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Health & Consumers

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

# Health Effects of Exposure to EMF

Scientific Committees
- on consumer products
- on emerging and newly identified health risks
- on health and environmental risks



The SCENIHR adopted this opinion at the 28th plenary on 19 January 2009

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

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http://ec.europa.eu/health/ph_risk/risk_en.htm

**ABSTRACT**

The purpose of this opinion is to update the SCENIHR opinion of 21 March 2007 in the light of newly available information, and to provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment.

**1. Update**

**Radio frequency fields (RF fields)**

It is concluded from three independent lines of evidence (epidemiological, animal and in vitro studies) that exposure to RF fields is unlikely to lead to an increase in cancer in humans. However, as the widespread duration of exposure of humans to RF fields from mobile phones is shorter than the induction time of some cancers, further studies are required to identify whether considerably longer-term (well beyond ten years) human exposure to such phones might pose some cancer risk.

Regarding non-carcinogenic outcomes, several studies were performed on subjects reporting subjective symptoms. In the previous opinion, it was concluded that scientific studies had failed to provide support for a relationship between RF exposure and self-reported symptoms. Although an association between RF exposure and single symptoms was indicated in some new studies, taken together, there is a lack of consistency in the findings. Therefore, the conclusion that scientific studies have failed to provide support for an effect of RF fields on self-reported symptoms still holds. Scientific studies have indicated that a nocebo effect (an adverse non-specific effect that is caused by expectation or belief that something is harmful) may play a role in symptom formation. As in the previous opinion, there is no evidence supporting that individuals, including those attributing symptoms to RF exposure, are able to detect RF fields. There is some evidence that RF fields can influence EEG patterns and sleep in humans. However, the health relevance is uncertain and mechanistic explanation is lacking. Further investigation of these effects is needed. Other studies on functions/aspects of the nervous system, such as cognitive functions, sensory functions, structural stability, and cellular responses show no or no consistent effects.

Recent studies have not shown effects from RF fields on human or animal reproduction and development. No new data have appeared that indicate any other effects on human health.

From the risk assessment perspective it is important to recognise that information on possible effects caused by RF fields in children is limited. Furthermore, there is a lack of information on diseases other than those discussed in this report.

**Intermediate frequency fields (IF fields)**

Occupational exposure to IF fields in certain areas is considerably higher than exposure to the general public. However, very little research on IF and health risks in occupational settings or for the general public have been presented since the previous opinion, and no epidemiological studies have appeared. Consequently, the data are still too limited for an appropriate risk assessment.

In view of the increasing occupational exposure to IF among workers in e.g. security, shops, and certain industries it is important that research in this area is given priority.

**Extremely low frequency fields (ELF fields)**

The few new epidemiological and animal studies that have addressed ELF exposure and cancer do not change the previous assessment that ELF magnetic fields are a possible carcinogen and might contribute to an increase in childhood leukaemia. At present, in vitro studies did not provide a mechanistic explanation of this epidemiological finding.

No new studies support a causal relationship between ELF fields and self-reported symptoms.

**ACKNOWLEDGMENTS**

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[1] Declared Interests in his annual Declaration of Interest:
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/doi_scenihr_mattsson_en.pdf

[2] Declared Interest (see minutes of the 23rd SCENIHR plenary meeting of 2 April 2008):
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_mi_023.pdf

[3] Declared Interest (see minutes of the 27th SCENIHR plenary meeting of 26 November 2008):
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_mi_027.pdf

[4] Declared Interest (see minutes of the 28th SCENIHR plenary meeting of 19 January 2009):
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_mi_028.pdf

New epidemiological studies indicate a possible increase in Alzheimer's disease arising from exposure to ELF. Further epidemiological and laboratory investigations of this observation are needed.

Recent animal studies provided an indication for effects on the nervous system at flux densities from 0.10-1.0 mT. However, there are still inconsistencies in the data, and no definite conclusions can be drawn concerning human health effects.

Very few recent in vitro studies have investigated effects from ELF fields on diseases other than cancer and those available have very little relevance. There is a need for hypothesis-based in vitro studies to examine specific diseases.

It is notable that in vivo and in vitro studies show effects at exposure levels (from 0.10 mT and above) to ELF fields that are considerably higher than the levels encountered in the epidemiological studies (μT-levels) which showed an association between exposure and diseases such as childhood leukaemia and Alzheimer's disease. This warrants further investigation.

**Static fields**

Although a fair number of studies have been published since the last opinion, the conclusion drawn there stands: there is still a lack of adequate data for a proper risk assessment of static magnetic fields. More research is necessary, especially to clarify the many mixed and sometimes contradictory results.

Short term effects have been observed primarily on sensory functions for acute exposure. However, there is no consistent evidence for sustained adverse health effects from short term exposure up to several teslas.

**Environmental effects**

The current database is inadequate for the purposes of the assessment of possible risks due to environmental exposure to RF, IF and ELF.

**Research recommendations**

The scientific rationale has identified a number of areas characterised by insufficient and contradictory information regarding possible health associated effects from the various frequency bands of the EMF spectrum. It is recommended that certain knowledge gaps are filled.

**2. Methodological Framework**

The SCENIHR is asked to provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment. The subject is covered in detail in chapter 3.8 of the opinion.

The present opinion provides a methodological framework and guidelines as:

- a general outline of criteria used for making EMF health risk assessment
- a description of the work procedure leading to the overall evaluation
- a specialised section where characteristics and quality criteria regarding dosimetry and exposure assessment, epidemiology, human laboratory studies, in vivo studies, and in vitro studies are presented.

Keywords:

EMF, electromagnetic fields, radiofrequency fields, intermediate frequency fields, extremely low frequency fields, static fields, health effects, human health, environmental effects, SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks

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## EXECUTIVE SUMMARY

The purpose of this opinion is to update the SCENIHR opinion of 21 March 2007 in the light of newly available information, and to provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment.

In order to update the opinion, a scientific rationale was established. This rationale contains relevant scientific knowledge from the physical, engineering, medical and biological sciences which is critically evaluated and summarised. When appropriate, gaps in knowledge are highlighted and suggestions for future important areas of research are included. This opinion also addresses the issue of children's sensitivity, and in particular dosimetry aspects of radiofrequency exposure of children.

The section on the methodological framework summarises the procedure of work which is the foundation of the opinion, namely the scientific rationale.

## 1. Update

### Radio frequency fields (RF fields)

Based on the scientific rationale the SCENIHR has updated the previous opinion and concludes the following:

The question receiving most attention is whether RF field exposure is involved in carcinogenesis. The previous opinion stated that, based on epidemiological findings, mobile phone use for less than ten years is not associated with cancer incidence. Regarding longer use, it was deemed difficult to make an estimate since few persons had used mobile phones for more than ten years.

Since then, a few additional epidemiological studies have been published. Unfortunately they do not significantly extend the exposure period. These studies do not change this assessment.

New improved studies on the association between RF fields from broadcast transmitters and childhood cancer provide evidence against such an association.

Animal studies show that RF fields similar to those from mobile phones, alone or in combination with known carcinogenic factors, are not carcinogenic in laboratory rodents. Certain studies have also employed higher exposure levels (up to 4 W/kg), still with no apparent effects on tumor development.

Furthermore, the in vitro studies regarding genotoxicity fail to provide evidence for an involvement of RF field exposure in DNA-damage.

It is concluded from three independent lines of evidence (epidemiological, animal and in vitro studies) that exposure to RF fields is unlikely to lead to an increase in cancer in humans. However, as the widespread duration of exposure of humans to RF fields from mobile phones is shorter than the induction time of some cancers, further studies are required to identify whether considerably longer-term (well beyond ten years) human exposure to such phones might pose some cancer risk.

Regarding non-carcinogenic outcomes, several studies were performed on subjects reporting subjective symptoms. In the previous opinion, it was concluded that scientific studies had failed to provide support for a relationship between RF exposure and self-reported symptoms. Although an association between RF exposure and single symptoms was indicated in some new studies, taken together, there is a lack of consistency in the findings. Therefore, the conclusion that scientific studies have failed to provide support for an effect of RF fields on self-reported symptoms still holds. Scientific studies have indicated that a nocebo effect (an adverse non-specific effect that is caused by expectation or belief that something is harmful) may play a role in symptom formation. As in the previous opinion, there is no evidence supporting that individuals, including

those attributing symptoms to RF exposure, are able to detect RF fields. There is some evidence that RF fields can influence EEG patterns and sleep in humans. However, the health relevance is uncertain and mechanistic explanation is lacking. Further investigation of these effects is needed. Other studies on functions/aspects of the nervous system, such as cognitive functions, sensory functions, structural stability, and cellular responses show no or no consistent effects.

Recent studies have not shown effects from RF fields on human or animal reproduction and development. No new data have appeared that indicate any other effects on human health.

From the risk assessment perspective it is important to recognise that information on possible effects caused by RF fields in children is limited. Furthermore, there is a lack of information on diseases other than those discussed in this report.

**Intermediate frequency fields (IF fields)**

Occupational exposure to IF fields in certain areas is considerably higher than exposure to the general public. However, very little research on IF and health risks in occupational settings or for the general public have been presented since the previous opinion, and no epidemiological studies have appeared. Consequently, the data are still too limited for an appropriate risk assessment.

In view of the increasing occupational exposure to IF among workers in e.g. security, shops, and certain industries it is important that research in this area is given priority.

**Extremely low frequency fields (ELF fields)**

In its opinion from 2007 the SCENIHR concluded that the previous conclusion regarding ELF fields is still valid, i.e. ELF magnetic fields are a possible carcinogen. It was also concluded that no consistent relationship between ELF fields and self-reported symptoms had been demonstrated. In addition, for breast cancer and cardiovascular disease, an association was considered unlikely. For neurodegenerative diseases and brain tumours, the link to ELF fields remained uncertain.

Based on the scientific rationale presented here the SCENIHR has updated the previous opinion and concludes the following:

The new information available is not sufficient to change the conclusions of the 2007 opinion.

The few new epidemiological and animal studies that have addressed ELF exposure and cancer do not change the previous assessment that ELF magnetic fields are a possible carcinogen and might contribute to an increase in childhood leukaemia. At present, in vitro studies did not provide a mechanistic explanation of this epidemiological finding.

No new studies support a causal relationship between ELF fields and self-reported symptoms.

New epidemiological studies indicate a possible increase in Alzheimer's disease arising from exposure to ELF fields. Further epidemiological and laboratory investigations of this observation are needed.

Recent animal studies provided an indication for effects on the nervous system at flux densities from 0.10-1.0 mT. However, there are still inconsistencies in the data, and no definite conclusions can be drawn concerning human health effects.

Very few recent in vitro studies have investigated effects from ELF fields on diseases other than cancer and those available have very little relevance. There is a need for hypothesis-based in vitro studies to examine specific diseases.

It is notable that in vivo and in vitro studies show effects at exposure levels (from 0.10 mT and above) to ELF fields that are considerably higher than the levels encountered in

the epidemiological studies (μT-levels) which showed an association between exposure and diseases such as childhood leukaemia and Alzheimer's disease. This warrants further investigation.

**Static fields**

In its opinion from 2007 the SCENIHR concluded that data for proper risk assessment regarding static magnetic fields are very sparse.

Based on the scientific rationale presented here the SCENIHR has updated the previous opinion and concludes the following:

Although a fair number of studies have been published since the last opinion, the conclusion drawn there stands: there is still a lack of adequate data for a proper risk assessment of static magnetic fields. More research is necessary, especially to clarify the many mixed and sometimes contradictory results.

Short term effects have been observed primarily on sensory functions for acute exposure. However, there is no consistent evidence for sustained adverse health effects from short term exposure up to several teslas.

**Environmental effects**

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

The current database is inadequate for the purposes of the assessment of possible risks due to environmental exposure to RF, IF and ELF fields.

**Research recommendations**

The scientific rationale has identified a number of areas characterised by insufficient and contradictory information regarding possible health associated effects from the various frequency bands of the EMF spectrum. It is recommended that certain knowledge gaps are filled.

## 2. Methodological Framework

The SCENIHR is asked to provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment. The subject is covered in detail in chapter 3.8 of the opinion.

The present opinion provides a methodological framework and guidelines as:

- a general outline of criteria used for making EMF health risk assessment
- a description of the work procedure leading to the overall evaluation
- a specialised section where characteristics and quality criteria regarding dosimetry and exposure assessment, epidemiology, human laboratory studies, in vivo studies, and in vitro studies are presented

## 1. BACKGROUND[5]

Council Recommendation 1999/519/EC of 12 July 1999[6] on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz) fixes basic restrictions and reference levels for the exposure of the general public 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)[7]. In response to a questionnaire sent to Member States in 2000, all MS notified the Commission to have implemented the provisions of Council Recommendation. The Commission is currently preparing a second report to the Council on the implementation of the Recommendation, updating the earlier implementation report of 2002[8] based on replies to a new questionnaire sent to the 27 Member States.

For workers, the Council and the Parliament have adopted Directive 2004/40/EC of 29 April 2004[9] on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (EMFs). However, the Commission intends to postpone the deadline for implementation of this Directive in order to present a proposal for amendment based on the ongoing revision of the international guidelines.

The ICNIRP guidelines had been endorsed by the Scientific Steering Committee (SSC)[10] in its opinion on health effects of EMFs of 25–26 June 1998. The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) prepared an update of the Scientific Steering Committee's opinion and concluded in its opinion on "Possible effects of Electromagnetic Fields (EMF), Radio Frequency Fields (RF) and Microwave Radiation on human health", of 30 October 2001, 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[11].

The SCENIHR had been requested to update this opinion due to the potentially increasing exposure to EMF consequent to the further growth in the use of electricity from the telecommunications industry, including 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, 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. Furthermore, a substantial number of scientific publications and reviews on the possible health effects of EMF (focusing mostly on mobile telephones) had become available since the CSTEE opinion in addition to Community funded and other research activities.

The opinion delivered by the SCENIHR in March 2007[12] confirmed the earlier conclusion of the CSTEE and highlighted again the need for additional data and research on this issue. The SCENIHR has recommended that specific research areas, as outlined in the opinion, be addressed.

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[5] Chapters 1 and 2 reflect the mandate to the SCENIHR as provided by the EC.

[6] http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_199/l_19919990730en00590070.pdf (OJ L 199/59, 30.7.1999)

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

[8] http://europa.eu.int/comm/health/ph_determinants/environment/EMF/implement_rep_en.pdf

[9] http://eur-lex.europa.eu/LexUriServ/site/en/oj/2004/l_184/l_18420040524en00010009.pdf (OJ L 184/1, 24.5.2004)

[10] http://europa.eu.int/comm/food/fs/sc/ssc/index_en.html

[11] 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, and mobile telephony. The 2.45 GHz frequency is mainly used in domestic and industrial microwave ovens.

[12] http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_007.pdf

As part of its mandate, the SCENIHR is asked to continuously monitor new information that may influence the assessment of risks to human health in this area and to provide regular updates on the scientific evidence base to the Commission. Recently, there have been several articles and broadcasts in the general press and media referring to new scientific evidence on possible effects on human health of exposure to EMF notably from mobile phone technology. Some of these, in particular the BioInitiative Report[13] state that new evidence proves the carcinogenic nature of exposure to EMF. The BioInitiative Report is one of several reports and statements by scientists diverging from the scientific position taken by other research groups, including that of the SCENIHR.

Consequently, the SCENIHR is being asked to examine this and other relevant publications that were published after its own scientific opinion in March 2007 and to address in particular the questions listed in the Terms of Reference.

## 2. TERMS OF REFERENCE

1. The Committee is requested to update the SCENIHR opinion of 21 March 2007[12] in the light of newly available information.
2. The Committee should provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment. The Committee shall use as its starting point the relevant sections of its previous scientific opinion on EMF.

[13] http://www.bioinitiative.org/report/index.htm

# 3. SCIENTIFIC RATIONALE

## 3.1. Introduction

The purpose of this opinion is to update the SCENIHR opinion of 21 March 2007 in the light of newly available information, and to provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment.

In order to update the opinion, this section establishes the scientific rationale which is needed to provide the requested opinion. Relevant scientific knowledge from the physical, engineering, medical and biological sciences is critically evaluated and summarised. When appropriate, gaps in knowledge are highlighted and suggestions for future important areas of research are included. This opinion also addresses the issue of children's sensitivity, and in particular dosimetry aspects of radiofrequency exposure of children.

As in the previous opinion, the section is divided into four separate sub-sections based on frequency bands (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 fields, respectively. 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 organised according to outcome. For each outcome, relevant human, in vivo, and in vitro data are covered.

There are also frequency bands that are not covered in this opinion since relevant data regarding possible effects on human health are not available or not directly mentioned in the mandate. This includes a part of the radio frequency spectrum which is the lower frequency Terahertz (THz) radiation. Terahertz applications operate between the optical spectrum on the short wavelength side and the radio frequency fields on the longer wavelength side. Applications are mainly imaging and spectroscopy. Other parts of the electromagnetic spectrum that are not discussed include the infrared and ultraviolet frequency bands.

## 3.2. Methods

This opinion represents an update of the earlier opinion of SCENIHR (2007). It is principally based on original scientific work published between January 2007 and December 2008 in English-language peer-reviewed scientific journals. The specific references that are cited constitute only a part of all the literature considered. The aim has been to cite only those studies that contribute significantly to the opinion. The inclusion criteria are discussed in detail in chapter 3.8 - Methodological framework.

## 3.3. Radio Frequency Fields (RF fields)

### 3.3.1. Sources and distribution of exposure in the population

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. However, information on the exposure of individual persons is still scarce. Such information is mainly needed for epidemiological studies, and there is a need to optimise methodology to assess

individual exposure, e.g. by using and further developing existing exposimeters. It is furthermore important to consider multi-source exposure and not to focus on single sources, e.g. mobile phone base stations. The fact that there is a continuous change of technologies, e.g. from analogue to digital TV, or appearance of new technologies like ultra-wide band (UWB) on the market, leads to changing exposure patterns of the population on a long term scale. This requires identification of exposure patterns at adequate intervals. The existing RF sources are operated in different frequency bands and can be subdivided into several categories:

**Sources operated close to the human body**

Many devices of this type are mobile RF transmitters such as mobile phones. Worldwide, there are more than 2.5 billion people using mobile phones, a number which has been continuously increasing during recent years. The most common mobile communication technologies in Europe are the digital technologies GSM 900, GSM 1800 and UMTS. Analogue technologies are hardly used any more in Europe.

