numbers are still small and the results of the whole Interphone dataset should be awaited before drawing conclusions.

No striking new results appeared for studies on occupational and residential RF fields exposures since the previous opinion. While some positive associations have been reported from occupational studies, the overall picture is far from clear (Ahlbom et al. 2004). Many studies lack individual exposure assessment and only job titles or branches were used as exposure proxies. Studies on exposure from transmitters are limited by crude exposure measures and small numbers of exposed subjects, and the ecological nature of most studies.

Discussion

Mobile phones in relation to health are now being studied with great effort and in comprehensive studies, particularly in the Interphone Study. The results of the Interphone Study will soon become available. It has to be doubted, however, that the results will be entirely conclusive, as the first results from published national components of this study already raise a number of questions with respect to the potential of bias. Another limitation is that also in the current studies, long-term mobile phone users have had hardly more than 10 years of regular use of mobile phones, which still may be a relatively short latency period, particularly for slowly growing benign tumours. Among those long-term users, most were initially users of analogue mobile phone and thus, the number of long-term users of the digital technology is even smaller. Prospective long term follow up studies overcome both the limitations of retrospective exposure assessment and the latency problem and are recommended as a powerful long-term surveillance system for a variety of potential endpoints, including cancer, to fill current gaps in knowledge.

Table 2. Results of epidemiological studies on mobile phone use and brain tumours. The table is modified from the report to the Swedish Radiation Protection board: Recent Research on EMF and Health Risks. Third annual report from SSI's Independent Expert Group on Electromagnetic Fields (SSI's Independent Group on Electromagnetic Fields 2005).

	Brain tumours		**Brain tumours short latency**		**Brain tumours longer latency**	
	No. exp cases	RR[16] estimate (95% CI[17])	No. exp cases	RR estimate (95% CI)	No. exp cases	RR estimate (95% CI)
[Hardell et al. 1999]	78	1.0 (0.7-1.4)	78	1.0 (0.7-1.4) >1 yr	34 16	0.8 (0.5-1.4) >5 yr 1.2 (0.6-2.6) >10 yr
[Muscat et al. 2000]	66	0.8 (0.6-1.2)	28	1.1 (0.6-2.0) 2-3 yr	17	0.7 (0.4-1.4) ≥4 yr
[Inskip et al. 2001]	139	0.8 (0.6-1.1)	51	1.0 (0.6-1.6) 0.5-3 yr	54 22	1.0 (0.6-1.6) ≥ 3 yr 0.7 (0.4-1.4) ≥5 yr
[Johansen et al. 2001]	154	1.0 (0.8-1.1)	87	1.1 (0.9-1.3) 1-4 yr	24	1.0 (0.7-1.6) >5 yr
[Auvinen et al. 2002]	40 analogue, 16 digital	1.3 (0.9-1.8)	15 analogue, 11 digital	1.2 (0.7-2.0) 1-2 yr	17 analogue, 1 digital	1.5 (0.9-2.5) >2 yr
[Hardell et al. 2002]	188* analogue 224* digital	1.3 (1.0-1.6) 1.0 (0.8-1.2)	188* analogue 224* digital	1.3 (1.0-1.6) >1 yr 1.0 (0.8-1.2) >1 yr	46* analogue 33* digital	1.3 (0.8-2.3) >10 yr 0.9 (0.6-1.5) >5 yr
[Lönn et al. 2005]	214 glioma 118 meningioma	0.8 (0.6-1.0) 0.7 (0.5-0.9)	112 64	0.8 (0.6-1.1) 1-4 yr 0.6 (0.4-0.9) 1-4 yr	25 12	0.9 (0.5-1.5) ≥10 yr 0.9 (0.4-1.9) ≥10 yr
[Christensen et al. 2005]	47 low-grade glioma 59 high-grade glioma 67 meningioma	1.1 (0.6-2.0) 0.6 (0.4-0.9) 0.8 (0.5-1.3)	19 24 35	0.9 (0.4-1.8) 1-4 yr 0.6 (0.3-1.0) 1-4 yr 0.8 (0.5-1.3) 1-4 yr	6 8 6	1.6 (0.4-6.1) ≥10 yr 0.5 (0.2-1.3) ≥10 yr 1.0 (0.3-3.2) ≥10 yr

[16] RR – Relative Risk

[17] CI – Confidence Interval

Table 2 (continued).

	Brain tumours		**Brain tumours short latency**		**Brain tumours longer latency**	
[Hardell et al. 2005a, Hardell et al. 2005b]	68 malignant, analogue	2.6 (1.5-4.3)	20 analogue	1.8 (0.9-3.5) 6-10 yr†	48 analogue	3.5 (2.0-6.4) >10 yr
	198 malignant, digital	1.9 (1.3-2.7)	100 digital	1.6 (1.1-2.4) 1-5 yr	19 digital	3.6 (1.7-7.5) >10 yr
	35 meningioma, analogue	1.7 (1.0-3.0)	1 analogue	1.2 (0.1-12) 1-5 yr	20 analogue	2.1 (1.1-4.3) >10 yr
	151 meningioma, digital	1.3 (0.9-1.9)	96 digital	1.2 (0.8-1.8) 1-5 yr	8 digital	1.5 (0.6-3.9) >10 yr
[Hepworth et al. 2006]	508 glioma	0.9 (0.8-1.1)	271 glioma	0.9 (0.7-1.1) 1.5-4yr	170 glioma	1.0 (0.8-1.3) 5-9 yr
					66 glioma	0.9 (0.6-1.3) ≥10yr
[Schüz et al. 2006]	138 glioma	1.0 (0.7 - 1.3)	82 glioma	0.9 (0.6 – 1.2) 1–4 yr	51 glioma	1.1 (0.8–1.7) ≥5yr
					12 glioma	2.2 (0.9-5.1) ≥10yr
	104 meningioma	0.8 (0.6 - 1.1)	73 meningioma	0.9 (0.6 – 1.2) 1–4 yr	23meningioma	0.9 (0.5-1.5) ≥5yr
					5 meningioma	1.1 (0.4-3.4) ≥10yr

* Discordant pairs

† No cases had shorter than 6 years latency

Table 3. Results of epidemiological studies on mobile phone use and acoustic neuroma. The table is modified from the SSI report, 2005 (SSI's Independent Group on Electromagnetic Fields 2005).

	Acoustic neuroma		Acoustic neuroma, short latency		Acoustic neuroma, longer latency	
	No. exp cases	RR[18] (95% CI[19])	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)
[Hardell et al. 1999]	5	0.8 (0.1-4.2)				
[Inskip et al. 2001]	22	1.0 (0.5-1.9)	8	1.8 (0.7-4.5) 0.5-2 yr	5	1.9 (0.6-5.9)
[Johansen et al. 2001]	7	0.6 (0.3-1.3)				
[Muscat et al. 2002]			7	0.5 (0.2-1.3) 1-2 yr	11	1.7 (0.5-5.1) 3-6 yr
[Hardell et al. 2002]	38* analogue 23* digital	3.5 (1.8-6.8) 1.2 (0.7-2.2)	12* analogue 21* digital	3.0 (1.0-9.3) 1-5 yr 1.2 (0.6-2.2) 1-5 yr	7* analogue 2* digital	3.5 (0.7-16.8) >10 yr 2.0 (0.2-22.1) >5 yr
[Lönn et al. 2004]	89	1.0 (0.6-1.5)	44	0.8 (0.5-1.3) 1-4 yr	14	1.9 (0.9-4.1) ≥10 yr
[Christensen et al. 2004]	45	0.9 (0.5-1.6)	23	0.9 (0.5-1.6) 1-4 yr	2	0.2 (0.0-1.1) ≥10 yr
[Hardell et al. 2005a]	20 analogue 53 digital	4.2 (1.8-10) 2.0 (1.0-3.8)	2 analogue 29 digital	9.9 (1.4-69) 1-5 yr 1.7 (0.9-3.5) 1-5 yr	11 analogue 7 analogue 23 digital	5.1 (1.9-14) 5-10 yr 2.6 (0.9-8.0) >10 yr 2.7 (1.3-5.7) 5-10 yr
[Schoemaker et al. 2005]†	360	0.9 (0.7-1.1)	174	0.8 (0.7-1.0) 1.5-4 yr	139 47	0.9 (0.7-1.2) 5-9 yr 1.0 (0.7-1.5) ≥10 yr

* Discordant pairs

† Partly overlapping with Lönn et al, 2004 and Christensen et al, 2004

[18] RR – Relative Risk

[19] CI – Confidence Interval

3.3.2.2. In vivo

What was already known on this subject?

The possible carcinogenicity of RF field exposure had been investigated in a number of experimental systems. Results had been essentially negative. An interesting exception is that of Repacholi et al. (1997), who had induced a two-fold increase in lymphoma incidence in a strain of lymphoma-prone transgenic mice (Eμ-Pim1) following exposure (2x30 min daily for up to 18 months) to 900 MHz RF fields with a signal similar to the GSM modulation (pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms). No attempt to replicate this finding had been published at the time of publication of the previous opinion.