Before mobile phones can be introduced 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. Standardised methods specified by the European Committee for Electrical Standardisation (CENELEC) are used to test mobile phones in Europe. 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. As an example, a 2 W peak power corresponds to 250 mW maximum time averaged transmitted power for GSM at 900 MHz. Maximum local SAR values averaged over 10 g of tissue range typically between 0.2 and 1.5 W/kg, depending on the type of mobile phone. The emitted power is often orders of magnitude lower than the maximum power, leading to a much lower actual exposure due to power control and discontinuous transmission mode (output power is different when the user is talking or listening) for GSM and UMTS phones. The power control of a mobile phone automatically reduces the emitted power, by up to a factor of 1,000 for GSM and about 100,000,000 for UMTS if higher intensity is not needed for stable transmission. The exposure arising from a UMTS mobile phone can typically be expected to be lower than the one from a GSM phone. The actual transmitted power depends in both cases on several factors, e.g. the cell size of the respective base station and the type of the mobile phone. A comparison showed that the exposure due to a UMTS phone was about 1,000 times lower compared to the exposure due to a GSM phone (Baumann et al. 2006). No exposure occurs from a mobile phone which is switched off. Phones in standby mode cause 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 transmission path to base stations and on the traffic requested by the communication protocol and by incoming/outgoing SMS and the position of the phone.

In addition to mobile phones, other wireless applications like cordless phones, e.g. DECT or WLAN systems are very common. They are usually operated with lower output power compared to mobile phones and the exposure is typically below the level of mobile phones. The maximum time averaged power level of a DECT base station is 250 mW (worst case for a professional application handling communication with 25 handsets in parallel, a typical household application communicating with one handset has a time averaged power of 10 mW), and for a DECT handset 10 mW. The peak value of a WLAN terminal is 200 mW; however the averaged power depends on the traffic and is usually considerably lower. Therefore, the exposure from such systems is usually below that of mobile phones. However, under certain circumstances, e.g. closeness to WLAN access points, exposure due to WLAN or DECT systems can become higher compared to exposure from GSM or UMTS mobile phones.

Another system starting to be used in Europe is UWB, where exposure can be expected to be well below 0.1 mW/m$^2$. Applications include communication as well as detection

and identification. Wireless microphone systems are already available and a number of office, home entertainment, and medical applications are likely to enter the market in the near future. Ground and wall penetrating systems can be used to detect buried persons, and UWB radar systems can be used to avoid traffic collisions and to transmit traffic data (Schmid et al. 2008; article in German).

Anti-theft devices that are typically operated at the exits of shops or similar areas have become more and more common during recent years. Some of the existing systems are operating in the RF range. The exposure depends on the type of system and is below the exposure limits. Finally, several industrial appliances are operated in the RF and microwave range, for heating (e.g. RF sealers) or maintenance of broadcasting stations. The exposure of workers operating such systems can reach values close to or even above the limits of the Directive 2004/40/EC.

### Sources operated far away from the human body

Such sources are typically fixed installed RF transmitters like mobile phone base stations and broadcast transmitters. In most European countries, base stations have become ubiquitous to guarantee connectivity in large areas; e.g. around 18,000 base stations are operated in Austria. The so called reference level for the exposure of the general population at 900 MHz (an important frequency for mobile communication) set in the European Council Recommendation 1999/519/EC is 4.5 W/m². The reference levels are frequency dependent and other limits have to be applied for other frequencies. 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 just 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. Exposure levels of ca 300 mW/m² have been noted close to the fences of very powerful transmitters. Regarding the new digital TV technology (DVB-T), exposures between 0.003 and 40 mW/m² were registered in an Austrian study (Giczi 2004; article in German). 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. 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 digital audio broadcasting systems and WiMAX.

### Medical applications

The usual frequencies that are allowed for industrial, scientific, and medical applications are similar to most industrial sources: 27 MHz, 433 MHz and 2.45 GHz. Several medical applications use electromagnetic fields in the RF range. Therapeutic applications include soft tissue healing appliances, hyperthermia for cancer treatment, and diathermy. These expose the patient to field strenghts well above the recommended limit values to achieve the beneficial intended biological effects, which include tissue heating (analgetic applications) or burning cells (to kill cancer cells). MRI devices commonly use 63 MHz RF fields in addition to static and time-variable gradient fields. In all 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.

### 3.3.2. Cancer

Studies on cancer in relation to mobile telephony have focused on intracranial tumours and acoustic neuromas because deposition of energy from RF fields from a mobile phone is mainly within a small area of the head near the handset. There are also some studies investigating the risk for other tumors in the head and neck region, notably tumors in the salivary glands. A small number of studies have investigated the association between exposure from RF fields from broadcast transmitters and tumour development. In animal studies, where sometimes whole body exposure is assessed, other forms of cancer have also been investigated. The in vitro studies considered aim to find out if biological effects relevant for carcinogenesis can occur at RF field levels that are typical for mobile telephony.

#### 3.3.2.1. Epidemiology

**What was already known on this subject?**

In the previous opinion of 2007 a detailed discussion of epidemiological studies on mobile phone use in relation to brain tumour risk was presented. Altogether these studies provided evidence that mobile phone use for up to ten years is not associated with an increased risk of any type of brain tumours. With regard to a longer duration of use, uncertainties remained, as the number of such long-term mobile phone users was still small. Although none of the well-conducted studies indicated a substantial risk increase, they left the possibility open for a small-to-moderate risk increase among frequent mobile phone users, especially for glioma and acoustic neuroma.

**What has been achieved since then?**

Mobile phones and the risk of brain tumours

More data on mobile phones and brain tumours (including acoustic neuroma) became available from the Interphone study (Cardis et al. 2007), although the pooled analysis of data of the 13 countries involved has not yet been published. 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. The new reports include the national studies from Norway (Klaeboe et al. 2007: glioma, meningioma, acoustic neuroma); France (Hours et al. 2007: glioma, meningioma, acoustic neuroma; article in French); Japan (Takebayashi et al. 2006: acoustic neuroma), Takebayashi et al. 2008 (glioma, meningioma); Germany (Schlehofer et al. 2007: acoustic neuroma); and two pooled analyses from the Nordic countries and the UK, one on glioma (Lahkola et al. 2007) and one on meningioma (Lahkola et al. 2008). Taken together, data based on about 60-70% of the total brain tumour cases of Interphone are published. As the remaining data were collected following the same study protocol, the already published majority of data defines limits of what is to be expected.

Most of the new Interphone reports were based on rather small sample sizes, particularly for acoustic neuroma (Takebayashi et al. 2006, Klaeboe et al. 2007, Hours et al. 2007, Schlehofer et al. 2007). For glioma and meningioma, the few new reports are consistent with the finding of no overall association derived from the previously published studies and hardly contributed to the state of knowledge about long-term mobile phone users (Klaeboe et al. 2007, Hours et al. 2007). The two pooled analyses by Lahkola et al. (2007, 2008) utilise larger numbers of subjects. However, as they combine the previously published data from Denmark, Sweden and the UK with new data from only Norway and Finland, the new insights are again limited. In the pooled analysis of glioma (Lahkola et al. 2007) including 1,521 cases, no increased relative risk was seen for long-term mobile phone users of ten years or more (odds ratio (OR) 0.95, 95% confidence interval (CI) 0.74-1.23). There were also no increased relative risk estimates for the highest categories of lifetime cumulative number of calls or lifetime cumulative duration

of calls. In the meningioma pooled analysis (Lahkola et al. 2008) including 1,209 cases, most relative risk estimates were slightly decreased, e.g. for mobile phone users of ten years or more (OR=0.91, 95% CI: 0.67-1.25). The Japanese study was the first to go beyond analyses based on the years and the amount of mobile phone use (Takebayashi et al. 2008), by attempting to estimate the maximal specific absorption rate (SAR) value inside the tumour. No consistent pattern of relative risk estimates emerged from the use of various SAR values and both increased and decreased ORs were observed in the highest exposure categories.

Absorption of RF EMF from mobile phones is localised; therefore the preferred side of the head during mobile phone use becomes an important parameter of the exposure estimation. At the same time, this parameter is highly susceptible to reporting bias as cases know which side of their head is affected by the tumour, while controls do not know which side of their head will be relevant for analyses (in a matched study, it is the side of the head where the tumour occurred in their corresponding matched case). Therefore overreporting of the affected side of the head among cases may occur. This problem has already been identified in the very first case-control study on mobile phones and brain tumours using the approach of ipsi- and contralateral analyses (Hardell et al. 2002). An increased relative risk estimate for ipsilateral mobile phone use (preferred side of the head during mobile phone use corresponds to the side of the head where the tumour occurred) was compensated by a decreased relative risk estimate for contralateral mobile phone use (preferred side of the head during mobile phone use is opposite to the side of the head where the tumour occurred). This continued to be a problem in all subsequent case-control studies. Hence, the finding by Lahkola et al. (2007) for glioma risk among long-term mobile phone users of ten years or more received some attention when an observed increased OR for ipsilateral use was not compensated by an accordingly decreased OR for contralateral use (ORs of 1.39 versus 0.98, Table 1). An increased OR for ipsilateral use and an OR close to 1.0 for contralateral use would be expected under a hypothesized real effect. However, assuming causality, one would also expect that the effect of laterality becomes stronger with increasing exposure, i.e. the ratio of the two ORs for ipsilateral and contralateral use would be more or less close to 1.0 among short-term or occasional mobile phone users, but would then grow with increasing exposure. As displayed by the ratio between the ORs for ipsilateral and contralateral use in Table 1, this was not the case in the Lahkola et al. (2007) study, with laterality ratios being similar across exposure categories and being increased already among short-term users.

Hence, severe concern about reporting bias remains. Moreover, as the overall OR for long-term users was still below 1.0, the effect of an increased OR for ipsilateral use may be compensated by decreased ORs for cases with centrally located tumours or a missing value in the preferred side of use variable (data not shown separately). In conclusion, there is evidence that laterality analyses of retrospective studies are affected by reporting bias. It remains an open question, however, whether increased ORs observed for ipsilateral use in many studies are a mixture of a true effect and reporting bias or are due to such reporting bias in their entirety.

Two meta-analyses of case-control studies have been published on this topic since the last opinion statement (Hardell et al. 2008, Kan et al. 2008). No overall risk for brain tumors were found in the work by Kan et al. (2008), whereas both meta-analyses show an increased risk for brain tumors in long-term users (≥ 10 years). However, both studies are non-informative because of inappropriate exclusion criteria and combination of studies.

**Table 1 Mobile phone use and the risk of brain tumours and parotid gland tumours: relative risk estimates for time since first use[a] and by ipsilateral versus contralateral use[b]**

| Study | | Regular Use | Ipsilateral | Contralateral | Ratio |
|---|---|---|---|---|---|
| | Exposure | RR (95% CI)[c] | RR (95% CI)[c] | RR (95% CI)[c] | i/c[d] |
| Lahkola et al. (2007): Glioma | | | | | |
| | Not exposed[e] | 1.00 | 1.00 | 1.00 | |
| | 1.5 - 4 years | 0.77 (0.65, 0.92) | 1.08 (0.88, 1.31) | 0.70 (0.57, 0.87) | 1.54 |
| | 5 - 9 years | 0.75 (0.62, 0.90) | 1.10 (0.89, 1.35) | 0.74 (0.59, 0.92) | 1.49 |
| | 10+ years | 0.95 (0.74, 1.23) | 1.39 (1.01, 1.92) | 0.98 (0.71, 1.37) | 1.42 |
| Lahkola et al. (2008): Meningioma | | | | | |
| | Not exposed[e] | 1.00 | 1.00 | 1.00 | |
| | 1.5 - 4 years | 0.72 (0.60, 0.86) | 0.77 (0.60, 0.99) | 0.62 (0.47, 0.80) | 1.24 |
| | 5 - 9 years | 0.78 (0.64, 0.96) | 0.78 (0.56, 1.04) | 0.78 (0.58, 1.05) | 1.00 |
| | 10+ years | 0.91 (0.67, 1.25) | 1.05 (0.67, 1.65) | 0.62 (0.38, 1.03) | 1.69 |
| Sadetzki et al. (2008): Parotid gland | | | | | |
| | Not exposed[e] | 1.00 | 1.00 | 1.00 | |
| | 1 - 4 years | 0.82 (0.61, 1.10) | 0.88 (0.63, 1.24) | 0.82 (0.56, 1.21) | 1.07 |
| | 5 - 9 years | 0.95 (0.70, 1.30) | 1.14 (0.79, 1.65) | 0.96 (0.63, 1.46) | 1.19 |
| | 10+ years | 0.86 (0.42, 1.77) | 1.60 (0.68, 3.72) | 0.58 (0.15, 2.32) | 2.76 |

[a] years since first regular use (one call per week or more over a period of six months or longer) of ten years or more

[b] ipsilateral use: preferred side of the head during mobile phone use corresponds to the side of the head where the tumour is located; contralateral use: preferred side of the head during mobile phone use corresponds to the side of the head opposite to the tumour

[c] relative risk estimated by the odds ratio and 95% confidence interval

[d] ratio of the relative risk estimates for ipsilateral use by contralateral use

[e] defined as never being a regular user (never one call per week or more over a period of six months or longer) or becoming a regular user less than 1.5 years ago in Lahkola et al. (2007, 2008) or less than 1 year ago in Sadetzki et al. (2008)

Validation studies conducted in the context of Interphone provided new information on the shortcomings of investigating this research question by means of an interview-based case-control study. Low response rates, particularly among controls, introduce bias if participation is related to mobile phone use (Cardis et al. 2007). This is a likely explanation for why many relative risk estimates in the Interphone study are actually below 1.0 (see for example Table 1). As ORs are particularly low in the subsets of shortest mobile phone use (Table 1), early symptoms before the diagnosis of the disease may impede regular mobile phone use among cases, which adds to the observation of a spurious protective effect. A comparison of self-reported mobile phone use and past traffic records from mobile phone operators confirmed previously observed general recall problems, but also indicated that there may be different patterns between cases and controls (Vrijheid et al. 2008). Although epidemiology is used to deal with imperfect measures, such bias-related uncertainty may seriously hamper straightforward conclusions.

Mobile phones and parotid gland tumours

In addition to the brain tumour data, the first two reports on parotid gland tumour risk have been published from the Interphone study. A pooled analysis of data from Denmark and Sweden showed no association with either short-term or long-term mobile phone

use, but the study included only 60 cases of malignant parotid gland tumours (Lönn et al. 2006). Another 58 cases were accrued in the Interphone study in Israel (Sadetzki et al. 2008), showing similar results. The number of benign parotid gland tumours was larger in Israel (n=402) than in Denmark/Sweden (n=112) (Lönn et al. 2006). The Israeli study did not show an association with long-term use of mobile phones of ten years or more for benign and malignant parotid gland tumour combined (OR=0.86, 95% CI: 0.42-1.77). Although an effect of ipsilateral exposure was seen particularly in the subset of long-term users (Table 1), the relative risk estimate in this subset was decreased accordingly for contralateral use (Sadetzki et al. 2008).

Radio and television broadcast transmitters and childhood leukaemia

Prior to the previous opinion, there were only few studies on environmental radiofrequency electromagnetic fields (RF-EMF) exposure and the risk of cancer. As all these studies were ecological studies or cluster analyses, no conclusions could be drawn. Some studies, however, indicated an increased risk of leukaemia in children living close to strong radio or television broadcast transmitters (Ahlbom et al. 2004). Results from two case-control studies have recently become available. The first case-control study in South Korea involved 1,928 childhood leukaemia cases diagnosed between 1993 and 1999 and an equal number of hospital-based controls (Ha et al. 2007). RF-EMF exposure was calculated using a field prediction program and also the distance to one of 31 included amplitude-modulated (AM) radio transmitters was estimated. Although there was an excess of leukaemias in a 2 km radius of the transmitters (OR=2.15, 95% CI: 1.00-4.67), no association was seen between childhood leukaemia risk and the predicted field strengths (OR=0.83, 95% CI: 0.63-1.08 for the highest quartile of exposure); in the intermediate categories, relative risks were also decreased (revised main results table in the reply to a letter by Schüz et al. (2008)). The second case-control study was conducted in German municipalities surrounding 16 AM radio and 8 frequency-modulated (FM) radio and television broadcast transmitters (Merzenich et al. 2008). An exposure assessment for 1,959 childhood leukaemia cases diagnosed between 1984 and 2003 and 5,848 population-based controls was performed using field prediction programs. The main OR was 0.86 (95% CI: 0.67-1.11), comparing the upper ≥ 95% and lower < 90% quantile of the field distribution. No increased risk was seen for the first exposure decade alone, which was the time period without potential dilution from mobile telecommunication networks. The OR was 1.04 (95% CI: 0.65-1.67) among children living within 2 km of the nearest broadcast transmitter compared to those living at a distance of 10-15 km.

#### 3.3.2.2. In vivo

**What was already known on this subject?**

The possible carcinogenicity of RF field exposure has been investigated in a number of experimental systems, with essentially negative results. The positive finding of increased lymphoma incidence in the lymphoma-prone transgenic *Eμ-Pim1* mouse strain (Repacholi et al. 1997) is an interesting exception. The previous opinion of 2007 discussed a study (Utteridge et al. 2002) that failed to confirm the results of the Repacholi study, as well as several other studies that had evaluated carcinogenicity of RF fields in a variety of experimental models. Several studies had tested carcinogenicity of RF fields alone in normal or genetically predisposed animals, and several other studies had tested possible co-carcinogenicity together with known chemical or physical carcinogens. No statistically significant ($p<0.05$) increase of tumour incidence was found in any of the studies reviewed. Questions that remained were relevance of the experimental models to human carcinogenesis and the relatively low exposure levels used in most of the studies.

**What has been achieved since then?**

A number of lifetime and chronic exposure studies have been performed on laboratory animals.

The study reported by Oberto et al. (2007) was another replication and an extension of the Repacholi et al. (1997) study with *Eμ-Pim1* transgenic mice exposed to a GSM-type signal. There were several methodological improvements compared to the original study by Repacholi et al. (1997) including use of several exposure levels (0.5, 1.4 or 4.0 W kg/kg), well-defined dosimetry and more uniform exposure (achieved by restraining the animals) and extensive histopathology of all animals. Compared to the sham-exposed controls, survival was reduced in the animals exposed to RF fields. The intergroup differences were statistically significant ($p<0.05$) in the male animals, but there was no trend with increasing exposure level (lowest survival at 0.5 W/kg). No increase in lymphoma incidence was observed in the RF exposed groups. Concerning other neoplastic findings, Harderian gland adenomas were increased in male mice, with a significant dose-related trend ($p<0.01$). However, this trend was not supported by the findings on female animals, i.e. no tumours were observed in the highest exposure groups. For the statistical analysis, the cage control and the sham-exposed control groups were combined, which is not a valid procedure given the differences in body weight development and tumour incidence between these groups (these differences are most likely related to restraint of the sham-exposed animals). However, based on the data reported in the paper, a different analysis strategy (comparison to the sham-exposed group only) would not essentially change the conclusion that there was no effect of RF electromagnetic fields on tumours at any site. The reduced survival in the exposed animals is not thoroughly discussed by the authors; this finding remains unexplained and difficult to interpret without detailed information about the causes of death.

In another study with lymphoma-prone animals (Sommer et al. 2007), unrestrained AKR/J mice, 160 animals per group, were chronically sham-exposed or exposed to a generic UMTS test signal for 24 h/day, 7 days/week at a SAR of 0.4 W kg/kg. No effect from exposure to RF electromagnetic fields was seen on lymphoma incidence, survival time or severity of the disease.

Two studies evaluated carcinogenicity of both a GSM signal at 902 MHz and a DCS signal at 1,747 MHz in conventional laboratory animals including B6C3F1 mice (Tillmann et al. 2007) and Wistar rats (Smith et al. 2007). Three exposure levels from 0.4 to 4 W/kg (and sham exposure) were used. The study on mice (Tillman et al. 2007) produced no evidence that RF field exposure increased the incidence or severity of neoplastic or non-neoplastic lesions, or resulted in any other adverse health effects. Interestingly however, the incidence of liver adenomas in males decreased with increasing exposure level, with a statistically significant ($p<0.05$) difference between the highest exposure and the sham exposed group. However, comparison with published tumour rates in untreated mice revealed that the observed tumour rates were within the range of historical control data. The study on rats (Smith et al. 2007) was a combined chronic toxicity and carcinogenicity study, and some of the animals (15 males and 15 females per group) were killed at 52 weeks from the start of the study. There were no significant differences in the incidence, multiplicity, latency or severity of neoplasms, or any other adverse responses to RF field exposure.

Saran et al. (2007) used *Patched1* heterozygous knockout mice, an animal model in which exposure of newborn animals to ionizing radiation enhances development of brain tumours (medulloblastoma). Newborn *Patched1* mice and their wild-type siblings were exposed to 900 MHz GSM-type radiation at 0.4 W/kg for 30 min twice a day for 5 days. No differences in survival were found between exposed and sham-exposed animals. Medulloblastomas (in 7 animals) and rhabdomyosarcomas (in 56 animals) were found in the *Patched1* mice but not in the wild-type animals. The incidence of rhabdomyosarcoma was higher (68%, 36 animals) in the exposed group than in the sham-exposed group (51%, 20 animals), but this difference was not statistically significant ($p>0.05$). The

incidences of medulloblastomas, other tumours or preneoplastic skin lesions did not differ between the exposed and sham-exposed groups.

Shirai et al. (2007) investigated possible promoting effect of 1.95 MHz RF fields (W-CDMA signal) on ethylnitrosourea (ENU)-induced brain tumours in Fischer 344 rats. The brain tumour incidences of both females and males tended to be higher in the two RF exposed groups (0.67 and 2 W/kg) than in the sham-exposed group, but no statistically significant ($p<0.05$) effects were reported. Moreover, an opposite trend (decreasing incidence with increasing exposure level) was observed in a previous similar study (Shirai et al. 2005), indicating that the trends observed are most likely incidental.

Hruby et al. (2008) treated 100 female Sprague-Dawley rats per group with 7,12-Dimethylbenz(a)anthracene (DMBA) to induce mammary tumours and then exposed the animals to 900 MHz GSM signals. The exposure groups included cage controls, sham-exposed controls and three exposure groups (0.4, 1.3 and 4.0 W/kg). The exposed and sham exposed animals were restrained during exposure. There were several statistically significant ($p<0.05$) differences between RF field-exposed groups and the sham-exposed group. All RF-exposed groups had significantly more palpable mammary gland tissue masses than the sham-exposed group, but there was no clear increase with increasing exposure level (no dose-response relationship). The incidence of malignant mammary tissue tumours was lowest in the sham-exposed group, and significantly increased in the high exposure group. However, the incidence of benign tumours was significantly lower in the three RF exposed groups than in the sham-exposed group. The number of animals with benign or malignant neoplasms was similar in the sham-exposed group and in the three RF-exposed groups. Given that the DMBA mammary tumour model is known to be prone to high variations in the results, the authors concluded that the differences between the groups were most likely incidental. Comparison with the results of the almost identical study of Yu et al. (2006) supports this conclusion: both studies reported similar development of mammary tumours in three groups, but lower rate of development (seen in the appearance of palpable tumours and/or reduced malignancy) in one group. Hruby et al. (2008) found the lowest rate of development in the sham-exposed group, while Yu et al. (2006) found it in the 0.44 W $kg^{-1}$ group. Both studies consistently reported highest incidence of tumours in the cage control group, which is most likely related to the different handling of the cage control animals (different stress level, differences in food intake).

#### 3.3.2.3. In vitro

**What was already known on this subject?**

In the previous opinion of 2007 a detailed description of in vitro studies was presented and discussed. Most of the studies did not provide evidence for any effect of RF field exposure at non-thermal intensity levels on cellular systems.

**What has been achieved since then?**

Many in vitro studies have been performed over the last two years. Both the genotoxic and non-genotoxic cancer-relevant effects are reviewed below.

Genotoxic effects

To test for genotoxicity, several techniques are available as no single assay is capable of detecting all genotoxic effects. These techniques include inter alia the micronucleus test (MN), DNA strand break test (comet assay), as well as tests for chromosomal aberration (CA) and sister chromatide exchange (SCE). The CA assay detects clastogenic (chromosomal breakage) or aneugenic (whole chromosome loss or gain) effects by direct examination of chromosomes in metaphase cells. The MN assay shows micronuclei containing nuclear DNA from chromosome fragments or whole chromosomes which were not incorporated into daughter nuclei at anaphase of mitosis. The assay detects the DNA

damage in interphase cells. The SCE assay assesses DNA breakage and repair. SCEs are reciprocal exchanges of DNA segments between sister chromatids during S-phase. The molecular basis is unknown and SCE induction does not necessarily indicate mutagenicity. The comet assay or single cell gel electrophoresis (SCGE) quantify and analyse DNA damage in individual interphase cells, and can detect double strand breaks, single strand breaks, alkali labile sites, oxidative base damage, and DNA cross-linking with DNA or protein. It is also used to monitor DNA repair.

Several genotoxicity studies have been performed, with different outcomes. Using the MN test and the alkaline SCGE/comet assay no effects were detected in human lymphocytes, when exposure was administered at different stages of the cell cycle (24 to 68 h using 1950 MHz, 6 min RF on, 2 h RF off, 2.2 W/kg) (Zeni et al. 2008). Also, no increase in DNA strand breaks was found in trophoblast cells (Valbonesi et al. 2008). Schwarz et al. (2008) used the alkaline comet and the MN assays to study genotoxic effects of UMTS exposure (24 h, SAR 0.05 and 0.1 W/kg) on human fibroblasts and lymphocytes. They found that the exposure increased DNA damage at both SAR values according to these assays in fibroblasts, but not in lymphocytes. However, the scientific validity of this study is unclear, making any interpretation of the study difficult at this point.

Kim et al. (Kim JY et al. 2008) investigated mammalian cells exposed to 835-MHz RF fields (4 W/kg) alone, and in combination with a clastogen (ethylmethanesulfonate (EMS)). Genotoxicity was studied using the alkaline comet assay, and also CA. The combined exposure to RF fields and EMS revealed no significant ($p>0.05$) effects compared to EMS alone. However, the applied RF field had a potentiating effect in the comet assay, when administered in combination with another clastogen (cyclophosphamide or 4-nitroquinoline 1-oxide).

Another study investigating aneuploidy found changes in the number of certain chromosomes. Increased levels of numerical chromosomal aberrations (missing or extra chromosomes) were identified in human peripheral blood lymphocytes in vitro after 72 h RF field exposure (800 MHz, continuous wave, 2.9 and 4.1 W/kg). An induced aneuploidy of chromosomes 1, 10, 11 and 17 was determined. The increased levels of aneuploidy observed depended on the chromosome studied and on the level of exposure. In chromosomes 1 and 10, an increased aneuploidy was detected at the higher SAR value, while for chromosomes 11 and 17, the increases were observed only for the lower SAR value (Mazor et al. 2008).

Increased DNA damage was shown after RF field exposure in human lens epithelial cells (hLECs) (Yao et al. 2008). This effect was blocked by superimposing electromagnetic noise (2 μT). Twenty-four hour intermittent exposure (1.8 GHz, 1, 2, 3 and 4 W/kg) was used, and the alkaline comet assay and microscope detection of the phosphorylated form of histone variant H2AX (gammaH2AX) foci (a novel and very sensitive method to detect DNA strand breaks) was applied. DNA damage was significantly increased ($p<0.05$) after 3 and 4 W/kg exposures.

Non-genotoxic effects

In vitro analyses can be performed on different cellular processes such as cell cycle, induction of cell death (apoptosis), as well as metabolic and molecular changes.

In addition to DNA damage, Yao et al. (2008) investigated the induction of apoptosis and the release of reactive oxygen species (ROS) after 24-hour intermittent exposure to 1.8 GHz (1, 2, 3 and 4 W/kg) in human lens epithelial cells (hLECs). Significantly ($p<0.005$) elevated intracellular ROS levels were detected at 3 W/kg and 4 W/kg. After exposure to 4 W/kg, cells also exhibited significant ($p<0.005$) G(0)/G(1) arrest. However, no detectable difference in apoptosis was identified. All the effects were blocked when the RF-EMF was superposed with 2 μT electromagnetic noise. The authors suggested that the increased ROS levels may be associated with the induced DNA damage. No increased apoptosis rate was detected in primary cultured neurons from cerebral cortices of

embryonic Wistar rats, exposed to 900-MHz GSM RF fields for 24 h (average SAR: 0.25 W/kg), using different techniques (Joubert et al. 2007).

The formation of ROS has been studied in L929 cells after exposure to 900 MHz RF fields with and without co-exposure to 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanonen (MX). Both continuous-wave and GSM mobile phone signals were applied for 10 or 30 min at specific absorption rates of 0.3 and 1 W/kg. The study provided no indication that 900 MHz RF-field exposure, either alone or in combination with MX, induces the formation of ROS (Zeni et al. 2007).

Using SH-SY5Y neuroblastoma and L929 cells, cell proliferation, oxidative stress and apoptosis were investigated in the presence of menadione (inducing ROS) or tert-buthylhydroperoxidase (inducing lipid peroxidation) and 872 MHz RF field exposure (CW or 217 Hz modulated, 5 W/kg for 1 or 24 h) (Höytö et al. 2008a). The authors detected an increased lipid peroxidation in SH-SY5Y cells using tert-buthylhydroperoxidase and 217 Hz modulated signal, whereas L929 cells showed an increased caspase 3 activity after co-exposure to menadione and a 217 Hz modulated signal. The other endpoints investigated (proliferation, viability, DNA fragmentation, glutathione levels) were not affected.

Höytö et al. (2007b) investigated the ornithine decarboxylase (ODC) activity in murine L929 fibroblasts using 872 or 835 MHz RF fields (CW or 50 Hz modulated) at 2.5 or 6.0 W/kg for 2, 8, or 24 h. The study was planned to replicate earlier studies reporting increased ODC activity in L929 cells but no effects were observed. In further studies by the same group, a lack of effects was confirmed in various cell culture conditions (Höytö et al. 2008b), and in several secondary cell lines (Höytö et al. 2007a) using 872 MHz CW or 217 Hz modulated fields at 1.5, 2.5, 5.0 or 6.0 W/kg. However, ODC activity in rat primary astrocytes was decreased consistently in all experiments performed at two exposure levels (1.5 and 6.0 W/kg), using GSM modulated or CW RF fields (Höytö et al. 2007a).

Exposure of the human trophoblast cell line HTR-8/SVneo to 1817 MHz sinusoidal waves (GSM-217 Hz; 1 h; SAR 2 W/kg) provided no evidence for increase of the HSP70-mediated stress response (Valbonesi et al. 2008). Another study showed that modulated 900 MHz RF fields (SAR 1 W/kg) lead to an anti-proliferative activity after 24 h in SH-SY5Y neuroblastoma cells, causing a G2-M arrest. In addition, markers of apoptosis were detected after a 24-h exposure, including a significant decrease ($p<0.01$) in mRNA levels of Bcl-2 and survival genes. On the molecular level it was also shown that RF field induced a transient increase in Egr-1 mRNA level paralleled with the activation of the MAPK pathway (Buttiglione et al. 2007).

It has been reported that mobile phone exposure (1.3 W/kg) alters the expression of a few proteins in human skin (Karinen et al. 2008); however the biological relevance of this finding is not clear. Zhao et al. (2007) studied the influence of 1.8 GHz RF fields on the gene expression of rat neurons. Among 1,200 candidate genes, 24 were up-regulated and 10 down-regulated after 24-h intermittent exposure at an average SAR of 2 W/kg. These genes are associated with multiple cellular functions (cytoskeleton, signal transduction pathway, metabolism, etc.).

#### 3.3.2.4. Discussion on cancer

Due to the introduction of mobile phone technology in the early 1980s and the beginning of its widespread use only in the mid 1990s, current epidemiological studies had difficulties in investigating brain tumour risk under the assumption of an induction period of about 10-20 years, because of the low number of users. The hypothesis of an induction period of more than 20 years could not be addressed in the current studies. In this context it needs to be noted that the digital mobile phone technology was only introduced in the early 1990s.

The evidence from epidemiological studies indicates that the use of mobile phones for less than ten years is not associated with an increased risk of developing a brain tumour. A major limitation of the current studies is that the diagnostic period of the cases ended in 2003 at the latest, hence, only a few long-term mobile phone users were included in those studies. This limitation together with uncertainties in reconstructing past exposures and difficulties in the ascertainment of representative study participants, circumvent firm conclusions related to long-term mobile phone use.

Altogether, the data collected until now provide no evidence of an increased brain tumour risk. This is consistent with the observation that no visible increases are seen in the age-specific incidence rates of tumours of the central nervous system in the Nordic countries over the last decade (Figure 1, 2). As many more men (most of them between 30 and 60 years old) than women started to use mobile phones in the early days of the technology, an impact on incidence rates would be expected to appear first in men. A noticeable increase in the CNS tumour incidence rates from 1970 to the late 1980s, particularly in older men and women, is assumed to be an effect of improved diagnostic methods and appeared long before the widespread use of mobile phones. However, follow up of gender- and age-specific incidence rates remains important.

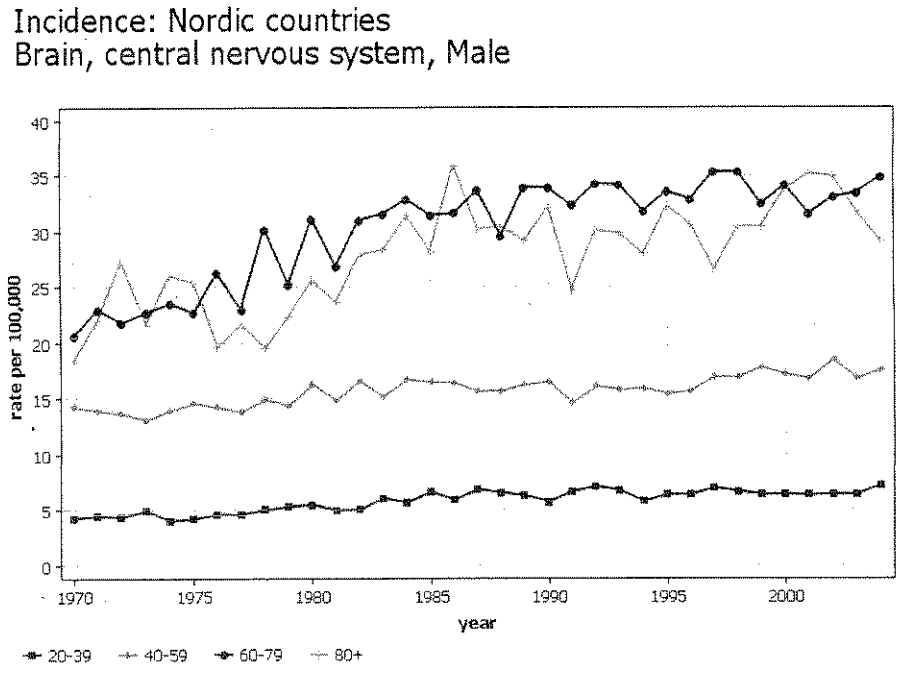


**Figure 1** **Incidence of tumours of the central nervous system (CNS) from 1970 to 2003 among men in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden), by age groups 20-39, 40-59, 60-79 and 80+ years (Engholm et al. 2008)**

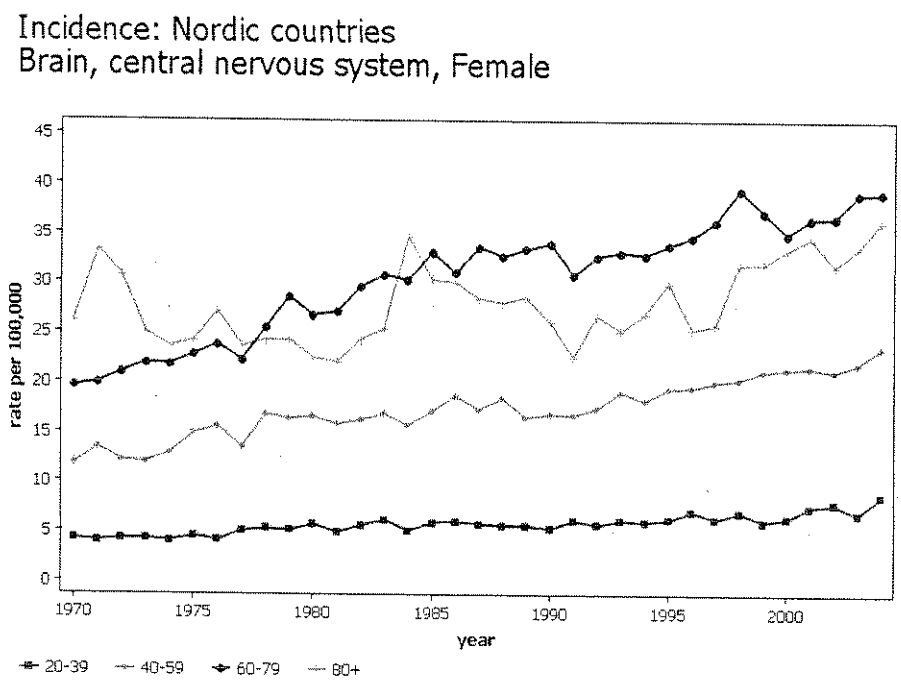


**Figure 2: Incidence of tumours of the central nervous system (CNS) from 1970 to 2003 among women in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden), by age groups 20-39, 40-59, 60-79 and 80+ years (Engholm et al. 2008)**

However, despite new data, the existence of a small risk increase cannot be ruled out and therefore a similar level of uncertainty as in the previous SCENIHR report remains. This assessment may or may not change when the complete Interphone material is published. 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.

Recent well-conducted epidemiological studies provide evidence against an association between RF-EMF exposure from broadcast transmitters and the risk of childhood leukaemia. Although new exposure sources such as mobile phone base stations, cordless phone base stations or wireless networks are relatively recent, exposures from these sources are generally lower than the ones investigated in these studies on broadcast transmitters. Thus, there appears to be no immediate need for further studies related to these sources. However, no studies on mobile and cordless phone use among children and adolescents have been completed so far.

Seven recent studies with rodents have evaluated carcinogenicity of RF electromagnetic fields in vivo. Several different animal models were used including classical bioassays, studies using genetically predisposed animal models and co-carcinogenicity studies involving combined exposure to RF fields and known carcinogens. A few differences were reported for some endpoints, but no consistent dose-response pattern was observed, and the direction of the differences varied (increase or decrease in exposed animals), indicating that the few statistically significant differences are just statistical noise (false

positive findings are unavoidable when many studies with multiple endpoints are conducted).