What has been achieved since then?

Utteridge et al. (2002) failed to confirm the results of the Repacholi et al. (1997) study. Utteridge and co-workers found that exposure to RF fields (898 MHz; GSM modulation; 0.25/1.0/2.0/4.0 W/kg; 1 h/d, 5 d/wk for 104 weeks) had no statistically significant effects (95%-CI) on the incidence of lymphoma. Utteridge et al. (2002) used the same strain of mouse as the earlier study and they were obtained from same supplier; the investigators also fed the same food to the mice. The later study had some refinements in experimental design: four SAR levels were used instead of one in the original study, animals were restrained during the exposure for better control of variations in exposure level, and full necropsy was performed on all mice at the end of the study. Other differences from the Repacholi et al study were that animals were exposed once per day instead of during two episodes of 30 minutes 5 days per week.

Several other recent studies have evaluated carcinogenicity of RF fields in a variety of experimental models. Several studies have tested whether RF fields alone induce any type of cancer in normal or genetically predisposed animals (Zook and Simmens 2001, La Regina et al. 2003, Anderson et al. 2004, Sommer et al. 2004b), and several other studies investigated whether exposure to RF fields could enhance the development of tumours induced by chemical carcinogens, X-rays or UV radiation (Zook and Simmens 2001, Anane et al. 2003a, Bartsch et al. 2002, Imaida et al. 2001, Huang et al. 2005, Shirai et al. 2005, Heikkinen et al. 2001, 2003, 2006). No statistically significant increase of tumour incidence has been reported in any of these studies.

Most of the recent and earlier co-carcinogenicity studies on RF fields have used initiation-promotion protocols, which, however, may not be sufficient to test all aspect of co-carcinogenicity (Juutilainen et al. 2000). In addition, most of the carcinogenicity studies have used only one, relatively low, RF field exposure level.

3.3.2.3. In vitro

What was already known on this subject?

A variety of biological endpoints have been investigated after RF field exposure in vitro. Much of the work had focused on genotoxic effects, although there was no prior indication that non-thermal RF fields induce DNA damage. However, since some reports indicated genotoxic effects from RF fields, the earlier CSTEE opinion recommended the confirmation of these findings.

What has been achieved since then?

Genotoxic effects

The photon energy of radiation from mobile phones is much lower than the energy necessary to break chemical bonds. It is therefore generally accepted that RF fields do not directly damage DNA. However, it is possible that certain cellular constituents altered by exposure to EMF, such as free radicals, indirectly affect DNA. In most studies, the genotoxic effects have been investigated after short-term exposure (for review see Moulder et al. 1999, Vijayalaxmi and Obe 2004).

The REFLEX study performed by twelve research groups in seven European countries, investigated basic mechanisms induced by EMF using toxicological and molecular biological technologies at cellular and sub-cellular levels in vitro. The REFLEX investigators (Diem et al. 2005) reported DNA strand breaks (measured by both the neutral and alkaline versions of the "comet" assay) in human diploid fibroblasts and cultured rat granulosa cells after RF field exposure (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; during 4, 16 and 24h; intermittent 5 min on/10 min off or continuous wave). Statistically significant increases in micronucleus formation and in chromosomal aberrations were observed in fibroblasts as well. Nicolova et al. (2005) reported after a 6-h but not after a 48-h RF field exposure a low and transient increase of DNA strand breaks in embryonic stem cell-derived neural progenitor cells.

Non-genotoxic effects

Several studies investigated the influence of RF fields on cell cycle kinetics, but in the majority of the investigations no effects were detected (Vijayalaxmi et al. 2001, Higashikubo et al. 2001, Zeni et al. 2003, and Miyakoshi et al. 2005, Lantow et al. 2006c). Alteration in cell proliferation was described only in a few reports (Pacini et al. 2002, Capri et al. 2004b).

Programmed cell death which is also called apoptosis is a physiological mode of cell death occurring in development and cell differentiation and in response to mild damaging stimuli. It is an important protection mechanism against cancer, as it removes potential tumour cells. Several reports have investigated whether RF fields can induce apoptosis in human peripheral blood mononuclear cells (Capri et al. 2004a), lymphoblastoid cells (Marinelli et al. 2004), epidermis cancer cells (Caraglia et al. 2005), human Mono Mac 6 cells (Lantow et al. 2006c) and in Molt4 cells (Hook et al. 2004). No difference in apoptosis induction was detected between sham-exposed and RF field exposed cells. On the other hand, Marinelli et al. reported better survival rate of T lymphoblastoid leukaemia cells exposed to 900 MHz non-modulated RF fields and Caraglia et al. (2005) found apoptosis induction in human epidermoid cancer cells after exposure to .95 GHz RF fields.

Participants of the REFLEX-study reported no effects of RF fields on cell cycle, cell proliferation, cell differentiation, apoptosis induction, DNA synthesis, and immune cell functionality. The authors described some findings after RF fields exposure on the transcript level of genes related to apoptosis and cell cycle control; however, these responses were not associated with detectable changes of cell physiology (Nikolova et al. 2005).

Heat-shock proteins (Hsp) are an important group of cell response proteins. They act primarily as molecular chaperones to eliminate unfolded or miss-folded proteins, which can also appear from cellular stress. This stress response can be induced by many different external factors, including temperature, chemicals, oxidative stress, heavy metals, ionizing and non-ionizing radiation and ultrafine carbon black particles. Hsp70 has been shown to interfere with post-

mitochondrial events to prevent free radical mediated apoptosis (Gotoh et al. 2001). An increased expression level of Hsp70 can thus confer protection against cellular stress. On the other hand, it is discussed that heat-shock proteins are also involved in oncogenic processes (Jolly et al. 2000, Inoue et al. 1999, French et al. 2001). Some investigators have described increased heat-shock protein level after RF field exposure (Leszinsky et al. 2002, Kwee et al. 2001, de Pomerai et al. 2000). However, these results are controversial, because there are other negative findings (for review see (Cotgreave 2005). Interestingly, de Pomerai and his co-workers could not confirm their earlier findings, and the new data indicate that small temperature differences may have contributed to the earlier results (Dawe et al. 2006).

Nicolowa et al. (2005), authors of the REFLEX-study, described modulation in gene regulation after RF fields exposure at a SAR of 1.5 W/kg in p53-deficient embryonic stem cells. Proteomic analyses of human endothelial cell lines showed RF fields induced changes in the expression and phosphorylation state of numerous proteins including the heat shock protein hsp27.

Free radicals are able to interact with DNA or other cellular components and are involved in many cell regulatory processes.

In leukocytes, physiological activation is associated with the onset of phagocytosis and leads to increased formation of reactive oxygen species (ROS). These cells exert a wide variety of functions including the regulation of the immune response (pro and anti inflammatory processes), scavenging of senescent cells, phagocytosis of infected or malignant cells, wound healing, repair, and detoxification, but also the generation of free radicals to kill invading micro-organisms. Each type and source of free radicals enhances important physiological processes, e.g., signal transduction of various membrane receptors and further immunological functions. An imbalance between excessive formation of reactive oxygen species and the limited antioxidant defense, known as oxidative burst (Sies and Cadenas 1985), can cause damage to nucleic acids, membranes, proteins, lipids and polysaccharides (Beckman et al. 1998). During healthy conditions free radicals are neutralized by an elaborate defense system. Only a few publications are available describing the capacity of RF fields to affect free radical dependent processes in cells. In recent studies (Lantow et al. 2006a, Lantow et al. 2006b, Simkó et al. 2006) no increased free radical level was detected.

Influences on immune system cells were investigated in a few studies. No significant effects were observed on intracellular production of interleukin-2 (IL-2) and interferon (INF) gamma in lymphocytes, IL-1 and tumour necrosis factor (TNF)-alpha in monocytes, on immune-relevant genes (IL 1-alpha and beta, IL-2, IL-2-receptor, IL-4, macrophage colony stimulating factor (MCSF)-receptor, TNF-alpha, TNF-alpha-receptor) (Tuschl et al. 2005, Black and Heynick 2003).

Discussion

Effects of RF fields on different biological systems have been investigated. Although the majority of studies have found no evidence of genotoxic effects, there are a few positive findings that should be followed up. Some in-vitro studies provide evidence that gene expression is affected at RF exposure close to the guideline. If these studies continue to be confirmed they will be important for a mechanistic understanding of the interaction of RF fields with cellular tissue. Overall, there is little evidence of any health-relevant in vitro effects of RF electromagnetic fields below guidelines. While it seems appropriate to perform experimental studies using pure experimental RF fields, it may be needed to emulate the complex modulation patterns and

intensity variations typical to real mobile phone use in future studies. This way data can be obtained which is better suited for comparison to epidemiologic studies.