Overall, the results of the new studies are consistent with results from previous studies, and add to the evidence that the RF fields such as those emitted by mobile phones are not carcinogenic in laboratory rodents. Some of the new studies have also used exposure levels up to 4 W/kg which is high, compared to most previous studies. Thus, these studies provide additional evidence that carcinogenic effects are not likely even at SAR levels that clearly exceed human exposure from mobile phones.

Different biological endpoints have been investigated in vitro after RF field exposure using a variety of cell types and exposure conditions with diverse outcome. In the majority of studies no genotoxic effects were shown. A few studies suggest various biological effects (including genotoxic effects) from RF fields, alone or in combination with other factors, mostly at higher SAR values (above 2 W/kg). The biological relevance of these findings is however unclear. Inconsistent in vitro findings and a lack of dose response relationships render any mechanistic understanding of potential non-thermal interactions between RF and living systems difficult. For RF fields below the recommended limits (2 W/kg) for energy absorption due to mobile phones, in vitro studies have not identified reproducible effects by which carcinogenicity in living systems could be explained.

### 3.3.3. Symptoms

**What was already known on this subject?**

The evaluation of the scientific data at the time of the 2007 opinion suggested that symptoms are not correlated to RF field exposure, but few studies had addressed this issue directly. The 2007 opinion concluded that scientific studies had failed to provide consistent support for a causal relationship between RF field exposure and self-reported symptoms (e.g. headache, fatigue, dizziness and concentration difficulties or well-being), sometimes referred to as electromagnetic hypersensitivity (EHS, see also chapter 3.5.3).

**What has been achieved since then?**

Several studies on symptoms and RF field exposure relevant to the mobile phone user situation have been published since the last opinion. Two studies (Oftedal et al. 2007; Hillert et al. 2008) included subjects who reported having experienced symptoms (headache, vertigo etc) in relation to mobile phone use, but no ill health attributed to other types of electrical equipment. Oftedal et al. (2007) included only subjects who reported headache during an initial open provocation when the subjects knew that they were exposed to RF fields. However, no effect on headache or physiological reactions such as heart rate and blood pressure was observed in the double blind tests. Hillert et al. (2008) observed an increase in reported headache (OR=2.49, 95% CI: 1.16-5.38) at the end of a three hour RF field exposure (double blind tests, time-averaged SAR 10 g 1.4 W/kg). Although more subjects in the group with a history of mobile phone related symptoms reported headache after exposure, the difference between sham and RF exposure was mainly due to a difference between the two exposure conditions in the group without a history of symptoms in relation to mobile phone use. The percentage of subjects in the non-symptom group who reported headache was 45.4 after RF exposure and 25.8 after sham; the corresponding percentages in the symptom group were 48.6 and 57.9. Thus, the results do not support a higher sensitivity in the group who reported symptoms in relation to their every day mobile phone use. No effect was observed with regard to any other symptom (including fatigue, vertigo, nausea and difficulties concentrating). Cinel et al. (2008) analysed a possible effect of RF fields with regard to reported symptoms in three separate studies primarily focusing on cognitive functions in healthy volunteers. In one of the studies the effect of RF exposure was observed on

dizziness (p=0.001), but the two other studies by the same research group did not support such a relationship. Further analyses revealed that the significant difference appeared to be due to higher scores on dizziness in males at the end of RF exposure. Headache, fatigue and skin symptoms were unaffected in all three studies, and no other significant gender differences were observed.

In a Swedish cross-sectional study Söderqvist et al. (2008) reported that regular mobile phone users had headaches, difficulties concentrating and asthmatic symptoms more often than less frequent users. An Egyptian study on symptoms and base stations was published in 2007 (Abdel-Rassoul et al. 2007). Participants who lived close to base stations reported more symptoms. Another cross-sectional study, initiated by public concern of health effects from a military antenna system, compared reported health in two villages classified as "exposed" (based on RF measurements in the villages) to an "unexposed" village in Cyprus (Preece et al. 2007). The percentage of responders who reported migraine, headache, dizziness and depression was higher in exposed villages. These cross-sectional studies suffer from the same methodological limitations as earlier cross-sectional epidemiological studies addressing the same question and do not provide any firm basis for a conclusion on a possible causal relationship (see SCENIHR 2007 and chapter 3.8.3.2). In a German study the subjects were provided with personal exposimeters for 24 hours to investigate the association between exposure to mobile phone related RF fields and well-being (Thomas et al. 2008). Three mobile phone frequency ranges were assessed. Participants were randomly chosen from registration offices in four Bavarian cities. Acute symptoms as well as five groups of chronic symptoms were reported in a diary. No statistically significant association between exposure and symptoms was observed (all p values>0.05).

Provocation studies relevant to base station RF field exposure published since the last opinion have given additional support for the lack of a causal relationship proposed by the study by Regel et al. (2006) which followed-up the initial finding of an effect on well-being in the TNO study (Zwamborn et al. 2003). Eltiti et al. (2007a) performed open tests before the double blind experiment. In the open tests the possibly sensitive group (EHS) reported more symptoms and lower well-being during GSM as well as UMTS exposure as compared to sham (Eltiti et al. 2007a). During double blind testing, no difference in symptoms was observed between actual exposure and sham, neither in the EHS group nor in the reference group. During UMTS exposure the EHS group reported elevated levels of arousal which according to the authors may be due to an effect of sequence of exposure administration rather than the exposure itself. More subjects in the EHS group were exposed to UMTS during the first session. No effect on physiological functions was observed. A Danish study by Riddervold et al. (2008) investigated cognitive functions and self-reported subjective symptoms in adults and adolescents in relation to RF field exposure from UMTS base stations. No effects were seen on any of the cognitive tasks that were performed. A subjective headache rating did not reveal any difference between exposure conditions and sham for the two separate groups, but when data from the two groups were combined, a significant increase in headache was observed during UMTS exposure. The authors suggest that this finding may be due to differences at baseline (higher scores were reported for headache before UMTS exposure than before sham). A number of studies investigated the ability of the participants to detect GSM RF fields (e.g. Eltiti et al. 2007a, Bamiou et al. 2008, Furubayashi et al. 2008, Hillert et al. 2008, Kwon et al. 2008). The studies by Eltiti et al. (2007a) and Furubayashi et al. (2008) tested a base station-like signal (including UMTS exposure), while the three other tested GSM signals relevant to the user situation. Possibly sensitive subjects, reporting a sensitivity to EMF from mobile phones (Kwon et al. 2008), mobile phone related symptoms (Bamiou et al. 2008, Furubayashi et al. 2008, Hillert et al. 2008) or EHS (Eltiti et al. 2007a) were also included. The participants could not report correct exposure conditions better than by chance, and the possibly more sensitive groups could not do this better than the control groups. In the study by Kwon et al. (2008) two subjects had initially correct response rates over 90%. However, when tested again one month later these two subjects could not detect the true exposure conditions

better than could be expected just by chance. In a meta-analysis Röösli (2008) investigated the ability to discriminate between sham and actual RF field exposure. Seven studies were included in the meta-analysis, including 182 subjects reporting symptoms attributed to electromagnetic fields and 332 non-symptomatic subjects. The results showed numerically a slightly better ability to detect the true exposure conditions than expected by chance. This finding is, however, within the limits of uncertainty of the analysis (Effect size, i.e. the relative difference between observed and expected correct answers, 0.04, 95%CI -0.02 - 0.11). The ability to detect the true exposure conditions did not differ between study groups (participants with EMF-related symptoms versus non-symptomatic participants), exposure sources (mobile phones versus base stations) or longer versus shorter exposure duration.

There is a discrepancy between results in open and double blind tests in studies of subjects with mobile phone related symptoms. In open tests, where the true exposure condition is known to the participant, the participants reported that they do react to the exposure under study. In double blind tests, there is a lack of consistent association between exposure and symptoms. Furthermore, subjects could not correctly detect exposure conditions during double blind tests. It is noted that symptoms are also triggered during sham exposure. These observations suggest that other factors, e.g. expectations of symptoms to be triggered based on prior experiences, i.e. a "nocebo" effect, may play a role in triggering symptoms (Rubin et al. 2006; Landgrebe et al. 2008; Stovner et al. 2008).

**Discussion**

In the previous opinion, it was concluded that scientific studies had failed to provide support for a relationship between RF exposure and self-reported symptoms. The 2007 opinion also stated that the knowledge at that time suggested that symptoms are not correlated to RF field exposure. Although an association between RF exposure and single symptoms was indicated in some new studies, taken together, there is a lack of consistency in the findings. Therefore, the conclusion that scientific studies have failed to provide support for an effect of RF on symptoms still holds.

The background for symptoms reported to be triggered by RF fields in everyday life has been discussed. There is a discrepancy between open exposures to RF fields where symptoms are triggered when the subjects are aware of the exposure, and double-blind provocations studies where there is no consistent association between RF and symptoms when subjects do not know if they are exposed to RF or not. These results indicate that a nocebo effect plays a role in symptom formation. This does not exclude the possibility of a RF field effect, but so far the support from scientific studies is stronger for a nocebo effect.

With regard to detection of fields, scientific studies have not provided any evidence that either so-called sensitive groups or healthy control groups can detect RF fields better than expected by chance.

### 3.3.4. Nervous system effects

**What was already known on this subject?**

SCENIHR concluded in the previous opinion that no clear neurotoxic effects due to RF exposure were seen (SCENIHR 2007). Certain changes in electrical activity and neurotransmitter biochemistry were noted but did not suggest any pathological hazard. It was also suggested that care must be taken in future cognitive animal experiments to reduce the stress effects related to restraint of animals.

**What has been achieved since then?**

A number of studies on human volunteers as well as on various animal species have been published since the previous opinion. They can mainly be divided into studies focusing on behaviour and cognition, electrophysiological measurements, sensory related functions, and studies focusing on cell and tissue integrity, including the blood-brain-barrier. Exposures have mostly been to GSM-related signals and UMTS-signals.

Human studies

Several studies employing healthy human volunteers have investigated possible effects on various behaviours and cognitive functions after acute exposures to GSM and/or UMTS signals. Most of the studies were randomised cross-over studies, and have used double-blind protocols. Several of these studies did not find any effects of exposure (Kleinlogel et al. 2008a, Kleinlogel et al. 2008b, Thomas et al. 2008, Riddervold et al. 2008, Unterlechner et al. 2008). Also the work by Curcio et al. (2008) was essentially negative, although they found a trend of shorter reaction time in a finger tapping test of subjects exposed to a 900 MHz GSM signal (SAR 0.5 W/kg). Hung et al. (2007) reported that GSM in "talk-mode" delayed sleep latency. Recently, Wiholm et al. (2009) found that subjects with self-reported symptoms who were performing a virtual spatial navigation test scored better after exposure to 884 MHz at an average SAR of 1.4 W/kg. Augner et al. (2009) studied psychological symptoms (good mood, alertness, calmness) in subjects exposed to GSM base station signals for 50 minutes. Exposure levels were 5.2 $\mu W/cm^2$ ("low"), 153.6 $\mu W/cm^2$ ("medium"), and 2126.8 $\mu W/cm^2$ ("high"). None of the exposure situations had any effect on mood or alertness, but calmness was increased during medium and high exposure. This finding could be due to chance, since multiple endpoints were investigated.

Electrophysiological measurements such as EEG allow for studying effects on specific parts of the central nervous system and thus specific functions in a non-invasive manner. Since the previous opinion, several papers have tried to replicate the study of Huber et al. (2002) which found that GSM-exposure enhanced the power of the so-called alpha-band. Recent studies show contradictory results. Perentos et al. (2007) exposed 12 subjects for 15 minutes to both modulated and non-modulated GSM signals, without finding any effects on any EEG component. In contrast, Croft et al. (2008) exposed 120 subjects for 30 min and measured EEG signals before, during, and after the exposure. This study found an alpha-power enhancement during exposure, which disappeared when exposure was terminated. Vecchio et al. (2007) also reported similar findings (exposure for 45 min to a telephone signal at maximal power which generated a calculated SAR of 2 W/kg). They found modulations of both alpha-1 and alpha-2 bands and also enhanced interhemispheral connectivity. In another study, Inomata-Terada et al. (2007) investigated whether mobile phone signals influenced cortical motor evoked potentials that were triggered by transcranial magnetic stimulation (TMS) but did not find any effects. An in vitro study employing rat cortical neurons, using the patch-clamp technique, did not show any changes in voltage-gated $Ca^{2+}$-channels that could explain effects of modulated and un-modulated GSM signals on EEG (Platano et al. 2007).

Additional studies that have investigated if there are effects on sleep and sleep EEG have been published recently. Regel et al. (2007) exposed healthy male subjects to GSM handset-like signals (sham, 0.2 W/kg, 5 W/kg) for 30 minutes and found dose-dependent effects on sleep EEG and on cognitive tasks. Hung et al. (2007) also exposed volunteers for 30 minutes to various modulated GSM signals. The only modulation that influenced sleep EEG was the "talk-mode" signal (simulating the exposure when talking into a GSM handset), where sleep latency was delayed compared to the other exposure situations. In contrast, Fritzer et al. (2007) found neither short- nor long-term effects on sleep or on a battery of cognitive tasks when subjects were exposed to GSM signals (approximately 1 W/kg) during entire nights.

Due to the vicinity of the mobile phones to various head and face structures during use, there is interest in finding out if sensory functions are affected by exposure to mobile phone signals and specifically their RF components. In particular, properties of the acoustic and visual senses are of interest. Since the previous opinion, several papers have been published that experimentally investigated if electric potentials and muscle activity concomitant with hearing and vison are influenced by exposure. No effects relating to exposure were found in any of the studies investigating hearing parameters (Stefanics et al. 2007, Parazzini et al. 2007, Bamiou et al. 2008, Paglialonga et al. 2007, Cinel et al. 2007, Kleinlogel et al. 2008a) or visual parameters (Irlenbusch et al. 2007, Bamiou et al. 2008, Terao et al. 2007, Kleinlogel et al. 2008b).

Animal studies

There are recognised animal murine and rodent models that are very suitable for studies of various kinds of cognitive functions and behaviour. However, few studies have been performed recently that address the question if RF exposure typical for mobile phones has any neurological effects in animals. The exceptions have used long-term exposure to GSM signals in protocols for studies of learning and memory in rats. Nittby et al. (2008) found that 2 h exposure per week for 55 weeks at SAR levels as low as 0.6 and 60 mW/kg could impair object memory, whereas exploratory behaviour and spatial memory was not affected. At considerably higher SAR values (0.3 and 3.0 W/kg), Kumlin et al. (2007) found that an exposure for 2 h/day, 5 days/week, for 5 weeks did not have any effects on several behaviour parameters or on the cellular/histological appearance of the brain. However, two end-points, i.e. memory and learning, as evidenced by the water maze test, improved after exposure to these RF fields. Interestingly, this study employed young male rats, and thus investigated the developing brain.

It was previously suggested that RF exposure at very low levels could irreversibly damage the blood-brain barrier, causing albumin leakage into the brain from the vasculature and also to changes in neuronal appearance ("dark neurons") (Salford et al. 2003). Such effects, if substantiated by replication studies and follow up experiments, could possibly indicate very detrimental consequences of mobile phone use. It was noted in the previous opinion that other groups did not find such effects. Since then, a few papers have studied blood-brain-barrier functions and brain histology. In most studies, no effects have been noted, even at relatively high SAR values (up to 4.8 W/kg) (Masuda et al. 2007a, Masuda et al. 2007b, Kumlin et al. 2007, Grafström et al. 2008). An exception is a study by Eberhardt et al. (2008), where rats were exposed for 2 h to a 900 MHz GSM signal yielding average whole body SAR values of 0.12, 1.2, 12, and 120 mW/kg. After exposure, rats were left until day 14 or 28 post exposure after which they were sacrificed and brain sections were investigated for parameters indicating blood-brain-barrier damage (albumin extravasation, albumin in neurons, dark neurons). The evaluation of the brain slices was performed as a subjective analysis/assessment of the investigated parameters in a blinded manner. Albumin extravasation was reversibly increased in the rats 14 days after exposure, at 120 mW/kg ($p<0.01$). Albumin uptake into neurons was also found at day 14 after exposure, but not at day 28. The effect was most pronounced at the lowest intensity, 0.12 mW/kg and also at 1.2 and 12 W/kg. Finally, dark neurons were significantly more numerous at 28 days post exposure, at 0.12 mW/kg and 1.2 W/kg. These remarkable findings regarding strongest effects at the lowest SAR values are in line with a previous paper from the group (Persson et al. 1997), but contradict their findings reported by Salford et al. (2003) where the strongest effects on dark neuron appearance was at the highest SAR value (200 mW/kg). It is difficult to evaluate these findings, particularly as the authors themselves do not have an explanation for the surprising results. However, the experiments do not include any positive controls which could show the effect level of blood-brain-barrier opening on the chosen end-points and thus what could be considered to be normal variation and strong effects, respectively. Furthermore, the subjective scoring of the microscopy slides may lead to variation in response determination and could pose evaluation problems.

Two papers demonstrate activation of glial cells and possible gliosis after 900 MHz GSM exposure, both after a single exposure for 15 min at 6 W/kg (Brillaud et al. 2007), and after chronic exposure (15 minutes a day, 5 days a week for 24 weeks) at the same SAR value (Ammari et al. 2008a), whereas exposure to 1.5 W/kg did not cause any glial cell activation.

**Discussion**

With the exception of a few findings in otherwise negative studies, there is no evidence that acute or long-term RF exposure at SAR levels relevant for mobile telephony can influence cognitive functions in humans or animals. There is some evidence that RF exposure influences brain activity as seen by EEG studies in humans. Human studies also indicate the possibility of effects on sleep and sleep EEG parameters. However, certain findings are contradictory and are furthermore not substantiated by cellular studies into mechanisms. There is a need for further studies into mechanisms that can explain possible effects on sleep and EEG.

There is no evidence that acute exposures to RF fields at the levels relevant for mobile telephony have effects on hearing or vision. Furthermore, there is no evidence that this kind of exposure has direct neurotoxicological effects. Most studies show lack of effects on supporting structures like the blood-brain-barrier. The positive finding is lacking dose-response relationships and needs independent replication in studies with improved methodology. The findings of activated glial cells at relatively high SAR-values could indicate gliosis and thus subsequent neurodegeneration after exposure, although exposures at lower levels did not reveal any such effects.

### 3.3.5. Reproduction and development

**What was already known on this subject?**

The previous opinion of 2007 discussed epidemiological and animal studies on adverse developmental effects of RF fields. Numerous animal studies have clearly shown that RF fields are teratogenic at exposure levels that are sufficiently high to cause significant (>1°C) increase of temperature. There was no consistent evidence of adverse effects at nonthermal exposure levels. The limited number and statistical power of epidemiological studies available at that time, as well as their inconsistent findings precluded any definite conclusions.