3.3.3. Symptoms

What was already known on this subject?

In the 2001 opinion it was concluded that the knowledge was insufficient for the implementation of measures aimed at the identification and protection of a highly sensitive sub-group of the population. With regard to reports of subjective symptoms from individuals (possibly "hypersensitive"), the limited number of studies on volunteers had found no connection between reported symptoms and exposure to electromagnetic fields. There was a lack of information on the role of conditions of exposure (frequency, concentration duration etc) and possible biological mechanism. While, epidemiological studies had not shown any consistent evidence of effects on humans, it was pointed out that this could not be taken to mean that RF field exposure does not pose any hazard to human health.

What has been achieved since then?

A variety of non-specific symptoms (for example neurovegetative symptoms like headache, fatigue, dizziness and concentration difficulties) has been suggested to be triggered by exposure to RF fields. These possible health effects have been discussed and studied mainly from two different aspects: 1) a possible increase in symptoms in populations living close to mobile communication base stations and 2) reports from individuals that exposure to RF from mobile phones (and sometimes also base stations) triggers symptoms. In the latter case, some individuals attribute their health problems to an increased sensitivity (hypersensitivity) to electromagnetic fields. The term "electromagnetic hypersensitivity" (EHS) has been used to describe such cases of non-specific health problems attributed by the afflicted individuals to electromagnetic fields or to being in the vicinity of electrical equipment (see also the section on ELF fields 3.5.3 Symptoms).

There have only been a few attempts to study symptom prevalence and symptom severity in relation to exposure to RF fields from base stations. The methodological limitations of these cross-sectional epidemiological studies, which were used for this, preclude conclusions regarding a possible relationship between an increase in symptoms and exposure to RF. A relationship between RF and symptoms in healthy volunteers was investigated in one provocation study (Koivisto et al. 2001). No increase in symptoms was observed during RF exposure as compared to sham exposure. The limited number of studies on detection of RF at exposure levels relevant to mobile communication systems under blind conditions has not provided any consistent proof of ability to detect the fields, neither in healthy individuals nor in subjects who report EHS.

Health complaints described as EHS and reported to be triggered by mobile phones have also been studied in a limited number of provocation studies. A WHO Workshop on Electrical Hypersensitivity (WHO 2005) and recent reviews of the literature on subjective health complaints associated with electromagnetic fields of mobile phone communication (Seitz et al. 2005) and provocation studies including subjects reporting EHS (Rubin et al. 2005) have presented similar conclusions. The main conclusion is that although symptoms described as EHS

are real and may be severe and disabling, a relationship between symptoms and RF field exposure has not been proven. Most likely, the health problems described as EHS are not related to the physical presence of EMF and more research is needed to learn more about the conditions inducing EHS.

Discussion

Scientific studies have failed to provide support for a relationship between RF exposure and neurovegetative symptoms sometimes referred to as EHS. Present knowledge suggests that symptoms are not correlated to RF field exposure, but few studies have addressed this issue directly. The exposure levels from base stations are very low compared to the exposure during the use of a mobile phone. Research regarding health effects from base stations where exposure is significantly lower than for mobile phone users is mainly driven by concern in the general population.

3.3.4. Nervous system effects

What was already known on this subject?

Due to the proximity of mobile phones to the head, public concerns were raised regarding a potentially toxic effect of RF on the central nervous system. Five aspects are usually considered in toxicology regarding the nervous system: morphology, brain function, electrophysiology, behaviour and development (which is addressed in a later paragraph).

Several studies had been published concerning the potential neurotoxic effects of radiofrequencies emitted by the mobile phones. Transient minor effects were observed on the electroencephalogram (EEG), sleep structure, and on cognitive processes in human subjects (Mann and Röschke 1996, Preece et al. 1999, Huber et al. 2000, Koivisto et al. 2000a, Koivisto et al. 2000b, Krause et al. 2000). Some of the observations could not be replicated (Wagner et al. 1998, Wagner et al. 2000), and studies with negative outcomes were also published (Röschke and Mann 1997).

In animals, some previous studies did show disturbance of work memory in rats exposed to RF (Lai et al. 1994, Wang and Lai 2000). However, the most surprising effect was that very low SAR values (mW/kg) caused increased permeability of the blood-brain-barrier (BBB) in rats (Salford et al. 1994, Persson et al. 1997). Alterations of the BBB had also been found in another study (Neubauer et al. 1990), but not by Tsurita et al. (2000). In rats exposed to 2 W/kg Fritze and co-workers demonstrated effects on BBB only at SAR levels above 7.5 W/kg (Fritze et al. 1997). The BBB isolates the CNS from the rest of the organism, controls molecule fluxes, and protects the brain (Purves et al. 2001). Increased permeability of BBB can allow unwanted substances to reach the CNS, with possible pathological consequences (inflammation, neurone death).

What has been achieved since then?

<u>Human studies</u>

In humans, transitory minor effects (both positive and negative) have been observed on EEG patterns, sleep structure, and cognitive processes (D'Costa et al. 2003, Cook et al. 2002, Hossmann and Hermann 2003, Sienkiewicz et al. 2005). Also studies where no effects were documented have been published, even after a repeated exposure (Besset et al. 2005).

Since the ear is very close to the exposure source, some studies have checked the auditory system under or after exposure, and even after repeated cumulative exposure. No effect has been observed (Ozturan et al. 2002, Arai et al. 2003, Bak et al. 2003, Parazzini et al. 2005, Uloziene et al. 2005).

Animal studies

Slight changes in EEG activity and neurotransmitters have been observed in animals at low SARs (reviewed by Sienkiewicz et al. 2005). Regarding cognitive functions, a recent report showed that a disturbance of learning and memory in rats exposed at 2.45 GHz CW could be inhibited by a magnetic field (incoherent noise) (Lai 2004a). Results from earlier studies on learning and memory at non-thermal RF levels have not been corroborated (Dubreuil et al. 2003, Yamaguchi et al. 2003, Cobb et al. 2004, Cassel et al. 2004). No morphological effects have been observed below thermal thresholds (D'Andrea et al. 2003).

Salford and co-workers published another work showing changes in BBB permeability at low SAR (Salford et al. 2003), whereas others did not find any such alteration (Finnie et al. 2001), even with repeated exposures up to 2 years (Finnie et al. 2002).

No effects have been seen on auditory system function (Aran et al. 2004) or on development of multiple sclerosis in rats (Anane et al. 2003b).

What are the overall conclusions?

Overall analyses do not show any clear neurotoxic effect, at any level studied. Slight changes in electrical activity or neurotransmitter biochemistry have been observed. Those changes do not act on cognitive processes, behaviour or memory and do not suggest pathological hazards. Furthermore, no clear role of modulation has appeared.

Although extrapolation from animals to humans raises some difficulty, the rat or the mouse are common models to look for toxicity and the few studies showing significant alterations are to be considered carefully. For all cognitive experiments in animals, stress effects due to restraint must be clearly be identified and prevented when looking at effects of RF fields.

3.3.5. Miscellaneous human

Initial observations of a blood pressure decrease after mobile phone exposure have not been replicated (Braune et al. 1998, Braune et al. 2002). The only effects on cardio-vascular functions that have been replicated are increased blood-flow in the external ear (Monfrecola et al. 2003, Roelandts 2003). Local temperature increases during exposure have been reported (Paredi et al. 2001, Curcio et al. 2004), possibly related to vasodilation caused by heating of mobile phone electronics and battery.

3.3.6. Reproduction and development

Epidemiological studies of adverse pregnancy outcomes following exposure to RF fields have been reviewed by Verschaeve and Maes (1998), Heynick and Merrit (2003) and Feychting (2005a). The evidence on possible effects of RF fields on pregnancy outcomes is virtually limited to occupational exposures among physiotherapists. The endpoints studied include spontaneous abortions, birth weight, gender ratio, and congenital malformations Although some

positive findings have been reported, no specific type of malformation or other adverse outcome has been consistently reported. Several of the studies have limited statistical power, especially for rare outcomes such as malformation, and there is a potential for recall bias. The available results do not allow any definite conclusions.

Numerous studies have evaluated developmental effects of RF fields on mammals, birds, and other non-mammalian species. These studies, reviewed recently by Heynick and Merritt (2003) and Juutilainen (2005), have clearly shown that RF fields are teratogenic at exposure levels that are sufficiently high to cause significant increase of temperature and exceed reference levels from exposure guidelines. There is no consistent evidence of effects at nonthermal exposure levels. However, only a few studies have evaluated possible effects on postnatal development using sensitive endpoints, such as behavioural effects.

3.3.7. Sensitivity of children

Concerns about the potential vulnerability of children to RF fields have been raised because of the potentially greater susceptibility of their developing nervous system; in addition, their brain tissue is more conductive than that of adults since it has a higher water content and ion concentration, RF penetration is greater relative to head size, and they have a greater absorption of RF energy in the tissues of the head at mobile telephone frequencies. Finally, they will have a longer lifetime exposure.

Few relevant epidemiological or laboratory studies have addressed the possible effects of RF field exposure on children. Owing to widespread use of mobile phones among children and adolescents and relatively high exposures to the brain, investigation of the potential effect of RF fields in the development of childhood brain tumour is warranted. The characteristics of mobile phone use among children, their potential biological vulnerability and longer lifetime exposure make extrapolation from adult studies problematic.

There is an ongoing debate on possible differences in RF absorption between children and adults during mobile phone usage. One crucial aspect is the possibility that the absorption might increase due to the smaller head of the children. Several scientific questions like possible differences of the dielectric tissue parameters remain open (Wiart et al. 2005, Christ and Kuster 2005).

The anatomical development of the nervous system is finished around 2 years of age, when children do not yet use mobile phones although baby phones have recently been introduced.

Functional development, however, continues up to adult age and could be disturbed by RF fields.

3.3.8. Conclusions about RF fields

Since the adoption of the 2001 opinion, extensive research has been conducted regarding possible health effects of exposure to low intensity RF fields. This research has investigated a variety of possible effects and has included epidemiologic, in vivo, and in vitro research. The overall epidemiologic evidence suggests that mobile phone use of less than 10 years does not pose any increased risk of brain tumour or acoustic neuroma. For longer use, data are sparse, since only some recent studies have reasonably large numbers of long-term users. Any conclusion therefore is uncertain and tentative. From the available data, however, it does appear that there is no increased risk for brain tumours in long-term users, with the exception of

acoustic neuroma for which there is limited evidence of a weak association. Results of the so-called Interphone study will provide more insight, but it cannot be ruled out that some questions will remain open.

Scientific studies have failed to provide support for a relation between RF exposure, lower than the reference values in the present ICNIRP guidelines and neurovegetative symptoms (sometimes referred to as electromagnetic hypersensitivity). Available studies suggest that self-reported symptoms are not correlated to an acute exposure to RF fields, but the limited number of studies does not allow any firm conclusion.

Currently available studies on neurological effects and reproductive effects have not indicated any health risks at exposure levels below guidelines.

Animal cancer studies have not provided evidence that RF radiation could induce cancer, enhance the effects of known carcinogens, or accelerate the development of transplanted tumours. The open questions include adequacy of the experimental models used and scarcity of data at high exposure levels. These questions are addressed by the still ongoing and planned carcinogenicity studies.

There is no reliable indication from in vitro research that RF fields affect cells at nonthermal exposure. However, recent results suggesting genotoxic effects need to be better understood.

Thus, no health effect has been consistently demonstrated at exposure levels below existing exposure guidelines for the general public. However, data on long term exposure and intracranial tumours are still sparse and in particular for acoustic neuroma some data indicate that an association with RF fields from mobile telephony is possible. For diseases other than cancer, very little epidemiologic data are available. A particular consideration is mobile phone use by children. While no specific evidence exists, there is a general concern that children or adolescents may be more sensitive to RF field exposure than adults. Children, as adults, will also have a much higher cumulative exposure compared to today's adults. To date no epidemiologic studies on children are available.

The technical development is very fast and sources of RF exposure become increasingly common. Yet, there is a profound lack of mechanistic understanding of effects below the guidelines and of information on individual RF exposure and the relative contribution of different sources to the overall exposure.

3.4. Intermediate Frequency Fields (IF fields)

Intermediate frequencies are, in the frame of this report, defined as frequencies between 300 Hz and 100 kHz. They involve two different mechanisms, namely induced currents and dielectric absorption. The frequency limit when one predominates over the other is not precisely defined. Existence of effects depends upon two superimposed phenomena: absorption of the external field in the organism at the macroscopic level and the stimulation of biological effects by the penetrating fields. Those two phenomena depend on the kind of field, electric or magnetic, and on the frequency. Well-known biological effects are nerve stimulation at low frequencies and heating at high frequencies.

3.4.1. Sources and distribution of exposure in the population

The number of applications in this frequency range has been increasing in recent years. Examples are anti theft devices operated, e.g., at the exits of shops. Depending on the type of system, they are operated at very different frequencies ranging from some tens of Hz to a few GHz. The majority of these applications are operated in the intermediate frequency range. Close to some systems the so called reference levels can be exceeded under worst case conditions, but for most of the systems the exposure is well below the recommended limits. Other applications are induction hobs and hotplates typically operated at frequencies between 20 to 50 kHz, electric engines, and badge readers (typical frequency about 100 kHz). Information on the exposure due to such applications is scarce. Still common sources are visual display units containing cathode ray tubes which are causing emissions in the ELF range and the IF range, in the order of 1 nT up to 50 nT. Radio transmitters operated in the long wave range (30 kHz to 300 kHz) can cause exposure in the intermediate frequencies with levels above the recommended limits. Therefore, safety precautions need to be implemented both for the general public and workers. Some industrial applications like induction heating and welding need to be mentioned. Induction heaters are operated in a frequency band from typically some tens of Hz to some tens of kHz, the exposure levels can reach values of about 100 µT or more. Welding is a complex process that can cause emissions up to a few 100 kHz. The sparse information on IF field exposure due to welding devices available so far indicates that safety measures need to be implemented in some cases.

Some medical applications exist in the IF range. One example is electrosurgery used very commonly in hospitals. These systems are operated at some hundred kHz.

3.4.2. Health Effects

Epidemiological studies on IF fields were reviewed at a workshop organized by the WHO and by ICNIRP in 1999 (Hietanen 1999). It seems that very few useful data are available for health risk assessment. The few studies that do exist are relatively old occupational studies using occupations or job titles but no actual exposure estimation. Groups that have been studied include VDU (video display units) users and radio and telegraph operators. One study looked at radio amateurs. The studied outcomes include ocular effects, cardiovascular effects, cancer, and reproductive effects.

The available *in vivo* and *in vitro* evidence was reviewed in articles published in the proceedings of the WHO/ICNIRP seminar on IF fields (Juutilainen and Eskelinen 1999, Glaser 1999, Litvak and Repacholi 1999). In contrast to the active experimental and epidemiological research on ELF and RF fields, only a very limited number of studies have addressed the biological effects of IF fields. While there is limited evidence for effects on reproduction and development (Juutilainen 2005, Huuskonen et al. 1998), studies on other effects (such as carcinogenicity, genotoxicity, nervous system effects and general toxicity) are almost totally lacking.

3.4.3. Conclusions about intermediate frequencies

It is considered that the well established hazard mechanisms in the IF range are associated with a limited number of phenomena and apply to acute exposures. However the extension to long term effects is based on weak grounds and on possibly unjustified assumptions about frequency

dependence of effects (Litvak et al. 2002). In addition to established mechanisms, comprehensive risk assessment should consider also other information, such as well-conducted epidemiological and laboratory studies. Studies on possible effects associated with chronic exposure at low exposure levels (below exposure limits) are particularly relevant for assessing risks to human health and for confirming adequacy of current exposure limits.

Proper evaluation and assessment of possible health effects from exposure to IF fields is essential because human exposure to such fields increases due to new and emerging technologies.

3.5. Extremely low frequency fields (ELF fields)

3.5.1. Sources and distribution of exposure in the population

The exposure due to electric fields and magnetic flux densities in the ELF range arises from a wide variety of sources (IARC 2002). The most prominent frequencies are 50 and 60 Hz and their harmonics, often called power frequencies. For residential exposure, the major sources are household appliances, nearby power and high voltages transmission lines, and domestic installations. In some cases trains have to be considered, too. Looking at occupational exposure, installations of the electric power industry, welding, induction heaters and electrified transporting systems are important examples of ELF exposure sources. The highest electric field strengths typically occur close to high voltage transmission lines and can reach 5 kV/m and in a few cases more. The highest magnetic flux densities can be found close to induction furnaces and welding machines. Levels of a few mT are possible.