**What has been achieved since then?**

Development

A recent study on a big Danish cohort found that children aged seven whose mothers had used mobile phones either during or after pregnancy had increased overall scores for behavioral problems (Divan et al. 2008). In light of the very low exposure to the children that would occur as a consequence of the mothers' use of the phone during or after pregnancy it is doubtful that RF exposure from mobile telephony could have anything to do with the observed association. Yet, the explanation for this association is unknown at this time.

Two recent studies have evaluated developmental effects of RF fields in animals. Odaci et al. (2008) investigated effects of prenatal exposure to a 900 MHz field (60 min/day) on the number of granule cells in the dentate gyrus of the hippocampus of young rats. Three pregnant rats were used in both the exposed and the control groups. The brains of six offspring from the exposed group and five offspring from the control group were examined at the age of 4 weeks. The exposure level was described as a "peak" SAR of 2 W/kg, but details of the dosimetry were not given. The number of granule cells was 20%

lower ($p<0.01$) in the exposed group than in the control group, suggesting that prenatal exposure to RF fields might cause inhibition of granule cell neurogenesis. No conclusions can be drawn from this study because of the low number of animals and inadequate reporting of dosimetry. Batellier et al. (2008) studied embryo mortality in fertile chicken eggs exposed to 900 MHz mobile phone fields. The exposure was generated by a mobile phone that was programmed to call once at 3 min intervals during the entire period of incubation. A single mobile phone was placed over a group of 60 eggs, resulting in a very inhomogenous exposure level. Significantly higher mortality was observed in the exposed group compared to the sham-exposed group. However, this difference was obvious in only two of four replicate experiments, and there was no significant dependence on exposure level (which varied with distance to the mobile phone). Interpretation of the results of this study is difficult because of the poorly controlled exposure and lack of proper dosimetry.

Reproduction

Two cross-sectional studies have examined fertility among men exposed to RF fields in the Norwegian Navy. Møllerløkken and Moen (2008) collected data from 1,487 military men (response rate 63%) using a questionnaire covering exposure to electromagnetic fields, lifestyle, reproductive health, previous diseases, work and education. Exposure to RF fields was assessed by an expert group; the work categories "tele/communication", "electronics" and "radar/sonar" were considered as being exposed. Self-reported infertility assessed by a single question ("Have you and your partner ever tried for more than 1 year to get pregnant without success?") was associated with working in the tele/communication category (OR=1.72; 95% CI: 1.04-2.85) and in the radar/sonar category (OR=2.28; 95% CI: 1.72-4.09). These results were obtained by logistic regression analysis adjusted for age, smoking, military education and physical exercise at work. However, the work categories did not differ with respect to objective measures of fertility (number of biological children and paternal age at birth of first child). No differences were observed in congenital anomalies, chromosomal errors, preterm births, stillbirths or infant deaths within 1 year. Associations with self-reported RF field exposure were found also for several self-reported diseases such as food and drug allergy, testicular cancer, cardiac infarction, and skin cancer. Baste et al. (2008) collected questionnaire data from 10,497 current and former male military employees of the Norwegian Navy. Self-reported exposure to RF electromagnetic fields (working close to equipment emitting such fields) was shown to be associated with self reported infertility (assessed as by Møllerløkken and Moen (2008)) by logistic regression analysis adjusted for age, smoking, alcohol consumption, and exposure to organic solvents, welding and lead. For self-reported work closer than 10 m to high frequency aerials to a "very high", "high", "some" and "low" degree, the odds ratios were 1.86 (95%CI: 1.46-2.37), 1.93 (95%CI: 1.55-2.40), 1.53 (95%CI: 1.25-1.84) and 1.39 (95%CI: 1.15-1.68). In addition, self-reported work within less than 3 m distance from communication equipment and within less than 5 m distance from radar were associated with self reported infertility. However, exposure to RF fields was neither associated with the ability of having biological children nor with the number of biological children. Self-reported exposures to high frequency aerials and communication equipment were associated with a decreased ratio of boys to girls. The weaknesses of these two studies include self-reporting of the endpoints, lack of objective assessment of RF field exposure and possibility of confounding factors such as long stays away from home (exposure to the RF field emitting equipment is associated with being on board of ships). Because of these limitations, it is not possible to draw conclusions about the potential causal role of RF fields.

Although the exposure of male reproductive organs to RF fields from mobile phone use is extremely low, two studies have addressed effects of mobile phone use on sperm quality among men attending infertility clinics. The authors reported that reduced sperm quality was associated with duration of daily exposure to mobile phones assessed by interview (Agarwal et al. 2008) and with duration of use of mobile phones assessed by

questionnaire (Wdowiak et al. 2007). However, possible confounding due to lifestyle differences (associated with differences in the use of mobile phones) may have biased the results of both studies.

Two animal studies have addressed the effects of RF fields on male fertility. Dasdag et al. (2008) found no effects on caspase-3 activity (used as a measure of apoptosis) in the testes of male rats exposed to 900 MHz GSM-type fields 2 h/day for 10 months. Fourteen animals were exposed, seven animals served as sham-exposed controls and ten as cage controls. The dosimetry of the testes is not sufficiently characterised. The negative finding of this study has limited value, because only one endpoint was measured. Yan et al. (2007) exposed young male rats (eight animals per group) to mobile phone emissions 6 h/day for 18 weeks. Exposures were performed by placing a mobile phone at a distance of 1 cm from the head of immobilised animals. No information is given on how the mobile phone emissions were controlled during exposure, and there is no description of dosimetry. However, it is obvious that exposure of the testes must have been extremely low. No effects were observed on total sperm cell count or structural abnormalities of sperm cells. Sperm cell death was significantly higher in the exposed group compared to the control group. However, this seems to be mainly related to an unusually low number of live cells in two animals of the exposed group. Abnormal clumping of sperm cells and increased mRNA levels of two cell surface adhesion proteins, CAD-1 and ICAM-1, was also reported in the exposed animals. No conclusions can be drawn from this study because of the poorly controlled exposure and the possibility of individual differences not related to exposure.

**Discussion**

The recent studies that addressed RF field effects on prenatal development in animals and the association of maternal mobile phone use with behavioural effects in children have not provided new information that would change the conclusions of the previous opinion that there are no adverse effects at nonthermal exposure levels.

Studies on male fertility are inadequate due to low statistical power and/or methodological problems.

### 3.3.6. Miscellaneous human

The previous report concluded that there are no substantiated indications for other (miscellaneous) health effects and no studies that change this have been published since the previous report.

### 3.3.7. Dosimetric aspects of children's exposure

Due to the increasing discussion of the potential vulnerability of children to RF fields it was decided to include this section on dosimetric aspects of children's RF exposure in this opinion. Relevant citations published earlier than 2007 have also been included since this subject was not covered in the previous opinion. Certain other aspects of children's exposure are already included in previous chapters, e.g. on childhood leukaemia in chapter 3.3.2.1 or on life time exposure of test animals (chapter 3.3.4)

Concerns about the potential vulnerability of children to RF fields have been raised as their nervous system is developing and therefore potentially more susceptible than the nervous system of adults. Another aspect is that starting to use mobile phones in childhood will result in a longer cumulative lifetime exposure compared to starting to use mobile phones as an adult. While the anatomical development of the nervous system is completed at around two years of age, functional development continues up to adulthood and could possibly be disturbed by RF fields. Although children do not usually use mobile

phones before two years of age, they can nevertheless be exposed from sources such as the recently introduced DECT baby phones.

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 tumours is important. However, the characteristics of mobile phone use among children, their potential biological vulnerability and longer lifetime exposure render extrapolation from adult studies difficult.

Many scientific questions such as possible differences of the dielectric tissue parameters remain open. Several studies demonstrated a decrease of the dielectric properties permittivity and conductivity of animal tissue with age (Gabriel 2005, Martens 2005, Schmid and Überbacher 2005, Peyman et al. 2007). Possible reasons for this are the decrease of water content in the tissue with increasing age, increased myelination of the neurons and changes of the thickness of the dura matter. However, the extrapolation from animal data to children remains questionable. In addition there are still considerable uncertainties regarding the extrapolation from dead tissue to living conditions. Although there are studies on post-mortal human tissue (Schmid et al. 2003b) and living porcine tissue (Schmid et al. 2003a), additional studies are recommended.

There are conflicting opinions regarding possible differences in RF absorption between children and adults during mobile phone usage (Wiart et al. 2005, Christ and Kuster 2005b). The outcomes of existing studies are not consistent. The way the human is modelled is one important factor which explains the different views. The investigation of the exposure of humans in electromagnetic fields and analysis of the arising electromagnetic field distributions inside the human body requires the use of sophisticated numerical software tools. For this purpose numerical phantoms of humans were developed which allow very accurate calculation of the field distributions inside different parts of the body. However, such numerical phantoms may be representing the general population to a limited extent due to the great variability in morphology among humans. Thus, results from one or a few phantom models may be insufficient. Consequently, it is necessary to use a "family" of phantoms that have different anatomical and morphological characteristics, and also to use appropriate statistical approaches when analysing the obtained data (Conil et al. 2008). Additional factors that have to be considered are the impact of the hand on the exposure, the impact of external objects like glasses, the pinna thickness and elasticity, and the design of the phone and the antenna matching (Christ et al. 2005a, Fernández et al. 2005, Hadjem et al. 2005a, Hadjem et al. 2005b, Beard et al. 2006, Lee et al. 2007, Wiart et al. 2007).

Protection limits given in international guidelines, standards and other documents (e.g. ICNIRP 1998) are intended to protect the population against adverse effects arising due to the exposure to electromagnetic fields from 0 Hz to 300 GHz. To ensure reaching the protection goal of these guidelines, compliance with the basic restriction specific absorption rate is warranted. Because the measurement of the SAR is very challenging, reference levels of the electric and magnetic field strength were defined. These magnitudes are rather easy to assess: compliance with the reference levels should guarantee compliance with the basic restrictions.

However, recent studies on whole body plane wave exposure of both adult and children phantoms demonstrated that when children and small persons are exposed to levels which are in compliance with reference levels, exceeding the basic restrictions cannot be excluded (Dimbylow and Bolch 2007, Wang et al. 2006, Kühn et al. 2007, Hadjem et al. 2007). While the whole frequency range has been investigated, such effects were found in the frequency bands around 100 MHz and also around 2 GHz. For a model of a five year old child it has been shown that when the phantom is exposed to electromagnetic fields at the reference levels, the basic restrictions were exceeded by 40% (Conil et al. 2008). Several factors are relevant for the specific exposure conditions, e.g. size, anatomy, BMI (Body Mass Index). Moreover, a few studies demonstrated that multipath

exposure can lead to higher exposure levels compared to plane wave exposure (Neubauer et al. 2006, Vermeeren et al. 2007).

It is important to realise that this issue refers to far-field exposure only, for which the actual exposure levels are orders of magnitude below existing guidelines.

The exposure of possibly sensitive groups of the population such as children should be investigated using adequate numerical phantoms taking multi-source and multi-path exposure conditions into account. Finally, such investigations should not be restricted to the radio frequency range only.

### 3.3.8. Conclusions about RF fields

The question receiving most attention is whether RF field exposure is involved in carcinogenesis. The previous opinion stated that, based on epidemiological findings, mobile phone use for less than ten years is not associated with cancer incidence. Regarding longer use, it was deemed difficult to make an estimate since few persons had used mobile phones for more than ten years.

Since then, a few additional epidemiological studies have been published. Unfortunately they do not significantly extend the exposure period. These studies do not change this assessment.

New improved studies on the association between RF fields from broadcast transmitters and childhood cancer provide evidence against such an association.

Animal studies show that RF fields similar to those from mobile phones, alone or in combination with known carcinogenic factors, are not carcinogenic in laboratory rodents. Certain studies have also employed higher exposure levels (up to 4 W/kg), still with no apparent effects on tumor development.

Furthermore, the in vitro studies regarding genotoxicity fail to provide evidence for an involvement of RF field exposure in DNA-damage.

It is concluded from three independent lines of evidence (epidemiological, animal and in vitro studies) that exposure to RF fields is unlikely to lead to an increase in cancer in humans. However, as the widespread duration of exposure of humans to RF fields from mobile phones is shorter than the induction time of some cancers, further studies are required to identify whether considerably longer-term (well beyond ten years) human exposure to such phones might pose some cancer risk.

Regarding non-carcinogenic outcomes, several studies were performed on subjects reporting subjective symptoms. In the previous opinion, it was concluded that scientific studies had failed to provide support for a relationship between RF exposure and self-reported symptoms. Although an association between RF exposure and single symptoms was indicated in some new studies, taken together, there is a lack of consistency in the findings. Therefore, the conclusion that scientific studies have failed to provide support for an effect of RF fields on self-reported symptoms still holds. Scientific studies have indicated that a nocebo effect (an adverse non-specific effect that is caused by expectation or belief that something is harmful) may play a role in symptom formation. As in the previous opinion, there is no evidence supporting that individuals, including those attributing symptoms to RF exposure, are able to detect RF fields. There is some evidence that RF fields can influence EEG patterns and sleep in humans. However, the health relevance is uncertain and mechanistic explanation is lacking. Further investigation of these effects is needed. Other studies on functions/aspects of the nervous system, such as cognitive functions, sensory functions, structural stability, and cellular responses show no or no consistent effects.

Recent studies have not shown effects from RF fields on human or animal reproduction and development. No new data have been reported that indicate any other effects on human health.

From the risk assessment perspective it is important to recognise that information on possible effects caused by RF fields in children is limited. Furthermore, there is a lack of information on diseases other than those discussed in this report.

## 3.4. Intermediate Frequency Fields (IF fields)

### 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 and will likely continue to do so. 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. For most systems, exposure is well below the recommended limits. However, under worst case conditions, the so-called reference levels can be exceeded when in close proximity to some systems. 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. Visual display units containing cathode ray tubes are still common sources of exposure and emit in the ELF range and the IF range, in the order of 1 nT up to 50 nT. The emissions from new types of lighting bulbs (compact fluorescence lamps, CFLs) have been investigated recently (see also BFE 2004, SCENIHR 2008). Available results showed compliance with existing limits; i.e. the levels measured in the near vicinity (30 cm) were for IF fields (typically 30-60 kHz in this case) from single nT levels up to 30 nT and ELF fields (50 Hz) in the order of 10 nT. Even these levels decrease rapidly beyond 30 cm. This means that in normal domestic use for room illumination, the exposure of CFL users to IF fields is almost negligible. Radio transmitters operated in the long-wave range (30 kHz to 300 kHz) can cause exposure in the intermediate frequency range 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. Welding devices can cause considerable exposure up to a few hundred kHz. Induction heaters are operated in a frequency band from typically some tens of Hz to some tens of kHz, and 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 common example is electrosurgery. These systems are operated at some hundred kHz. In addition, the IF fields of typically up to 10 kHz arising from MRI applications need to be mentioned.

### 3.4.2. Health effects and conclusions about IF fields

The previous opinion expressed its concern that very little useful epidemiologic data on intermediate fields and health risks are available. Furthermore, it was noted that in vivo and in vitro data are very sparse. Well established acute effects occur and these are explained by extrapolation from ELF and RF field mechanisms. Thus it was concluded that there was no basis for an appropriate assessment of long term effects.

Occupational exposure to IF fields in certain areas is considerably higher than exposure to the general public. However, very little research on IF and health risks in occupational settings or for the general public have been presented since the previous opinion, and no

epidemiological studies have appeared. Consequently, the data are still too limited for an appropriate risk assessment.

In view of the increasing occupational exposure to IF among workers in e.g. security, shops, and certain industries it is important that research in this area is given priority.

## 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 also need to be considered. Regarding occupational exposure, electric power installations, welding, induction heaters and electrified transport 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 than 5 kV/m. The highest magnetic flux densities can be found close to induction furnaces and welding machines. Levels of a few mT are possible.

It should 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 specify time weighted average exposure, in many cases the arithmetic mean or the geometric mean or the median value are applied). 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.

**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 typically 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 note 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 from 100 to 400 V/m and 0.5 to 3 μT can be reached, and the exposure is usually instantaneous. 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 overhead 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 for both electric and magnetic fields in areas accessible to the general public are below the limits set by ICNIRP. These reference levels are dependent on the frequency of the field. Regarding 50 Hz fields, the reference level for the E-field strength is 5 kV/m and the reference level for the magnetic flux density is 100 μT. 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, exposure is occasional. 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. Regarding individual exposure, a few percent of the European population are exposed to levels above a median magnetic flux density of 0.2 μT in their homes.

**Exposure of workers**

In a few locations in installations within the electric power industry the exposure limits given in the directive 2004/40/EC for occupational exposure can be reached or even 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 into the ELF and into 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.

**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. Personnel exposure has to comply with the directive 2004/40/EC for occupational exposure.

### 3.5.2. Cancer

#### 3.5.2.1. Epidemiology

**What was already known on this subject?**

In the previous opinion of 2007, the evaluation of the "International Agency for Research on Cancer (IARC)" of carcinogenic risks of static and extremely low-frequency (ELF) electric and magnetic fields to humans (IARC 2002) was endorsed. In the IARC evaluation, ELF magnetic fields were classified into group "2B" ("possibly carcinogenic to humans"). Limited evidence of carcinogenicity in humans was chiefly based on epidemiological studies showing a consistent association between magnetic fields above 0.3/0.4 μT and the risk of childhood leukaemia. Experimental studies showing overwhelmingly negative results provided inadequate evidence of carcinogenicity in cell lines and experimental animals. For cancers other than childhood leukaemia there was either inadequate evidence or some evidence against an association.

**What has been achieved since then?**

An extension of a pooled analysis of studies on magnetic fields and childhood leukaemia (Ahlbom et al. 2000) showed that focussing on exposure during the night time period gives basically the same results as for exposures over 24 hours (Schüz et al. 2007). This does not support assumptions that exposure during the night is of higher biological relevance or that the restriction to the night time period reduces exposure misclassification. A replication study of a US study on magnetic fields and survival from childhood leukaemia (Foliart et al. 2006) utilising data from Germany, broadly confirms a somewhat poorer prognosis of exposed leukaemia patients, but numbers were very small

(Svendsen et al. 2007). There is a need for further studies. No new influential study appeared on any other cancer site.

A recent molecular epidemiological study by Yang et al. (2008) investigated the possible interaction between six mutated genes for DNA repair enzymes and ELF EMF exposure in acute leukaemia in children. There were 123 patients included in this study, and their genotype and residential vicinity to power lines and electric transformers was documented. An interaction between a specific mutation (but not the other investigated alleles) and presence of transformer station and power lines within 50 and 100 m was noted (COR=4.39, 95% CI: 1.42-13.54 and COR=4.31, 95% CI: 1.54-12.08, respectively). Average spot-measured magnetic field intensity levels for houses of a smaller number of patients were done within 50 m (0.18 μT), 100 m (0.14 μT), and 500 m (0.13 μT) of the installations. The study is potentially interesting as it suggests an association between defects in DNA-repair systems and childhood leukaemia caused by residential EMF However, there are too many weaknesses in this study to allow any conclusions to be drawn.