It needs to be mentioned that the maximum possible exposure next to a specific source often differs by some orders of magnitude from the average individual exposure of a person. To evaluate the distribution of the exposure in the population, meters are used. For assessment of compliance with exposure limits, the maximum possible exposure next to devices must be measured. An example might be a lineman: the average exposure due to magnetic flux density could be about 4 μT (IARC 2002), but the maximum exposure close to a transmission line can reach 40 μT or more. For the general population even larger variations between maximum and average exposure can be expected. Information on ELF exposure is mainly based on US and Western European data.

a. Exposure of the general population

   Several fixed installed sources are operated in our environment. Prominent examples are high voltage transmission lines operated between 110 and 400 kV at 50 or 60 Hz. The exposure of bypassing people can reach values of 2 to 5 kV/m for the electric field strength. The exposure due to magnetic flux density depends on the actual current on the line; fields up to 40 μT are possible but are usually lower. It is important to notice that such exposure levels occur only directly below the lines; exposure decreases with the square of distance to the lines. In addition, intermediate voltage transmission lines (10 kV to 30 kV) and distribution lines (400 V) have to be considered; exposure levels are in such cases much lower. Typically values of 100 to 400 V/m and 0.5 to 3 μT can be reached. Another approach to establish power supply is the use of underground buried cables. Electric field strength exposure can be neglected in this case; the distribution of the magnetic flux density differs compared to power lines. Substations and power plants are usually not accessible to

the general public. Railway power supply installations are often operated at 16 2/3 Hz. The exposure decreases linearly with the distance. The exposure levels in areas accessible for the general public are below the limits. The highest magnetic flux densities can be found close to several domestic appliances that incorporate motors, transformers, and heaters. Such exposure levels are very local and decrease rapidly with the distance. An example is a vacuum cleaner: at a distance of 5 cm magnetic flux densities of about 40 μT can occur, but at 1 m the exposure will be around 0.2 μT. Looking at the individual exposure of persons, a few percent of the European population are in their homes exposed above a median magnetic flux density above 0.2 μT.

b. Exposure of workers
In a few locations in installations of the electric power industry the exposure limits of occupational exposure can be reached or exceeded. Safety measures for such areas have to be implemented. An example is a peak electric field strength of more than 20 kV/m that was measured in a power station. Other examples of industrial applications in the ELF range are induction and light arc ovens or welding devices. The frequencies of such applications fall both in the ELF and in the intermediate frequency range. Exposure of workers has to be controlled for such devices. Next to welding devices maximum flux densities of several hundred μT are possible, depending on the welding current and the type of application.

c. Medical applications
Bone growth stimulation is used as a therapeutic application in the ELF range. In this case coils are applied where the fracture is located to stimulate the healing process. Other applications include Transcranial Magnetic Stimulation, wound healing, or pain treatment. A diagnostic application is the bioimpedance measurement for cancer detection.

3.5.2. Cancer

3.5.2.1. Epidemiology

What was already known on this subject?

In 2002, the "International Agency on Research on Cancer (IARC)" published a monograph on the evaluation of carcinogenic risks of static and extremely low-frequency (ELF) electric and magnetic fields to humans (IARC, 2002). ELF magnetic fields were classified into group "2B" ("possibly carcinogenic to humans"). While the outcome of this evaluation was already known at the time of the last opinion report, the IARC reasons for this decision were not yet published. The justification states limited evidence in humans based on consistent results from sound epidemiological studies showing an association with an increased leukaemia risk in children at field strengths above 0.3/0.4 μT (Ahlbom et al. 2000), but bias in these studies could explain some of the raised risk. The findings from observational studies are not supported by studies in experimental animals, which provide inadequate evidence of carcinogenicity.

Furthermore, the IARC monograph concluded, there was no evidence for an association of ELF magnetic fields with any other type of cancer. ELF electric fields were grouped into "3" ("is not classifiable as to its carcinogenicity to humans").

What has been achieved since then?

Only a few studies on childhood leukaemia were conducted since the adoption of the previous opinion, and they did not add anything substantially to the previous studies. At a workshop of WHO in 2004, possible explanations for the childhood leukaemia finding have been put forward (summarized in (Kheifets et al. 2005)). None of them reaches a level beyond speculation. One recent study has observed a decreased survival in children with leukaemia being exposed to ELF magnetic fields above 0.3 μT (Foliart et al. 2006). This finding, however, is based on small numbers and no mechanism has been proposed, so confirmation studies have to be awaited before conclusions should be drawn. Most new ELF studies have been looking into breast cancer or brain tumour risk. Breast cancer caught particular interest because of experimental results suggesting that melatonin synthesis was related to ELF field exposure and because melatonin might play a role in the development of breast cancer. Several studies also reported an increased breast cancer risk among subjects with elevated ELF exposure. However, later big and well controlled studies have been entirely negative and the hypothesis of a link between ELF field exposure and breast cancer risk is essentially written off (Forssen et al. 2005). While some new data on brain tumours have appeared since the previous opinion, firm conclusions can still not be drawn.

Discussion

Little data that have an impact on the evaluation have appeared since the previous opinion. Therefore, the previous assessments stay the same. The fact that the epidemiologic results for childhood leukaemia have little support from known mechanisms or experimental studies is intriguing and it is of high priority to reconcile these data.

3.5.2.2. In vivo

What was already known on this subject?

The previous opinion did not evaluate evidence of carcinogenicity from animal studies. However, such data were included in the monograph by IARC that classified ELF magnetic fields into group 2B, “possibly carcinogenic to humans”, based on epidemiological studies showing an association between residential ELF magnetic fields and childhood leukaemia (IARC 2002). The long-term animal carcinogenicity studies reviewed by IARC provided very little evidence that exposure to ELF magnetic fields alone could induce any type of cancer, including hemopoietic, mammary, brain and skin tumours. Negative results were also obtained from studies that evaluated the effects of ELF magnetic fields on growth of transplanted tumour cells. Animal studies that combined magnetic fields with known carcinogenic agents produced more equivocal results, although also these co-carcinogenicity studies were mostly negative. Among the few positive findings are enhanced development of UV-induced mouse skin tumours in one study (Kumlin et al. 1998) and accelerated development of rat mammary tumours induced by 7,12-dimethylbenz(a)anthracene (DMBA) in several experiments by a German research group (Löscher et al. 1993, Baum et al. 1995, Mevissen et al. 1996, Mevissen et al. 1998, Thun-Battersby et al. 1999). The latter findings were not substantiated in independent replication studies (Anderson et al. 1999, Boorman et al. 1999), but there are differences in experimental details that could potentially explain the differences in results (Anderson et al. 2000, Löscher 2001). Based on the available experimental studies, IARC concluded that there is *inadequate evidence* for carcinogenicity of ELF magnetic fields in experimental animals.

What has been achieved since then?

Motivated by the epidemiological findings of increased leukaemia risk in children, Sommer and Lerchl (2004a) investigated the influence of 50 Hz (1 or 100 μT) magnetic fields in the AKR/J mouse strain genetically predisposed to thymic lymphoblastic lymphoma. There was no effect of magnetic field exposure on survival, and the time to lymphoma development did not differ between exposed and sham-exposed animals. The results do not support the hypothesis that chronic exposure to 50 Hz magnetic fields increases the risk of hemopoietic malignancy in this experimental model. However, the relevance of the model to human childhood leukaemia is limited.

New results have been published by German researchers who have reported accelerated development of DMBA-induced rat mammary tumours. In their most recent study (Fedrowitz et al. 2004) they tested the hypothesis that use of different sub strains of SD rats explains the difference between their previous results and those of the replication studies. The results were consistent with the hypothesis: exposure to a 100 μT, 50 Hz magnetic field enhanced mammary tumour development in one sub strain of SD rats, but not in another sub strain obtained from the same breeder. The tumour data were supported by the finding that exposure to MF increased cell proliferation in the mammary gland of the MF-sensitive strain, but no such effect was seen in the insensitive sub strain. The finding is potentially important for explaining the inconsistent results, if the sub strain-specific effect of MF exposure is confirmed in further independent experiments.

Although short-term animal studies are considered less relevant for cancer risk assessment than long-term carcinogenicity and co-carcinogenicity studies, they can provide important contributions to understanding the mechanisms of carcinogenic effects. *Genotoxicity* of ELF magnetic fields was studied by Lai and Singh (2004b), who reported significantly increased DNA damage after exposure to a 60 Hz, 10 μT magnetic field for 24 or 48 hours. Although the effect was relatively small, it was seen in several independent experiments. The effects were blocked by treatment with a radical scavenger, a nitric oxide synthase inhibitor and an iron chelator, suggesting involvement of free radicals and iron in the effects of magnetic fields. The same authors have previously reported similar effects after short (2 hour) exposure to higher magnetic flux densities of 0.1-0.25 mT. Environmental agents can promote the development of cancer also through *non-genotoxic* mechanisms such as stimulation of cell proliferation and inhibition of apoptosis. In support of their previous results suggesting co-carcinogenic effects of ELF magnetic fields (described above), two research groups have reported increase in cell proliferation markers in rat mammary gland (Fedrowitz et al. 2002) and inhibition of UV radiation-induced apoptosis in mouse skin (Kumlin et al. 2002) after short-term exposure to magnetic fields at 100 μT. The results of the short-term animal studies are interesting and, if confirmed in further independent experiments, potentially important for understanding possible cancer-related effects of magnetic fields.