#### 3.5.2.2. In vivo

**What was already known on this subject?**

Animal studies discussed in the previous opinion of 2007 did not provide evidence that ELF magnetic field exposure alone causes tumours or enhances the growth of implanted tumours. Some inconsistent evidence suggested that ELF magnetic fields might be co-carcinogenic (enhance the effects of known carcinogens) and that they may cause cancer-relevant biological changes in short-term animal studies. However, it was concluded that the data were not sufficient to challenge IARC's evaluation that the experimental evidence for carcinogenicity of ELF magnetic fields is *inadequate.*

**What has been achieved since then?**

Much of the evidence for co-carcinogenicity of ELF magnetic fields has originated from one research group, which has published several studies showing accelerated development of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumours in female Sprague-Dawley rats (See SCENIHR 2007 for references and a discussion). These findings, however, were not supported by experiments of two other groups. The group that published the positive findings has recently published a study showing similar effects in Fisher 344 rats exposed to a 100 μT, 50 Hz magnetic field for 26 weeks (Fedrowitz and Löscher 2008). The choice of this strain of rat was based on prior experimental comparison of different rat strains (Fedrowitz and Löscher 2005), which showed that Fischer 344 was the only strain in which magnetic field exposure significantly increased cell proliferation in the mammary epithelium.

Cytogenetic effects were studied in bone marrow cells from Wistar rats exposed to a 50Hz, 1.0 mT magnetic field for 45 days, 4h/day (Erdal et al. 2007) using the chromosomal aberration (CA) and micronucleus (MN) assays. A statistically significant ($p<0.01$) increase of MN was detected. However, this was a small study (four animals per group).

#### 3.5.2.3. In vitro

**What was already known on this subject?**

In the opinion of 2007 (SCENIHR 2007) it was concluded that in vitro studies conducted so far had shown inconsistent results regarding cellular effects. Since a possible interaction mechanism was not known, it was concluded that published in vitro studies cannot explain the epidemiologic findings of increased childhood leukaemia incidence in relation to ELF magnetic fields, but that they do not contradict these results either.

**What has been achieved since then?**

Co-exposure to ELF magnetic fields and bleomycin showed a cooperative or synergistic effect on chromosomal instability in normal human fibroblast (Cho et al. 2007). As a marker for genotoxicity, apurinic/apyrimidinic (AP) sites were investigated using 5.0 mT exposure of human glioma A172 cells, showing that co-exposure to ELF magnetic fields and genotoxic agents (methyl methane sulfonate (MMS) or hydrogen peroxide) induce increased number of AP sites (Koyama et al. 2008). Treatment with menadione (inducing radical production and DNA damage) of L929 cells pre-exposed to 50 Hz, 0.10 mT for 24 h showed an altered cell cycle (Markkanen et al. 2008). The authors concluded that pre-exposure to ELF-EMF alter cellular responses to other agents.

Changes in the redox and differentiation status were reported in neuroblastoma cells (Falone et al. 2007). The results suggest that a 50 Hz, 1 mT magnetic field modulates the redox status of the cells. Although no major oxidative damage was detected, positive modulation of antioxidant enzyme expression, as well as a significant increase in reduced glutathione level was observed, indicating a shift of cellular environment towards a more reduced state. A 96-h MF treatment also enhanced $H_2O_2$-induced reactive oxygen species production and DNA strand breaks.

#### 3.5.2.4. Discussion on cancer

The previous assessments are unchanged. The fact that the epidemiology findings of childhood leukaemia have little support from known mechanisms or experimental studies is intriguing and it is of high priority to reconcile these data. A recent study on rats has provided additional evidence of co-carcinogenic effects from exposure to ELF magnetic fields at 100 μT. However, the findings still need independent confirmation.

Although many earlier in vitro studies did not show any effects, some studies indicated that ELF magnetic fields alone and in combination with carcinogens induce both genotoxic and other biological effects in vitro at flux densities of 100 μT and higher. Recent studies support this effect. Direct field-inducing damage to DNA is unlikely; therefore alternative mechanisms must be hypothesised. As already pointed out in the last opinion there is still 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 and their effects on free radical homeostasis.

### 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 for example 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 use based on the reported experience by the afflicted individuals that electric and/or magnetic fields, or vicinity to activated electrical equipment trigger the symptoms. The 2007 opinion concluded that no consistent relationship between ELF fields and self-reported symptoms (sometimes referred to as EHS) had been demonstrated in scientific studies.

**What has been achieved since then?**

Possibly as an effect of the failure of scientific studies to provide support for a relationship between ELF fields and symptoms (WHO 2005, Rubin et al. 2005), studies on EHS have come to focus on characterisation and alternative possible factors influencing the well-being of the group that reports EHS. The prevalence of individuals who report EHS was estimated to be 4% in the study by Eltiti and al. (2007b) as compared to 1.5% in Sweden (Hillert et al. 2002), 3% in California (Levallois et al. 2002) and 5% in

Switzerland (Schreier et al. 2006). The British study (Eltiti et al. 2007b), designed to evaluate a symptom questionnaire also confirmed the results in an earlier Swedish study (Hillert et al. 2002), i.e. no specific symptom profile was identified. The EHS group scored higher on all eight subscales (neurovegetative, skin, auditory, headache, cardiorespiratory, cold related, locomotor and allergy related symptoms). Another Swedish study investigating personality, mental distress and health complaints among persons with so called idiopathic environmental intolerance attributed to different factors also presented similar results (Österberg et al. 2007). The percentage of subjects who reported experiencing health complaints at least once a week was significantly higher in all eight subscales for the EHS group as compared to the reference group.

A study on personalities of individuals who report EHS observed that this group scored higher on somatic and psychic trait anxiety, stress susceptibility, embitterment and mistrust in Swedish university Scales of Personality (SSP) and on somatization, depression and anxiety as well as on global severity index (GSI) in SCL-35 (Symptom Checklist 35) as compared to referent groups (Österberg et al. 2007). Earlier published results from the same group showed that EHS subjects scored significantly higher on GHQ-12 (General Health Questionnaire-12) than the reference group (Carlsson et al. 2005). Higher scores indicate lower mental well-being. Rubin et al. (2008) did not find a higher prevalence of individuals classified as psychiatric cases using the GHQ-12, but EHS subjects showed a significantly higher level of depression symptoms than control subjects.

Schröttner et al. (2007) studied electric current perception thresholds in three different groups reporting electromagnetic hypersensitivity: a group recruited from a self aid group, a group who had responded to a newspaper call and a group who had actively contacted researchers in order to find help to investigate their health problems (primarily sleep problems attributed to RF fields). When the three groups were pooled together, the EHS subjects differed significantly from a general population sample (lower perception thresholds in the EHS subjects, $p<0.001$). There was however a considerable overlap in perception thresholds between the groups and the EHS groups also contained subjects with higher perception thresholds. As noted by the authors, this study was not designed to test whether electromagnetic fields trigger health complaints and it is thus not possible to draw any conclusion on a possible causal relationship between electromagnetic fields and health complaints. It is possible that the deviating results in the EHS groups may be a consequence of the health problems per se or of the dysbalance of the autonomic nervous system regulation indicated in these groups in other studies (e.g. Lyskov et al. 2001, Sandström et al. 2003).

**Discussion**

In conclusion, no new information has been published in support of a relationship between ELF field exposure and self reported symptoms.

### 3.5.4. Other health effects

#### 3.5.4.1. Epidemiology

The previous opinion concluded that while quite a number of health effects had been associated with ELF fields many of these had been dismissed based on information from later research. This holds, for example, for cardiovascular disease. However, for some diseases it was concluded that it still remains open as to whether there is a link to ELF exposure. This was true in particular for neurodegenerative diseases, such as ALS and Alzheimer's disease (Garcia et al. 2008, Hug et al. 2006). Some new Swiss data that were published after the previous opinion seem to support the previous notion that Alzheimer's disease indeed might be linked to exposure to ELF. These studies include one

study on railway workers (Röösli et al. 2007) and another on people residing in the proximity of power lines (Huss et al. 2009).

#### 3.5.4.2. In vivo

**What was already known on this subject?**

The previous opinion of 2007 discussed studies that have addressed ELF magnetic field effects on the nervous system and behaviour, reproduction and development, and endocrine, cardiovascular and immune systems. Although some studies have described ELF magnetic field effects on the nervous system, animal development, and melatonin production, the evidence for such effects was found to be weak and ambiguous, and inadequate for drawing conclusions concerning possible human health risks.

**What has been achieved since then?**

Three recent studies have provided suggestive evidence that long-term exposure of laboratory rodents to 50 Hz magnetic fields of 1.10 - 2.00 mT may impair (Fu et al. 2008) or improve (Liu et al. 2008b) memory and increase anxiety-related behaviour (Liu et al. 2008a) in behavioural tests. Effects on the alpha activity of human EEG have been reported in subjects exposed to special pulsed ELF magnetic field sequences with peak magnetic flux densities of 200 μT (Cook et al. 2009).

Falone et al. (2008) reported changes in the antioxidant defence system in the brain cortices of female rats (10 animals per group) exposed to 100 μT, 50 Hz magnetic fields for 10 days. The changes were of opposite direction in young (enhanced defence) and old (weakened defence) animals. This finding, if confirmed in further studies, might be relevant to neurodegenerative diseases (Alzheimer's disease, ALS) associated with ELF magnetic fields in some epidemiological studies. No effects were found in a mouse model of ALS, when seven animals per group were exposed for 7 weeks to 50 Hz magnetic fields at 0.10 or 1.00 mT (Poulletier de Gannes et al. 2008).

#### 3.5.4.3. In vitro

**What was already known on this subject?**

The previous opinion stated that few in vitro studies investigating associations between ELF and diseases other than cancer were published. ELF in vitro studies are important for mechanistic understanding.

**What has been achieved since then?**

Very few relevant in vitro studies have been published since the last opinion. Among the exceptions is a study by Del Giudice et al. (2007) which showed the stimulation of beta-amyloid peptide secretion in cultured human neuroglioma cells using 3.1 mT 50 Hz ELF magnetic fields. This peptide plays an important role during Alzheimer's disease development.

Another finding was presented by Sakurai et al. (2008b) using 5.0 mT flux density. In a hamster-derived insulin-secreting cell line (HIT-T15) an increased insulin secretion was reported after 2 or 5 days exposure, showing an activation effect of cells.

It has been suggested that a common and possibly general response to EMF exposure is the activation of the genes encoding the so-called heat shock proteins, a family of chaperone proteins that are up-regulated in response to many forms of stress. In two separate papers (Gottwald et al. 2007, Bernardinie et al. 2007) it was reported that a 50 Hz ELF magnetic field at various flux densities (2 μT-4 mT) in certain cases could increase the levels of the mRNAs for several HSP protein species. However, in none of

the cases with increased mRNA levels was there any concomitant increase in HSP protein level. The mRNA up regulation was thus not shown to have any biological significance.

#### 3.5.4.4. Discussion on Other Health Effects

Since the previous opinion, new epidemilogical data on both occupational and residential exposure support the notion that Alzheimer's disease might be linked to ELF exposure.

Recent animal studies have provided some additional evidence for effects on the nervous system from ELF magnetic fields above about 0.1-1.0 mT. However, there are still inconsistencies in the data, and no definite conclusions can be drawn concerning human health effects.

Very few recent in vitro studies have investigated effects from ELF fields on diseases other than cancer and those available have very little relevance for understanding any disease connection. There is a need for hypothesis-based in vitro studies to examine specific diseases.

### 3.5.5. Conclusions about ELF fields

The previous opinion stated that ELF magnetic fields are a possible carcinogen. This conclusion was chiefly based on childhood leukaemia results.

It was also concluded that a consistent relationship between ELF fields and self-reported symptoms has not been demonstrated.

Regarding breast cancer and cardiovascular disease, an association was considered unlikely. For neurodegenerative diseases and brain tumours, the link to ELF fields remained uncertain.

The new information available is not sufficient to change the conclusions of the 2007 opinion.

The few new epidemiological and animal studies that have addressed ELF exposure and cancer do not change the previous assessment that ELF magnetic fields are a possible carcinogen and might contribute to an increase in childhood leukaemia. At present, in vitro studies did not provide a mechanistic explanation of this epidemiological finding.

No new studies support a causal relationship between ELF fields and self-reported symptoms.

New epidemiological studies indicate a possible increase in Alzheimer's disease arising from exposure to ELF. Further epidemiological and laboratory investigations of this observation are needed.

Recent animal studies provided an indication for effects on the nervous system at flux densities from 0.10-1.0 mT. However, there are still inconsistencies in the data, and no definite conclusions can be drawn concerning human health effects.

Very few recent in vitro studies have investigated effects from ELF fields on diseases other than cancer and those available have very little relevance. There is a need for hypothesis-based in vitro studies to examine specific diseases.

It is notable that in vivo and in vitro studies show effects at exposure levels (from 0.10 mT and above) to ELF fields that are considerably higher than the levels encountered in the epidemiological studies (μT-levels) which showed an association between exposure and diseases such as childhood leukaemia and Alzheimer's disease. This warrants further investigation.

## 3.6. Static fields

Previous health risk assessments of static magnetic fields (SMF) principally focused on static fields only. However, the recent increasing use and further development of MRI equipment has also led to studies of exposures to MRI sequences which include combinations of static fields, RF fields, and variable gradient fields. The following section thus considers studies that focus on static fields only, as well as studies where MRI-relevant field combinations have been used.

### 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 welding processes, and in certain railway and underground systems. A very prominent application is MRI, where different types of tissues 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. Common SMF inside MRI scanners are 1.5 and 3 T. Recently developed devices which are currently only used for research purposes and for specialised teams in specific medical applications can generate fields up to 10 T and more.

### 3.6.2. Health effects

**What was already known on this subject?**

The previous opinion of 2007 stated that a large number of biological studies have been carried out in search of biological effects of static magnetic fields. The studies include in vitro and in vivo laboratory studies as well as studies on human volunteers (see also WHO 2006 for a comprehensive review). Known effects of magnetic fields are orientation of forces applied on biological molecules with magnetic properties such as haemoglobin, rhodopsin (visual pigment), free radicals, and nitric oxide. These effects are detectable at field levels of about 1 T, without known health consequences.

The WHO report concluded that 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 was deemed not sufficient to draw any conclusions about potential health effects of static magnetic field exposure.

The 2007 opinion concluded that adequate data for proper risk assessment of static magnetic fields are almost totally lacking and that the advent of new technology, and in particular MRI equipment, makes it a priority for research.

**What has been achieved since then?**

The results of studies on health effects and static magnetic fields carried out since the last opinion will be presented in the following chapters on human, in-vivo and in-vitro studies.

#### 3.6.2.1. Human studies

Several studies have been performed where volunteers were exposed to either the static field of an MRI only, or to a diagnostic procedure which also includes exposure to low and high frequency fields.

**Nervous system effects**

Toyomaki and Yamamoto (2007) observed an increase in the activity in the theta band of brain activity during exposure to a 1.5 T SMF of an MRI scanner, especially when a task was performed. Atkinson et al. (2007) observed no effects on vital signs and cognitive ability of a sodium imaging procedure in a 9.4 T MRI scanner. Patel et al. (2008) exposed MRI workers to the SMF of a 9.4 T MRI. All subjects noted sensory symptoms during exposure, but no effects on vestibular function could be detected at 30 min and 3 months after exposure.

De Vocht et al. (2007) studied cognitive effects of standardised head movements in a 0.8 or 1.6 T SMF. Negative effects were observed on a visual tracking task. A trend for decreased performance in two cognitive-motor tests was also found, but no effects on working memory were observed.

Kuipers et al. (2007) observed no effect of a 1 h exposure to a SMF of 0.06 T on pain perception, sympathetic function, and hemodynamics at rest or during noxious stimuli.

**Other studies**

Sirmatel et al. (2007a, b) observed contradictory effects on oxidative stress from a 30 min SMF exposure in a 1.5 T MRI scanner. In the first paper Sirmatel et al. (2007b) reported an increased total nitrite concentration in blood samples, an indicator for nitric oxide concentration and indicating increased oxidative stress. In the second paper Sirmatel et al. (2007a) reported an increased total antioxidant capacity and a decreased total oxidant status, and also calculated a decreased oxidative stress index.

No new epidemiological studies have been published since the 2007 opinion.

### 3.6.2.2. In vivo studies

**Nervous system effects**

The group of László has published a series of studies on the effects of SMF exposure on pain perception in mice. László et al. (2007) observed pain reduction with exposures between 0.4 and 1.47 mT for up to 30 min in preliminary experiments in search for an optimal exposure arrangement. Once found, it was used to study the effect of 0-45 min to approximately 1.6 mT (Sandor et al. 2007). Depending on the method used to inflict pain (by injection of chemicals such as acetic acid); pain reduction was already measurable after 5 min. It was concluded that capsaicin-sensitive nerves are involved in the SMF-induced antinociceptive action. In a subsequent paper, Gyires et al. (2008) concluded that the antinociceptive effect of SMF is likely to be mediated by opioid receptors. László and Gyires (2009) repeated these experiments by exposing the animals to the SMF in the bore of a 3 T MRI unit and observed a stronger antinociceptive action than with the weaker SMF.

Behaviour of rats was studied by Houpt et al. (2007a, b). In their first paper the animals were trained to climb though the bore of a sham NMR unit (large vertical magnet). When this was switched for a real magnet with a field strength of 14.1 T, half of the animals avoided climbing into the magnetic field. Upon further testing the animals had already stopped climbing at a field strength of about 2 T. Surgical removal of the peripheral vestibular apparatus abolished this avoidance behaviour. In a parallel study, Houpt et al. (2007b) found increased locomotor circling and aqcuired taste aversion when the animals were exposed to a uniform 14.1 T SMF, but not when exposed to a gradient field (maximally 54 T/m). Ammari et al. (2008b) exposed mice to a 128 mT SMF for 1 h/d, 5 d. No effect on anxiety was observed, but the mice developed an altered emotional behavior and cognitive impairment.

Effects on individual neurons have been studied in several species. Todorovic et al. (2007) exposed neurons of the beetle *Morimus funereus* to 2 mT for 5 min and observed both excitation and inhibition. Nikolic et al. (2008) studied the activity of neurons of the

snail *Helix pomatia.* In the Br neuron (an easily accessible nerve cell with a prominent axon and thus well suited for electrophysiological studies), exposure to 2.7 mT resulted in changes in amplitude and duration of the action potential, while 10 mT changed the resting potential, amplitude spike, firing frequency, and duration of the action potential. No effects were observed in the N(1) neuron. In the crayfish nerve cord, exposure to 8.08 mT for 30 min increased the efficacy of synaptic transmission in the tail-flip escape circuit (Yeh et al. 2008).

**Circulatory system**

Several groups studied the influence of SMF exposure on blood flow. Gmitrov (2007) exposed rabbits to 350 mT for 40 min and observed increased arterial baroreflex sensitivity as well as increased blood flow. Brix et al. (2008) studied blood flow in hamster muscle. At exposures higher than 500 mT for up to 3 h, red blood cell flow velocity was reduced by more than 40%. No effect was found on the capillary and arteriolar diameter and on the amount of functional vessels. In hamster A-Mel-3 tumours, an SMF of 150 mT and higher induced a ~40% reduction of red blood cell velocity already after 1 min, with no further increase thereafter (Strieth et al. 2008). With 587 mT these authors found also a decreased number of functional vessels and a time-dependent increase in platelet-endothelial cell adherence.