Discussion

Overall there is no evidence from animal studies that ELF magnetic field exposure alone causes tumours or that it enhances the growth of implanted tumours. There is some inconsistent evidence that ELF magnetic fields of about 100 μT may enhance the development of tumours induced by known carcinogens, but the majority of studies evaluating such co-carcinogenic effects have been negative. Results from recent studies are potentially helpful for explaining mechanisms and inconsistencies of previous findings, but they lack confirmation in independent experiments, and are not sufficient to change IARC's evaluation that the experimental evidence for carcinogenicity of ELF magnetic fields is *inadequate*.

3.5.2.3. In vitro

What was already known on this subject?

There are many observations of cellular responses induced by ELF magnetic fields in vitro. A large number of cellular components, cellular processes, and cellular systems can conceivably be affected by EMF exposure. However, because evidence from theoretical and experimental studies suggest that ELF fields are unlikely to induce DNA damage directly, most studies have been conducted to examine effects on the cell membrane, general and specific gene expression, and signal transduction pathways. In addition, a large number of studies have been performed to investigate effects on processes such as cell proliferation, cell cycle regulation, cell differentiation, metabolism, and various physiological characteristics of cells.

Summaries of in-vitro studies are found in Portier and Wolfe (1998) and IARC (2002). In particular, studies focusing on cell cycle kinetics, proliferation, differentiation, gene expression, DNA damage, signal transduction pathways, apoptosis and membrane characteristics have received attention and are useful in carcinogen evaluation.

What has been achieved since then?

It is generally accepted that ELF fields do not transfer energy to cells in sufficient amounts to cause direct DNA damage and subsequent genotoxic effects. However, it is possible that certain cellular processes, such as DNA repair, are altered by exposure to EMF, which could indirectly affect the structure of DNA causing strand breaks and other chromosomal aberrations, including sister chromatid exchange, or micronucleus formation.

A recent review of genotoxic effects after ELF field exposure (Vijayalaxmi and Obe 2005) analysed studies published 1990-2003 and found a very mixed picture. Overall, studies with positive or negative, or inconclusive, findings were more or less equal in frequency.

By analyzing studies using combinations of ELF and other factors (chemical as well as physical) with known carcinogenic or mutagenic effects, a recent review suggests that effects of these co-exposures are far more frequently appearing in the literature than effects of pure ELF exposure (Juutilainen et al. 2006). This finding suggests a possible interaction of ELF magnetic fields with other agents. Furthermore, this review suggests that since effects frequently appear from 0.10 mT and higher, the radical pair mechanism (Brocklehurst and McLaughlan 1996) could explain the presence of positive findings at such flux densities.

Regarding more recent experimental findings, studies on genotoxic effects performed as part of the REFLEX project have received considerable attention. Different types of human and other mammalian cells (including human fibroblasts and lymphocytes) were exposed to a range of frequencies, flux densities and exposure regimes (Ivancsits et al. 2003a, Ivancsits et al. 2003b, Ivancsits et al. 2005, Winker et al. 2005). Chromosomal damage (DNA strand breaks, micronucleus formation) due to exposure was found in some, but not all cell types (e.g. lymphocytes not affected), after intermittent but not after continuous exposure. Flux density, frequency, and exposure time were important for observed effects, as well as age of cell donors. Similar studies have been performed to ascertain the replicability of the results. The outcome of these studies are at present not completely available and do thus not allow for final interpretation of the data, although at least one study could not confirm the initial findings (Scarfi et al. 2005). Other recent studies using human cells have also shown inconsistent results regarding DNA damage after ELF exposure (alone or in combination with chemical or other physical agents).

These studies vary considerable both in exposure conditions and in techniques employed to test for clastogenic effects, making it difficult to draw firm conclusions at present.

During the last years, there has been increased attention towards effects by ELF fields on free radical homeostasis as an indirect mechanism for several biological responses (Simkó and Mattsson 2004). Experiments with several cellular systems have shown that exposure leads to increased radical levels (e.g. Simkó et al. 2001, Rollwitz et al. 2004, Lupke et al. 2004). Interestingly, DNA damage in human cells (Wolf et al. 2005) exposed to ELF magnetic fields was counteracted by addition of antioxidants, suggesting that ELF magnetic fields can indirectly, possibly via changes in radical homeostasis, affect integrity of DNA.

Finally, based on data obtained with modern high-throughput screening methods and real-time PCR, Lupke et al. (2006) have suggested a comprehensive pathway by which ELF fields could influence cells of the immune system. The suggested pathway includes that membrane-associated events are affected by the fields, causing changes in radical homeostasis, and leading to down-stream events that include changes in gene expression, which could be of importance for regulation of proliferation regulation.

Other biological endpoints relevant for carcinogenesis (e.g. cell cycle regulation, proliferation, apoptosis, gene expression have been investigated in a number of studies. There are mixtures of positive and negative findings, and not allowing for a general conclusion to be made regarding the overall potency for ELF EMF to participate in the carcinogenic process. However, an interesting exception is three replication studies of an older study showing that low intensity 60 Hz MF can inhibit the antiproliferative effect of tamoxifen on human MCF-7 breast cancer cells (Blackman et al. 2001, Ishido et al. 2001, Girgert et al. 2005). These are among the few EMF studies that have yielded reproducible results in several independent laboratories.

Discussion

Published in vitro studies cannot explain epidemiological findings, but do not contradict them either. There is a need for independent replication of certain studies suggesting genotoxic effects and for better understanding of combined effects of ELF magnetic fields with other agents, their effects on free radical homeoastasis, as well as of the possible implications of ELF field inhibition of tamoxifen effects.

3.5.3. Symptoms

What was already known on this subject?

A variety of symptoms (dermatological symptoms such as redness, tingling and burning sensations as well as neurovegetative symptoms such as fatigue, headache, concentration difficulties, nausea, heart palpitation) have been suggested to be caused by ELF field exposure. The term “electromagnetic hypersensitivity” (EHS) has come into common usage based on the reported experience by the afflicted individuals that electric and/or magnetic fields, or vicinity to activated electrical equipment trigger the symptoms.

In the CSTEE opinion of 2001, the possibility of hypersensitive individuals was said to require confirmation and the reports of such health problems did not provide a basis for changes in exposure limits.

What has been achieved since then?

Since the CSTEE opinion of 2001 only few new provocation studies have been published on symptoms and ELF fields (for EHS and RF fields see Chapter 3.3.3. As stated in the WHO Fact sheet on electromagnetic hypersensitivity, well controlled and conducted double-blind studies have not shown any correlation between symptoms and EMF (WHO 2005). Rubin (2005) reviewed 31 provocation studies (using different frequencies and EMF sources) testing more than 700 individuals reporting EHS (Rubin 2005). The results in 24 of these studies did not support a relationship between the health problems and EMF. In seven of the other studies some supporting evidence was found, but in two cases the same research group failed to replicate their own findings. For another three studies Rubin and co-authors suspected that the results were statistical artefacts and in the final two studies the results were mutually incompatible.

Discussion

A relationship between ELF field exposure and symptoms has not been shown in scientific studies. From these results it seems clear that ELF is neither a necessary nor a sufficient factor to trigger health complaints in individuals reporting EHS. Whether ELF may be a contributing factor under some conditions remains to be determined.

3.5.4. Other Health Effects

3.5.4.1. Epidemiology

Following the initial epidemiological study on childhood cancer a great number of other diseases have also been studied in relation to ELF. These diseases include cardiovascular disease, neurodegenerative disease and psychiatric disorders. An effect of heart rate variability seen in laboratory studies was the basis for a hypothesis that ELF exposure might affect the risk of cardiovascular disease and some initial epidemiologic results supported this. However, later well controlled studies have dismissed this hypothesis. For several of the other outcomes the support was never strong. Nevertheless, several neurodegenerative diseases are still considered worthy of study in this respect, and this refers particularly to ALS (amyotrophic lateral sclerosis) and Alzheimer disease (Ahlbom et al. 2001).

3.5.4.2. In vivo

What was already known on this subject?

The previous opinion did not evaluate evidence of health effects from animal studies. However, such data have been reviewed by IARC (2002) and ICNIRP (Bernhardt et al. 2003).

Nervous system and behaviour. While strong ELF fields are known to affect nerve and muscle cells and can be perceived, little evidence was found for effects on the nervous system or behaviour at environmental exposure levels. Effects of ELF magnetic fields on the EEG,

cognition, behaviour and neurotransmitter levels have been described in a few studies, but there are inconsistencies in these data.

Reproduction and development. Several independent studies have suggested effects of ELF magnetic fields on the embryonic development of birds and other non-mammalian species, but the results are inconsistent. The evidence in mammalian species is restricted to minor skeletal anomalies seen in some studies with rats and mice. No consistent effects have been seen in any other reproductive or developmental endpoints in mammals. Minor skeletal variations are relatively common findings in teratological studies on rodents and often considered biologically insignificant.

Endocrine system. There is limited evidence of effects on melatonin production in experimental animals exposed to ELF magnetic fields, but such effects are not supported by other animal studies, and no effects have been seen on human volunteers under controlled laboratory conditions.

Other effects. No consistent evidence have been found for cardiovascular or immune system effects of ELF fields.

What has been achieved since then?

Two recent animal studies have provided evidence that ELF magnetic field exposure may affect melatonin production by modifying the response of dairy cows to the length of photoperiod (Rodriguez et al. 2004) and by affecting the sensitivity of mice to circadian light variations (Kumlin et al. 2005). The results of two new studies are interesting biological observations suggesting EMF interactions with the effects of light (photoperiod) on melatonin production. These observations may help to explain the inconsistencies of earlier research on EMFs and melatonin. However, the results of both studies are only suggestive and should be confirmed in further experiments. The suggested EMF effects on melatonin are subtle and apparently observable only in specific conditions. For these reasons, these results are not helpful for human health risk assessment.

Discussion

Although some studies have described ELF magnetic field effects on the nervous system, animal development and melatonin production, the evidence for such effects is weak and ambiguous. No conclusions concerning possible human health risks can be drawn from these data.

3.5.4.3. In vitro

What was already known on this subject?

Very few in vitro studies have been directed at answering the question if ELF are involved in the onset of other diseases than cancer (Portier and Wolfe 1998). Naturally, many basic cell and molecular studies were performed, mostly to understand more about fundamental interaction mechanisms, but also to understand how certain ELF fields can be used for therapeutic purposes (bone and wound healing especially).

What has been achieved since then and discussion

Few studies are available that directly address any specific disease or group of disease. This is partly due to that few diseases are characterised in such a way that specific disease models exist on the cell level, but also due to that ELF fields have not been convincingly shown to be involved in specific non-cancerous diseases. However, continuously there are reports showing that ELF fields during certain circumstances can give rise to cellular responses that are relevant for diseases of the nervous system, the immune system, endocrine organs, the skeleto-muscular apparatus, etc. Such studies do not at the present time allow extrapolation from the in vitro finding to any specific health state.

3.5.5. Conclusions about ELF fields

The previous opinion came to a similar conclusion regarding carcinogenicity of ELF fields as IARC's evaluation, namely that ELF magnetic fields are possibly carcinogenic. This conclusion was mainly based on epidemiologic results indicating that ELF exposure might be a cause of childhood leukaemia. This assessment is still valid. The fact that the epidemiological results for childhood leukaemia have little support from known mechanisms or experimental studies is intriguing and it is a high research priority to reconcile these data.

For some other diseases, notably breast cancer and cardiovascular diseases, later research has indicated that an association is unlikely. For yet some other diseases, such as neurodegenerative disease and brain cancer, the issue of a link to ELF fields remains open and more research is called for. A relation between ELF fields and symptoms has not been demonstrated.

Of current interest is to arrive at a better understanding of recently published genotoxicity results such as those from the REFLEX study.

3.6. Static fields

3.6.1. Sources and distribution of exposure in population

The number of artificial sources of static magnetic fields is small but there is a rapid development of technologies using static magnetic fields. The number of people with implants that can be affected by static magnetic fields is also growing. Static magnetic fields up to some mT are found in certain occupational settings, e.g., in the aluminium and chloralkali industries, in arc-welding processes, and certain railway and underground systems. A very prominent application is MRI: different types of tissue in the human body can be identified and located by using static magnetic fields, magnetic gradients and RF fields. Close to the device a few hundred mT can be reached. Recently developed devices, currently only used by some research and specialised teams for specific applications, can use up to 10 T.

3.6.2. Health effects

There are only a few epidemiological studies available and the majority of these have focused on cancer risks. There are some reports on reproductive outcomes, and sporadic studies of other outcomes. Overall, few occupational studies have focused specifically on effects of static magnetic fields and exposure assessment has been poor. In summary, the available evidence from epidemiological studies is not sufficient to draw any conclusions about potential health effects of static magnetic field exposure (Feychting 2005b).

A large number of biological studies have been carried out in an effort to detect biological effects of static magnetic fields. The studies include in vitro and in vivo laboratory studies as well as studies on human volunteers. This research has been reviewed comprehensively in UNEP/WHO (2006). Known effects of magnetic fields are orientation of forces applied on biological molecules with magnetic properties: haemoglobin, rhodopsin (visual pigment), free radicals, nitric oxide; these effects are detectable at field levels of about 1 T, without known health consequences.

3.6.3. Conclusions about static fields

Adequate data for proper risk assessment of static magnetic fields is almost totally lacking. The advent of new technology, and in particular MRI equipment, makes it a priority for research.

3.7. Environmental Effects

What was already known on this subject?

The CSTEE opinion did not consider possible environmental impacts of EMF. It is noted that the majority of the relatively few published studies on environmental effects at the time of the CSTEE opinion were laboratory based using short exposure periods, in a single species. In addition some field investigations were reported around intense point sources of EMF particularly overhead power cables.

Certain species have been recognised as likely to be particularly sensitive to EMF namely:

- species that are strongly dependent on magnetic fields for orientation/migration (migratory birds, certain fish and insects, bats etc) and /or possess electric sense organs (e.g. sharks and rays).

- species with a high vulnerability to stress due to poorly developed or impaired defence mechanisms. For example animals with poor thermoregulation may be more vulnerable to the effects of high frequency EMF.

Nonetheless data to characterise this vulnerability and its implications has been very limited. Foster and Repacholi (2000) in their important review of the published data concluded that: ‘attempts at environmental analysis of the effects of environmental EMF, with few exceptions have been scattered in focus, sporadic in publication and uneven in quality’.

The available data thus provided a seriously inadequate basis to assess the risk of EMF to environmental species. However, apart from some local minor effects no significant effects of EMF on environmental species were identified.

What has been achieved since then?

Despite the obvious need for some definitive studies there has been no significant increase in the volume or general quality of research activity in this area since. The majority of these studies have focussed on ELF fields.

There has however been a substantial shift in the form of the studies, in particular in the nature of the endpoints examined. Thus the majority of studies published before 2000 used visible endpoints that are obviously associated with an adverse effect. These had the advantage that their interpretation is quite straightforward. However such endpoints in many cases lack sensitivity. In the last few years an increasing number of studies on the effects of EMF have concentrated on the measurement of more sensitive biomarkers. These have included:

- antioxidant status/ antioxidant enzyme measurements
- stress markers e.g. alanine (plants) heat shock proteins (animals)
- changes in cell growth (e.g. meristems in plants)
- DNA changes (e.g. using the comet assay).

The majority of the few publications on the impact of EMF on environmental species have been in plants. The paper by Monselise et al. (2003) illustrates the use of new markers of cell/tissue change. These authors found that in duck weed, exposed in the laboratory to low intensity sinusoidally varying magnetic fields at 60 and 100Hz, an accumulation of alanine occurred. Alanine accumulation is found as a stress signal following many other kinds of stress. (NB This effect may have parallels with the formation of heat shock proteins in the mammalian kidney in response to various stressors). The authors postulate that this effect arose from free radical generation by the EMF.

Regoli et al. (2005) have reported the effect in snails of low frequency 50Hz EMF fields both in the laboratory and under overhead power cables. A range of biological markers was employed. They demonstrated that the EMF had particular effects on markers of oxidative stress such as catalase and glutathione reductase both in the laboratory and in the field situations. The time to an effect was shown to be dose dependant with effects in the field occurring even at low levels (after 40 days at 0.75μT). The authors attribute the effects to the generation of free radicals by the low frequency electromagnetic fields. The authors also observed a reduction in lysosomal stability and of DNA integrity (at 2.88μT under field conditions). However no physical damage to the snails was reported.

These biomarkers do appear to be detecting changes at low much more environmentally relevant field strengths, however their interpretation in terms of species and ecosystem health is more challenging. Unfortunately these techniques have not focussed particularly on species that would be expected to be among the most sensitive to EMF.

Using more classical endpoints Zaidi and Khatoon (2003) have studied the impact on pollen production of plants growing under overhead power cables using plants grown nearby as a

control group. They found that plants growing under the high tension lines at higher voltages (132000 and 220000 volts) had some decrease in pollen fertility and that the pollen had a higher percentage of diads and diploid pollen grains which is an indicator of genetic change. This finding needs to be examined further.

Several studies have examined the impact of co-exposure to EMF and other stressors in plants. Thus Tafforeau et al. (2004) describe the impact of exposure to EMF combined with calcium deprivation, from either a GSM telephone or a single 2h exposure to 105GHz (from a Gunn oscillator) on meristem production in flax seedlings (i.e. increase in actively dividing cells in the hypocotyls of the growing seedling). An increase in meristem production was observed from each of these EMF sources. It should be noted however that no visible damage to the seedlings was observed in these studies and that other environmental stressors can also produce an increase in meristem production.

Yao et al (2005) have examined the impact of EMF (0.2 and 0.45T) together with UV-B radiation on cucumber seedling growth. EMF alone produced an increase in seedling germination, seedling growth in parallel with an increase in lipid peroxidation. However in combination with UV-B seedling growth and development were significantly decreased.