Morris et al. (2008) observed effects of SMF exposure on edema formation in rats after specific treatments. Exposure was to 10, 70 or 400 mT for 15 or 30 min, or 2 h. A reduction in histamine-induced edema formation was seen after 10 or 70 mT for 15 or 30 min, while $Ca^{2+}$-induced edema formation was reduced only after exposure to 70 mT for 2 h. The same authors also continuously exposed rat skin flaps to a 25–85 mT/cm SMF gradient for 7 days. They observed a reduction in arteriolar diameter and in venular diameter and length, indicating regulation of vessel growth.

**Growth and metabolism**

Abbasi et al. (2007) exposed mice to 50 mT for at least 10 h per day for 10 and 15 days and found no effect on weight gain and blood glucose levels. Hashish et al. (2007) exposed mice to gradient SMF of permanent magnets (-2.9 µT to +2.9 µT) for 30 d. They observed a gradual loss of body weight, coupled with decreased glucose and total protein levels and alkaline phosphatase activity in serum. Increased hepatic enzyme activity and lipid peroxidation levels were found. The numbers of monocytes, platelets, peripheral and splenic lymphocytes decreased, but the number of granulocytes increased.

Peric-Mataruga et al. (2008) exposed pupae of the mealworm *Tenebrio molitor* to 320 mT for 8 days and observed an increase in cell number, cell and nuclei size, number of nucleoli in the nuclei, and size of corpora allata in protocerebral neurosecretory neurons.

### 3.6.2.3. In vitro Studies

**Gene expression and genotoxicity**

In some studies using cultured cell lines, exposure to several hundreds of millitesla resulted in altered gene expression or DNA damage (Amara et al. 2007, Tenuzzo et al. 2008a, Tenuzzo et al. 2008b, Denaro et al. 2008), while in others, exposure to much stronger SMF such as those used in clinical MRI (up to several tesla) did not cause any effects (Schwenzer et al. 2007a, Schwenzer et al. 2007b). Sakurai et al. (2008a, 2009) observed in both insulin-secreting cells and osteoblasts an increased expression of specific mRNAs after exposure to 6 T / 41.7 T/m for 1 h, but not after 3 T / 26.9 T/m or 10 T / 0 T/m.

In the nematode *Caenorhabditis elegans* several genes were transiently induced after 3 or 5 T, but not after 2 T (Kimura et al. 2008). No DNA damage was observed.

Micronucleus (MN) induction is indicative of DNA damage. Simi et al. (2008) exposed lymphocytes taken from healthy volunteers to up to four consecutive sequences in a 1.5 T MRI scanner and investigated MN formation directly and 24 h after exposure. The baseline level of the MN frequency (the percentage of cells with MN) varied between 7 and 19%. A dose-response effect was observed with an increase in MN frequency at all four levels. After 24 h recovery at room temperature the MN frequency was decreased, returning to control levels at the two lowest levels. MN induction and recovery was also evaluated in lymphocytes taken from the volunteers after they had been submitted to a cardiac scan. The MN frequency was approximately doubled directly after the scan but returned to control level at 48 h.

### Oxidative stress, apoptosis and membrane effects

Several studies using different types of cancer cells have shown contradictory effects on oxidative stress. No effect was found in HL-60 cells exposured to 100 mT for 13 min by Rozanski et al. (2008), while a 2 h exposure to 6 mT increased oxidative stress in U937 monocytic tumour cells (De Nicola et al. 2006).

Reduction of apoptosis (programmed cell death) may result in an increased risk for carcinogenesis. Nuccitelli et al. (2006) observed in U937 monocytic tumour cells a correlation between reduction of apoptosis and modulation of membrane potential induced by exposure to 6 mT SMF. Combined with the results from De Nicola et al. (2006), who observed that modification of the redox balance prevented the antiapoptotic effect of SMF, this indicates a link between reduction of apoptosis and alteration of the intracellular redox balance induced by SMF.

These observations are supported by the study of Tenuzzo et al. (2008b). They exposed human lymphocytes to 6 mT for up to 24 h and observed a reduction of apoptosis and modification of the influx of free calcium. The effect of SMF exposure on the response of cytosolic free calcium to ATP stimulation was also studied in HL-60 cells by Belton et al. (2008). In this study, exposure to 1, 10 or 100 mT for 13 min had no effect.

Shen et al. (2007) studied the effects of exposure to 125 mT SMF on the voltage-gated potassium channel (VGPC) currents in trigeminal root ganglion neurons. Their observations are consistent with modification of physiological characteristics of ion channels in the membrane, resulting from membrane deformation.

### Cell growth, differentiation and viability

The formation of microtubules in human endothelial cells was influenced only by a gradient field, and not by a 120 mT SMF (Okano et al. 2007, Okano et al. 2008).

Exposure to a SMF of 5 mT for 24 h had no effect on growth of a Schwann cell line (Gamboa et al. 2007). No changes in cell proliferation were observed by Coletti et al. (2007) in L6 myogenic cells grown under continuous exposure to 80 mT SMF, but in MG63 osteoblast-like cells a 24-h exposure to 0.4 T reduced the proliferation effects of growth factors (Chiu et al. 2007). In rat GH3 cells (which are of pituitary origin) continuous exposure to 0.5 T increased cell size after 3 weeks and reduced cell growth by 51% after 4 weeks (Rosen et al. 2008). A 2 h exposure to 3 T did not have any effect on the clonogenic ability and proliferation of Hel 299 human embryonic lung fibroblasts (Schwenzer et al. 2007c).

Exposure to a SMF of 5 mT for 24 h had no effect on differentiation of a Schwann cell line (Gamboa et al. 2007), but increased differentiation was observed in U937 cells continuously exposed to 6 mT (Tenuzzo et al. 2008a), in L6 myogenic cells grown under continuous exposure to 80 mT SMF (Coletti et al. 2007), and in MG63 osteoblasts after exposure to 0.25 or 0.4 T for up to 8 h (Lin SL et al. 2008). In human neuronal SH-SY5Y and PC12 cells, exposure to 12 mT influenced the direction of outgrowth of neurites (Kim S et al. 2008).

A higher cell viability was observed in fibroblasts after exposure for 12 h to 0.4 T SMF (Lin CT et al. 2008), in U937 cells continuously exposed to 6 mT (Tenuzzo et al. 2008b), and in human chondrocytes after exposure for 72 h to 0.6 T (Stolfa et al. 2007).

### 3.6.3. Conclusions about static fields

The human volunteer studies indicate that instantanuous effects on neuronal functioning of movement in particular, through a SMF or SMF gradient as used in clinical practice might be possible. These studies need confirmation.

Recent animal studies confirm earlier findings that SMF of several mT can have direct effects on neurons in some in vivo systems. In vitro studies also show that exposure to SMF in the millitesla range may change membrane properties. These changes may lead to changes in neuronal functioning. The effects seem to be reversible.

The studies on pain reduction in animals by exposure to millitesla SMF are interesting. The question is whether rodents are an adequate model for humans in this respect, since no pain reduction in humans was observed after SMF exposure one order of magnitude higher.

Earlier studies indicated effects on rodent behaviour at SMF of 4 T and higher. The current findings at lower levels also need confirmation.

The recent results from animal experiments on blood flow and vessel growth, as well as on growth and development are contradictory and do not clarify the mixed results of previous studies.

The recent experimental data support results from earlier studies that SMF can affect the expression of specific genes in human and other mammalian cells and that these effects may depend on exposure duration and field gradients. Genotoxic effects have been reported, although it seems that these effects can be repaired and are not permanent.

The many earlier studies on cell growth showed contrasting results. The occurrence of effects appeared highly cell-type dependent. The more recent experimental results do not clarify this picture. The recent studies on apoptosis also provide contrasting results as in earlier studies.

Although a fair number of studies have been published since the last opinion, the conclusion drawn there still stands: there is still a lack of adequate data for a proper risk assessment of static magnetic fields. More research is necessary, especially to clarify the many mixed and sometimes contradictory results.

Short term effects have been observed primarily on sensory functions for acute exposure. However, there is no consistent evidence for sustained adverse health effects from short term exposure up to several teslas.

## 3.7. Environmental Effects

Studies on individual species living in close proximity to EMF sources are important in identifying whether ecosystems can be affected substantially by EMF. In addition such studies may be a potential source of information on the potential of EMF to cause adverse effects in man.

**What was already known on this subject?**

In the past the main themes of research have been:

- effects on reproduction
- influence on species that use magnetic fields for navigation purposes

Previous studies have given an indication that exposure of wild birds to EMF can under certain circumstances change their behaviour, reproductive success, growth and development, physiology and endocrinology and/or the parameters of oxidative stress. The literature on these effects is well reviewed by Fernie and Reynolds (2005) and Juutilainen (2005). However, the changes observed are neither all in the same direction nor consistent.

**What has been achieved since then?**

Since the previous opinion, only a few papers have been published, the majority of which have been on the effects of electromagnetic fields on birds.

RF fields

Two independent field studies have focused on the causes of the well reported decline in the population of house sparrow in a number of European countries. Balmori and Hallberg (2007) examined the hypothesis that EMF from phone masts might play a role in this decline. They measured the electric field strength (1MHz-3GHz range) and the house sparrow population at 30 points in Valladolid, Spain. A clear inverse correlation was observed between field strength and the number of house sparrows. In this study, the logarithmic regression of the mean bird density vs field strength groups (considering field strength groups (field strength being described in 0.1V/m increments) was R=0.87 (P=0.0001).

A similar observation has been described for six residential districts in Belgium at 150 point locations (Everaert and Bauwens 2007). In this study the number of male house sparrows was negatively correlated with electric fields from both 900 and 1,800 MHz downlink frequency bands in six different study areas. These studies support an association between electromagnetic fields and the observed decline in house sparrow populations. A number of other factors have also been identified as possible contributors to the decline in house sparrow populations including pollution and loss of preferred food sources. The interaction between EMF and these factors warrants further study. A further issue to be resolved is why the decline in house sparrows is apparently not mirrored by a decline in other species of birds in major conurbations.

Reijt et al. (2007) studied breeding tits in nesting boxes around a military radar station compared with a control location. The exposure levels were reported as being from 2.0 to 5.0 W/m$^2$. No change in breeding biology was observed. However there was a shift in the ratio of blue tits to great tits compared with the control location. Thus one interpretation of this study and those on house sparrows is that the electromagnetic fields may discourage some bird species from breeding there or alternatively might encourage other species to build their nests in the areas with higher RF EMF fields. It may be noted in this regard that there is some evidence that electromagnetic fields may modify the reproductive behaviour of insects (see for example Panagopoulos et al. 2007) that serve as food sources for various bird populations.

Radio telemetry is increasingly used to track species in the wild. For this purpose small transmitters are attached (often by a subcutaneous implant) to captured representatives of the species and the animals are then released back into the wild. In one such study in tufted puffins (Whidden et al. 2007) it was found that radio-marked adults tended to have poorer breeding success and the progeny had lower growth rates than puffins without transmitters. The cause of this difference is ascribed to the EMF from the transmitters.

*Discussion*

Field studies from two independent sources suggest a correlation between the reduction in house sparrow population in urban areas and exposure to electromagnetic fields. However, there are a number of possible interpretations of this data and further investigations are needed.

ELF fields

There have been a number of studies of the reproductive health of birds of prey living around overhead power lines. Conclusions from such studies vary widely. Key factors to explain these varying observations include duration and intensity of exposure, interspecies differences in sensitivity to the effects, breeding habits etc. Costantini et al. (2007) studied the breeding success of Eurasian kestrels living in boxes on overhead power lines. Traditional markers of breeding success such as body weight were determined. In addition, because oxidative stress has been hypothesised to be a coherent mechanism whereby EMF might produce adverse effects, serum antioxidant capacity and reactive oxygen capacity was also measured. In this study none of the parameters measured showed a correlation with field strength.

Publications on the effects of EMF on plants have continued to appear, however the prime interest has moved to the use of EMF commercially to facilitate plant growth in nurseries (De Souza et al. 2008, Florez et al. 2007, Ananta and Shantha 2008). The conclusions from such studies are that by application of magnetic fields the growth of several plant species can be promoted. Optimum growth was observed at levels of around 100-150 mT. From the published data it is difficult to assess the extent of variation in plant species' response to EMF, or whether the effects are purely on plant growth.

Single publications from laboratory studies have identified detectable effects of ELF on bacteria (50 Hz, 0.1 -1.0mT: Cellini et al. 2008), *Daphnia* (50Hz and above: Krylov 2008), and in vitro preparations from fish and chickens (200 Hz and above, [1.5-5mT]: Cuppen et al. 2007).

One study (Scalenghe 2007) has examined the effects of a buried electricity transmission cable on soil quality. While the electric field was near to zero close to the cable the magnetic field flux density was 20 times higher than background levels. After six months the levels of organic carbon, total nitrogen and microbial activity were inversely related to the distance from the cable indicating a reduction in biological activity due to the magnetic field.

*Discussion*

Several in vitro studies have shown changes in the mT range using preparations from fish, birds, *Daphnia* and bacteria. Two field studies have also detected some changes although their interpretation, in terms of environmental significance, is uncertain.

**Conclusion**

The current database is inadequate for the purposes of the assessment of possible risks due to environmental exposure to RF, IF and ELF.

## 3.8. Methodological framework

### 3.8.1. Introduction

The purpose of an opinion such as this is to provide the scientific background with respect to if exposure to electromagnetic fields (EMF) is a cause of disease or other health effects. The opinion is not a scientific review article which includes all papers that have been published on the subject. It has also to be stressed that it is not a tool for risk management, or a way to communicate opinions regarding exposure guidelines.

This section summarises the procedure of work which is the foundation of the opinion. It describes the process how the studies that have been included were identified and analysed. Furthermore, it gives information about the weighting process which is

underlying the final conclusions regarding various types of EMF and health effects. The criteria that have been governing the evaluation process of the different kind of studies (epidemiological, human experimental, in vivo, in vitro) are provided. Methods for obtaining data on exposure and dosimetry are explained, as well as criteria for evaluating from the perspective of exposure assessment and dosimetry. When appropriate, typical strengths and weaknesses of various methods and techniques are described.

### 3.8.2. Criteria used

In the previous opinion a methodological section was added in response to comments received during the public consultation process. The purpose was:

1. to explain the criteria for how studies were selected,

2. to explain how the scientific evidence was synthesised into an assessment of the evidence for a causal effect of exposure to electromagnetic fields and health effects.

The scientific rationales for both the previous and the present opinions were developed in a way as described below (Figure 3).

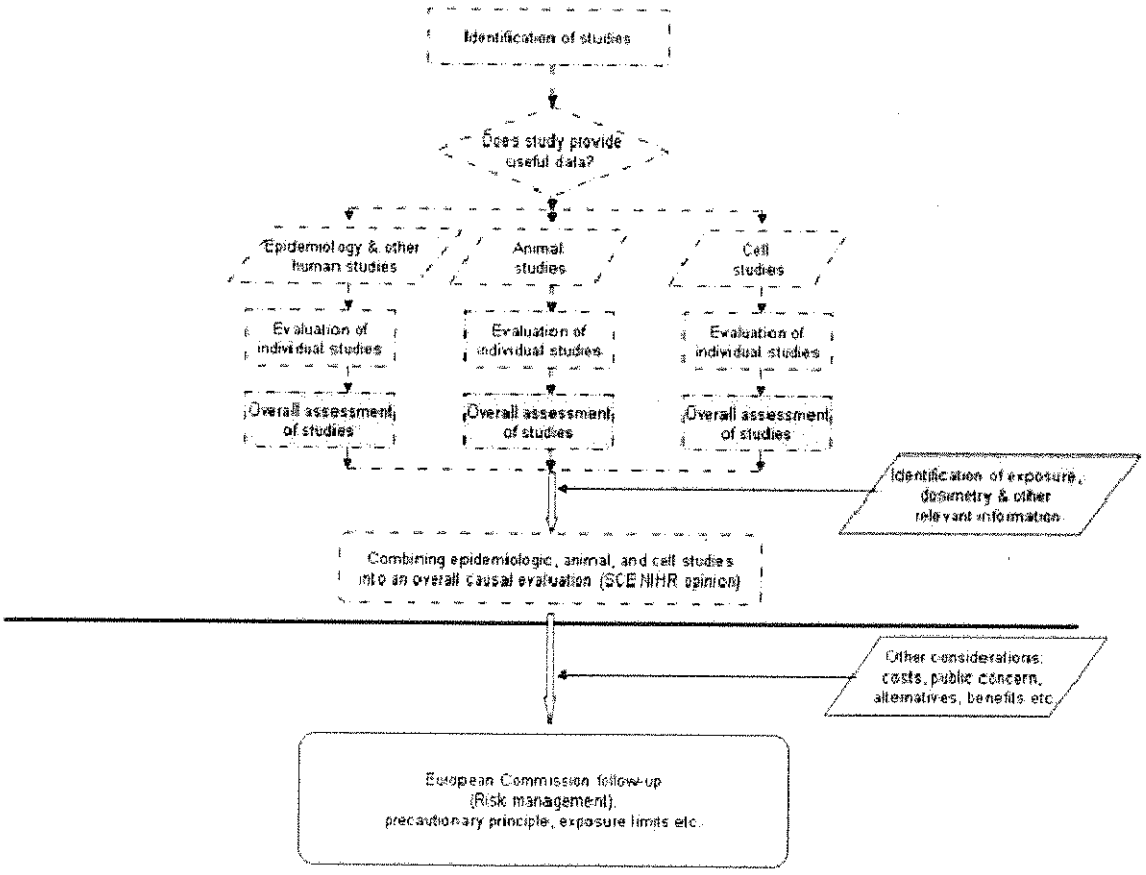


**Figure 3 Flow chart of the evaluation process used in the present opinion to evaluate possible health effects of EMF exposure. The vertical bold-face line marks the level at which the work of the SCENIHR is completed.**

As a general rule, scientific reports that are published in English language peer-reviewed scientific journals are considered primarily. Exceptions to this are specifically mentioned in the text. This does not imply that all published articles are considered to be equally valid and relevant for health risk assessment. On the contrary, a main task is to evaluate and assess the articles and the scientific weight that is to be given to each of them. Only studies that are considered relevant for the task are commented upon in the opinion. Many more reports were considered than are cited in the reference list. However, only articles that contribute significantly to the update of the opinion are cited and commented upon. In some areas where the literature is particularly scarce it has been considered important to explain why the results of certain studies do not add useful information to the database. The focus is on articles published after the presentation of the previous opinion.

The primary objectives of this health risk assessment are:

- to identify and characterise any hazardous properties (diseases, adverse health effects) of EMF in relevant biological systems
- to examine the relationship between exposure and these hazards (dose response relationship)
- to highlight the nature and extent of any uncertainties in the determination of hazards and dose response relationships
- to evaluate the plausibility of possible modes/mechanisms for each hazard of concern.

It should be emphasised that recommendations for risk management measures are excluded from the mandate of SCENIHR (see Figure 3).