These studies raise the question as to whether the impact of EMF may be additive with other significant environmental stressors in the field situation and if so the practical consequences of this for individual plants and ecosystems. The data presently available is inadequate to assess this.

Discussion

The continued lack of good quality data in relevant species means that there is insufficient data to identify whether a single exposure standard is appropriate to protect all environmental species from EMF. Similarly the data is totally inadequate to judge whether the environmental standard(s) should be the same or significantly different from those appropriate to protect human health.

The demonstration that the impact of EMF may be additive with some other environmental stressors at least in plants needs further examination to gauge its practical significance.

At present it is not possible to draw any conclusions regarding human health from this data base. Nonetheless, long-term monitoring of the viability of carefully selected species and/or ecosystems may be valuable to gauge the potential of EMF to influence human health.

4. COMMITTEE OPINION

Radio Frequency Fields (RF fields)

In its opinion from 2001 the CSTEE concluded regarding radiofrequency electromagnetic (RF) fields:

"The additional information which has become available on carcinogenic and other nonthermal effects of radiofrequency and microwave radiation frequencies in the last years does not justify a revision of exposure limits set by the Commission on the basis of the conclusions of the 1998 opinion of the Steering Scientific Committee. In particular, in humans, no evidence of carcinogenicity in either children or adults has resulted from epidemiological studies (the size of some of which was very large, although the period of observation was not long enough for a definitive statement). A relatively large series of laboratory studies has not provided evidence of genotoxicity. Subjective symptoms affecting some individuals possibly exist, but not enough information is available on: the levels of exposure producing such effect, on the features underlying individual susceptibility, on the possible biological mechanisms *or* the prevalence of susceptible individuals in different populations. Thus, current knowledge is insufficient for the implementation of measures aimed at the identification and protection of a highly sensitive sub-group of the population."

Based on the scientific rationale presented above the SCENIHR has updated the CSTEE opinion and concludes the following:

The balance of epidemiologic evidence indicates that mobile phone use of less than 10 years does not pose any increased risk of brain tumour or acoustic neuroma. For longer use, data are sparse and any conclusions therefore are uncertain. From the available data, however, it does appear that there is no increased risk for brain tumours in long-term users, with the exception of acoustic neuroma for which there are some indications of an association.

For diseases other than cancer, very little epidemiologic data are available.

A particular consideration is mobile phone use by children. While no specific evidence exists, children or adolescents may be more sensitive to RF field exposure than adults in view of their continuing development. Children of today may also experience a much higher cumulative exposure than previous generations. To date no epidemiologic studies on children are available.

Observational and provocation studies have failed to provide consistent support for a relation between RF exposure and neurovegetative symptoms (sometimes referred to as electromagnetic hypersensitivity).

Studies on neurological effects and reproductive effects have not indicated any health risks at exposure levels below the ICNIRP-limits established in 1998.

Animal studies have not provided evidence that RF fields could induce cancer, enhance the effects of known carcinogens, or accelerate the development of transplanted tumours. The open questions include adequacy of the experimental models used and scarcity of data at high exposure levels.

There is no consistent indication from in vitro research that RF fields affect cells at the nonthermal exposure level.

In conclusion, no health effect has been consistently demonstrated at exposure levels below the ICNIRP-limits established in 1998. However, the data base for this evaluation is seriously limited especially for long-term low-level exposure.

Intermediate Frequency Fields (IF fields)

In its opinion from 2001 the CSTEE did not comment specifically on intermediate frequencies (IF).

Based on the scientific rationale presented above the SCENIHR, however, updates the 2001 opinion with the following statement regarding intermediate frequencies:

Experimental and epidemiological data from the IF range are very sparse. Therefore, assessment of acute health risks in the IF range is currently based on known hazards at lower frequencies and at higher frequencies. Proper evaluation and assessment of possible health effects from long term exposure to IF fields are important because human exposure to such fields is increasing due to new and emerging technologies.

Extremely low frequency fields (ELF fields)

In its 2001 opinion the CSTEE reached the following conclusions regarding extremely low frequency (ELF) fields:
”

- Combined analyses of the epidemiological studies on the association between exposure to ELF and childhood leukaemia have strengthened the evidence of an association. However, given some inconsistencies in exposure measurements and the absence of other criteria commonly used in assessing causality (particularly a plausible explanation of underlying biological mechanisms, see above), the association does not meet adequate criteria for being considered causal. Thus the overall evidence for 50/60 Hz magnetic fields to produce childhood leukaemia must be regarded as being limited .
- The effect, if any, seems to be limited to exposures above 0.4 μT. In European countries, the proportion of children exposed to such levels is less than 1%. Assuming that the risk is doubled among the exposed, in the general population this would roughly correspond to an excess incidence of less than 1% childhood leukaemia. To put this in context, in European countries, the incidence of leukaemia is around 45 per million children (age 0-14) per year.
- Whether changes of recommended exposure limits to 50/60 Hz magnetic fields (12) ought to be recommended on this basis is a problem for risk managers, falling beyond the remit of the CSTEE.
- There is no convincing suggestion of any other carcinogenic effect of ELF on either children or adults. Current information on this respect does not provide clues for reconsidering exposure limits.
- Reports on possibly hypersensitive individuals require confirmation and do not provide a basis for proposing changes in the exposure limits.”

Based on the scientific rationale presented above the SCENIHR updates the previous opinion and concludes the following:

The previous conclusion that ELF fields are a possible carcinogen, chiefly based on childhood leukaemia results, is still valid. There is no known mechanism to explain how electromagnetic field exposure may induce leukaemia. The effects have not been replicated in animal studies.

The calculations in the previous opinion of the possible proportion of childhood leukaemia cases that might be attributed to ELF fields still hold.

A relation between ELF fields and symptoms (sometimes referred to as electrical hypersensitivity) has not been demonstrated.

In addition, for breast cancer and cardiovascular disease, recent research has indicated that an association is unlikely. For neurodegenerative diseases and brain tumours, the link to ELF fields remains uncertain.

Static fields

In its opinion from 2001 the CSTEE did not comment specifically on static magnetic fields.

Based on the scientific rationale presented above the SCENIHR, however, updates the 2001 opinion with the following statement regarding static magnetic fields:

Adequate data for proper risk assessment of static magnetic fields are very sparse. Developments of technologies involving static magnetic fields, e.g. with MRI equipment require risk assessments to be made in relation to the exposure of personnel.

Environmental Effects

The continued lack of good quality data in relevant species means that there is insufficient data to identify whether a single exposure standard is appropriate to protect all environmental species from EMF. Similarly the data is inadequate to judge whether the environmental standards should be the same or significantly different from those appropriate to protect human health.

The Committee is mindful of the mandate that requested particular attention to be paid to a wide variety of issues. In most cases the data available is very limited. Some of these issues will be addressed in further opinions as more data becomes available.

Research Recommendations

In view of the identified important gaps in knowledge the following research recommendations are being made.

RF fields

- A long term prospective cohort study. Such a study would overcome problems that were discussed in relation to existing epidemiological studies, including the Interphone study. These problems include recall bias and other aspects of exposure assessment, selection bias due to high proportions of non-responders, too short induction period, and restriction to intracranial tumours.

- Health effects of RF exposure in children. To date no study on children exists. This issue can also be addressed by studies on immature animals. This research has to take into consideration that dosimetry in children may differ from that in adults.

- Exposure distribution in the population. The advent of personal dosimeters has made it possible to describe individual exposure in the population and to assess the relative contribution of different sources to the total exposure. Such a project would require that groups of people with different characteristics are selected and that they wear dosimeters for a defined period of time.

There are several experimental studies that need to be replicated. Examples are studies on genotoxicity and cognition involving sleep quality parameters. For studies on biomarkers it is essential that the impact on human health is considered. Valid exposure assessment including all relevant sources of exposure is essential. A general comment is that all studies must use high quality dosimetry.

IF fields

- Data on health effects from IF fields are sparse. This issue should be addressed both through epidemiologic and experimental studies.

ELF fields

- The conflict between epidemiological results indicating an increased risk of leukaemia in children exposed to high levels of ELF fields and the lack of support for this from established mechanisms or experimental data is intriguing and requires a better understanding and clarification.

Static fields

- Cohort study on personnel dealing with equipment that generates strong magnetic fields. The start of this would have to be a thorough feasibility study.

- Relevant experimental studies such as studies on carcinogenicity, genotoxicity as well as developmental and neurobehavioural effects would have to be conducted as well.

Additional considerations

- Studies including exposure to combinations of frequencies as well as combinations of electromagnetic fields and other agents need to be considered.

5. MINORITY OPINION

None

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[20] Declared Interest (see minutes of the SCENIHR plenary meeting of 28-29 September 2005: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_mi_007.pdf).