Relevant research for EMF health risk assessment can be divided into broad sectors such as epidemiological studies, experimental studies in humans, experimental studies in animals, and cell culture studies. Studies on biophysical mechanisms, dosimetry, and exposure assessment are also considered. In a report of this nature it is not possible to consider the experiences of individuals. Nonetheless, such information often triggers a scientific study.

A health risk assessment evaluates the evidence within each of these sectors and then weighs the evidence across the sectors to produce a combined assessment. This combined assessment should address the question of whether or not a hazard exists i.e. if a causal relation between exposure and some adverse health effect exists. The answer to this question is not necessarily a definitive yes or no, but may express the weight of the evidence for the existence of a hazard. If such a hazard is judged to be present, the risk assessment should also address the magnitude of the effect and the shape of the dose-response function, i.e. the magnitude of the risk for various exposure levels and exposure patterns. A full risk assessment also includes exposure characterisation in the population and estimates of the impact of exposure on burden of disease.

Epidemiological and experimental studies are subject to similar treatment in the evaluation process. It is of equal importance to evaluate positive and negative studies, i.e. studies indicating that EMF has an effect and studies not indicating the existence of such an effect. In the case of positive studies the evaluation focuses on alternative explanations for the positive result: with what degree of certainty can one rule out the possibility that the observed positive result is produced by bias, e.g. confounding or selection bias, or chance. In the case of negative studies, one assesses the certainty with which it can be ruled out that the lack of an observed effect is the result of (masking) bias, e.g. because of too small exposure contrasts or too crude exposure measurements; one also has to evaluate the possibility that the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only one factor in

this evaluation. Rather, the evaluation considers a number of characteristics of the study. Some of these characteristics are rather general, such as study size, assessment of participation rate, level of exposure, and quality of exposure assessment. Particularly important aspects are the observed strength of association and the internal consistency of the results including aspects such as dose response relation. Other characteristics are specific to the study in question and may involve dosimetry, method for assessment of biological or health endpoint, the relevance of any experimental biological model used etc. Regarding experimental studies, additional important characteristics that are taken into consideration are the types of controls that have been used and to what degree replication studies have been performed. For a further discussion of aspects of study quality, refer for example to the Preamble to the IARC Monograph Series (IARC 2006). It is worth noting that the result of this process is not an assessment that a specific study is unequivocally negative or positive or whether it is accepted or rejected. Rather, the assessment will result in a weight that is given to the findings of a study.

The step that follows the evaluation of the individual studies within a sector of research is the assessment of the overall evidence from that sector with respect to a given outcome. This implies integrating the results from all relevant individual studies into an overall assessment. This is based on the evaluations of the individual studies and takes into account, for each study, both the observed magnitude of the effect and the quality of the study. Note again, that for this process to be valid, all studies must be considered equally irrespective of their outcome.

In the final overall evaluation phase, the available evidence is integrated over various sectors of research. This phase involves combining the existing relevant pieces of evidence on a particular end-point from studies in humans, animal models, in vitro studies, and from other relevant areas. The integration of the separate lines of evidence should take place as the last, overall evaluation stage, after the critical assessment of all (relevant) available studies for particular end-points. In the first phase, epidemiological studies should be critically evaluated for quality irrespective of the putative mechanisms of biological action of a given exposure. In the final integrative stage of evaluation, however, the plausibility of the observed or hypothetical mechanism(s) of action and the evidence for that mechanism(s) is a factor to be considered. The overall result of the integrative phase of evaluation, combining the degree of evidence from across epidemiology, animal studies, in vitro and other data depends on how much weight is given on each line of evidence from different categories.

### 3.8.3. Specialised sections

Specific considerations that are relevant for evaluation of the studies are presented in more detail in the text below. This gives the framework for how the present opinion is developed after evaluation of specific studies. Although some of the more important aspects to consider are discussed, it must be pointed out that this is not a complete text on the subject.

#### 3.8.3.1. Dosimetry and exposure assessment

Accurate and reliable dosimetry and exposure assessment are key requirements of scientific studies on biological effects of electromagnetic fields. It is imperative to select the adequate assessment tool to identify exposure conditions. There are several tools available, e.g. frequency selective measurement equipment, broadband probes, exposimeters or numerical methods. The adequate selection of the equipment depends on the type, the magnitude and the variability of the signals from the emitting sources and the purpose of the study. For in vitro, in vivo and human studies adequate exposure setups have to be selected to guarantee reproducible and accurate exposure of the biological samples or volunteers. Well defined exposure conditions at the site of the

biological test object are an imperative requirement. Only studies including the uncertainty of such determinations are complete.

To determine exposure arising from electromagnetic fields several approaches are available. The main possibilities are measurements and calculations. When performing measurements different methods exist. One can distinguish between spot measurements, monitoring, and individual exposure assessments (Neubauer et al. 2005).

Measurements of electromagnetic fields can be performed in two ways: broadband and frequency selective. Broadband measurements give the total contribution over a wide frequency range without distinguishing the contributions of different sources operating at different frequencies. Frequency selective measurements allow these specific contributions to be identified. Broadband measurements are performed with probes and hand-held measuring instruments, while for frequency selective measurements spectrum analysers attached to antennas are used. Both frequency selective and broadband measurement equipment can be used to perform spot measurements, i.e. measurements at a given location and at a specific time. A major shortcoming of spot measurements is that they do not reflect the variation of the exposure versus time and in space. When needing to assess the exposure of individuals, spot measurements therefore have limitations.

If it is necessary to assess the exposure variations versus time at a specific location, monitoring systems are adequate solutions. Such systems allow continuous monitoring of the whole frequency range for all types of signals in the frequency range of interest. Monitoring systems do usually not reflect the exposure of moving individuals. Due to the fact that exposure is often highly variable in space, other solutions are needed to assess individual exposure of persons.

Exposimeters allow personal exposure to electromagnetic fields over time to be determined. It is crucial for the evaluation of the electromagnetic fields that one can monitor different electromagnetic sources in a way that allows distinction between the contributions from different applications, e.g. mobile phones, GSM and UMTS base stations, or broadcast stations. Exposimeters are quite promising tools, although they also have some limitations. First, they have a limited bandwidth and do not allow the exposure from all electromagnetic sources to be assessed. Moreover, they have a limited dynamic range, i.e. very weak and very strong signals cannot be assessed. In addition, they give only a surrogate of the exposure. Exposimeters are usually worn on the back or on a belt, and therefore indicate the field level close to the body. This is in fact not exactly the exposure, since exposure is defined as the electromagnetic field level at the location of the exposed person assessed without the person being present.

In addition to measurements, calculations of the exposure are often an adequate approach. In many cases the combined use of measurements and calculations is appropriate. Analytical approaches are often used to get preliminary information regarding the exposure conditions. However, they are neither suitable for describing complex exposure conditions nor to describe the field distribution inside the human body in an accurate way. For such purposes numerical tools can be used. Such numerical methods can be divided into two different main types based on the used physical wave propagation model, i.e. field theoretical methods (solving Maxwell's equations) and optical methods. Examples of field theoretical methods are the Finite Elements Method (FEM), Finite Differences in Time Domain (FDTD) or the Methods of Moments (MOM). Examples of optical methods are ray launching and ray tracing. The literature contains also hybrid methods, which are a combination of field theoretical methods and optical methods. Field theoretical methods, e.g. FDTD, are often used for the investigation of small areas whileoptical methods like ray tracing are often applied to large areas.

The selection of an adequate exposure metric is imperative for scientific studies. As long as the biological mechanisms related to a specific exposure, e.g. low level RF exposure, are unknown, it might even turn out that several exposure metrics have to be evaluated. One approach is to focus only on the exposure above a certain threshold. Another

concept is to assess cumulative exposure when a linear dose-response association without a threshold is expected. It is also possible that the exposure variability might be relevant or a mixture of the three concepts mentioned has to be applied. Moreover, differences in signal characteristics might be of relevance. One viewpoint is that physical characteristics apart from intensity are not relevant; the other is to support the idea that frequencies, modulation, and intensities might play an important role. In addition, the exposure timing might also be of relevance (Neubauer et al. 2007).

Adequate and accurate exposure assessment is crucial for the evaluation of exposure conditions of both workers and the general population. The selection of suitable measurement equipment or adequate calculation tools is an imperative requirement. Moreover, both measurements and calculations should only be performed by highly qualified personnel. When performing in situ measurements it is necessary to take environmental factors such as the impact of objects or weather conditions into account. In addition, the variability of the exposure due to environmental conditions needs to be considered. Measurement equipment has to be calibrated in regular intervals. Moreover, the variability of exposure conditions due to factors such as changes of data rates or changes in the current on power lines has to be considered. Another crucial aspect is the impact of the human body on the measurement results. Moreover, results without uncertainty analysis are incomplete.

It is imperative to take multisource exposure into account to get reliable information on exposure. If measurements or calculations are performed, aspects like whole body or localised exposure need to be considered.

Similar considerations have to be made when performing in vitro, in vivo or human studies. The exposure set up needs to allow reproducible and accurate exposure, i.e. the electromagnetic field must be well defined at the site of the cell culture or in specific tissue of animals or volunteers. The sensitivity of experimental variations on the induced fields such as posture or size of test animals should be minimised. Moreover, environmental conditions such as temperature, humidity, and background electromagnetic fields have to be controlled. Uncertainty analysis of the exposure has to be developed because it is an important part of the overall study uncertainty. The exposure set up should minimize additional stress to test objects or volunteers apart from the exposure itself. The complete exposure set up including all controlling and monitoring devices should be immune against electromagnetic interference under worst case test conditions. The list of dosimetric requirements given here is not intended to be complete; more information can be found in different publications (e.g. Valberg 1995, Kuster and Schönborn 2000, Portier 1994, Lang 2004).

In recent years a trend towards improvement of dosimetric aspects in scientific studies on biological effects of electromagnetic fields could be observed. Exposure is in most cases sufficiently reported. However, in several cases the uncertainty of the assessment is not given. In some epidemiological studies the contribution of RF sources other than mobile phones to the exposure is not taken into account. Several experimental human studies suffer from non-optimised exposure set-up, and the assessment of the SAR is often based on phantom measurements which may be more or less representative for the actual subjects. Such approaches are suitable for compliance testing, but not adequate for scientific investigations.

### 3.8.3.2. Epidemiology

Epidemiology is concerned with the study of the occurrence and distribution of diseases in populations. Its ultimate goal is to learn about the causes of disease that may lead to effective preventive measures. However, in contrast to experiments or clinical trials, epidemiological studies are usually observational and are therefore vulnerable to bias and confounding. Thus, criteria are needed to assess whether observed empirical exposure-disease associations are possibly causal or more likely a play of chance or methodological artefacts. Making sense of results from epidemiological studies is particularly challenging

when they are conflicting, or when there is a discrepancy between epidemiological and experimental findings.

The range of observational study types reaches from rather simple descriptive studies to analytical studies. In evidence-based decision making, different observational study types contribute with different weights. More confidence relies on results derived from well-conducted prospective cohort studies than on results from case-control studies, whereas firm conclusions are rarely drawn from cross-sectional studies and particularly descriptive studies. Nevertheless, there is a considerable range of quality within study types. This applies especially to case-control studies which are the most commonly used in investigations of hazards of chronic diseases like cancer. Case-control studies are prone to selection bias and recall bias and a transparent description of the study material and procedures is a necessary requirement to evaluate the study's quality.

Criteria to be discussed when summarising the overall epidemiological evidence are temporality and strength of the observed association, a convincing dose-response pattern, internal and external consistency of results, the specificity of the association, and the absence of bias and confounding. Importantly, reported relative risk estimates have to be compatible with the absolute effects observed in the disease rates over time.

Meta-analyses are a useful tool to numerically summarise the evidence, but if substantial heterogeneity is identified, a structured approach trying to clarify the source of such heterogeneity is more important than the calculation of pooled estimates. A good meta-analysis or review can be seen as a study of studies; hence, like original studies, they vary considerably in quality. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement is an important guideline on how to report results of observational studies and is promoted by many influential journals as a new standard (e.g. von Elm et al. 2007).

#### 3.8.3.3. Human laboratory studies

Experimental studies in laboratory or other controlled settings are used to evaluate whether effects can be observed during or shortly after exposure to a causal (risk) factor. These studies are also called provocation studies, i.e. the study will try to answer the question whether a certain exposure will trigger (provoke) a certain effect, e.g. a physiological reaction or symptoms. The quality of experimental studies on humans may vary. It is of utmost importance that the design and protocol of the study are described in detail by the authors reporting the results of the study. If this is not the case, it may be impossible to judge if the results are valid or not.

Laboratory studies, as compared to epidemiological studies, have the advantage of providing better possibilities to control the exposure factor(s) under study, as well as possible confounding factors. On the other hand, the relevance of experimental laboratory studies to the real life situation may be less clear. For example, the absence in laboratory settings of contributing factors present in everyday life may influence the results and possibly reduce the chance to discover an effect.

A double blind experimental laboratory study where subjects are randomly allocated to two or more exposure conditions is considered the strongest design to study acute effects. The goal is to have contrasting exposure conditions but otherwise as similar conditions (and groups) as possible to compare in the analyses of possible effects. Subjects should be randomly allocated to the different exposure conditions. A cross-over design, where the same individuals are exposed to both (or several) conditions in a random order, is preferred. In the cross-over design, the subjects serve as their own controls in the comparisons between e.g. sham and the exposure under study. If two separate groups of participants are assigned either to sham or the exposure under study, other possible differences between the groups than the exposure conditions may influence the results. The cross-over design may however be biased by carry-over effects if the time between the two (or more) conditions are not long enough for possible effects to wash out. If that is the case, a true effect may be hidden. Effects due to the order in

which exposure conditions are applied may also obscure the results if the numbers of subjects that begin with the separate conditions are not balanced. For example, unfamiliar routines and environment may produce different reactions during the first experiment as compared to the later sessions. Habitation sessions during which the participants will be acquainted with the procedures and setups may be useful to avoid this problem. In order to prevent expectations of participants or researchers to distort the results it is important that the study is performed double blinded, i.e. neither the researchers that lead the experiments nor the participants are aware of the true state of the exposure conditions during the study.

The choice of study group will have an impact on the external validity of the study, i.e. which populations the results are valid for. A very homogenous group (e.g. with regard to age and gender or symptom profile) may limit the population that the results may be generalised to. On the other hand, a more heterogeneous study group may risk missing an effect present only in one or several sub-groups.

The outcomes that are assessed in a study may be more or less robust. If possible, objectively measured (e.g. heart rate, blood chemistry etc) data are desired. Self-reported effects are more difficult to assess. The choice of scales for self reported effects or interpretations of open questions may also have significant influence on the results.

#### 3.8.3.4. In vivo

Animal studies are frequently based on experiments using laboratory strains of mice or rats. The advantage of animal studies is that they provide information about effects on a whole living organism that displays the full repertoire of body structures and functions, such as nervous system, endocrine system and immune responses. In this respect, animal studies are usually a more powerful experimental tool than cellular studies for assessing health risks to humans. However, extrapolation to humans is not straightforward since there are obvious differences in e.g. body mass, life expectancy, physiology, and metabolism between species. Rodent carcinogenicity studies, for example, have been criticised because many agents that are carcinogenic in rodents (often only at very high doses) are not carcinogenic to humans, and some human carcinogens do not affect rodents in standard carcinogenicity tests (Ames and Gold 1990, Trosko and Upham 2005, Anisimov et al. 2005). Extrapolation from animal experiments to humans should always include consideration of the validity of the animal model used – good animal models do not exist at present for all human diseases. Nevertheless, at a molecular level, many basic processes, such as DNA damage and repair, are similar in animals and humans, and animal studies have remained a cornerstone in evaluating toxicity of chemical and physical agents. In the evaluations of IARC, for example, agents for which there is sufficient evidence of carcinogenicity in animals are considered to pose carcinogenic hazard to humans, unless there is scientific evidence that the agent causes cancer through a species-specific mechanism that does not operate in humans (IARC 2006).

Criteria for evaluating individual animal studies include the following questions: (i) Was the number of animals per group adequate? (ii) Were animals of both sexes used (if relevant)? (iii) Were animals randomly allocated to groups? (iv) Were exposure levels and treatment durations appropriate? (v) Was the duration of observation adequate with respect to the health endpoint addressed (for example, lifetime observation in carcinogenicity studies)? (vi) Apart from the exposure of interest, was treatment of exposed and control groups identical? (vii) Was there possibility of bias related to differences in survival between groups? (viii) Was the endpoint measured adequately? (ix) Was data reported adequately? (x) Was a dose-response relationship observed? (xi) Were the exposure system and dosimetry adequate?

These criteria are valid for any animal study, but quality of exposure system and dosimetry is particularly important in studies on RF fields. In such studies, the exposure system is often a compromise between restraint-related stress and the accuracy of RF

dosimetry. If animals are allowed to move freely during RF exposure, they change their position and orientation in relation to the electromagnetic wave and may also be shielded by other animals, which results in large uncertainties in dosimetry. Therefore, immobilisation of animals has been used in many animal studies to achieve well-defined dosimetry. However, immobilisation can cause restraint-related stress that might affect the outcome of the experiment (no experimental bias is caused if both exposed and the sham-exposed animals are restrained, but stress could act as an effect modifier and obscure possible RF-induced effects). Such effects of stress can be reduced by appropriate steps, such as the habituation of animals to restraint.

#### 3.8.3.5. In vitro

In vitro studies are used to investigate toxicological, mechanistic, and other relevant effects which can provide evidence for and possible understanding of the development of cancer and other diseases. In vitro assays can show potential effects of various agents on a wide variety of biological endpoints in a manner which is rapid and cost-effective. The role for in vitro assays in hazard identification is thus obvious.

Genotoxic studies include assays showing the interaction of the possible risk factor with the DNA. Non-genotoxic studies often aim to give mechanistic understanding by using a wide variety of endpoints. This can elucidate the machinery of action on the cellular level which can also be predictive to a certain extent for some hazardous effects. It has to be pointed out that in vitro studies contribute to acute toxicity testing and can provide information regarding tumorigenesis, and other physiological or pathological processes, but it cannot replace in vivo conditions or long term exposure conditions. Therefore information about genotoxic capacity for example, can only be indicative of a potentially serious public health risk.

For evaluation of published data, criteria are needed to distinguish between useful and not useful studies for the assessment. In general, for toxicological studies it is imperative to set up the accurate experimental control samples. Positive and negative controls within in vitro studies provide evidence for controlled experimental conditions. In EMF research it is preferable to use sham exposure as a control condition as well, and performing experiments in a blinded manner.

Exposure has to be performed under fully controlled conditions regarding field exposure (frequency conditions, flux density, SAR-values etc.), temperature, $CO_2$ etc. and has to be documented. Furthermore, a proper dosimetry has to be presented.

For risk evaluation, studies of dose dependency are needed to determine possible threshold values.

It is evident that the appropriate cell types have to be used for specific experimental approaches for proper identification of biological effect.

Concerning statistical power, both the number of parallel samples during the experiment and the number of independent replicates of an experiment have to be considered.

To provide information about genotoxic capacity, a battery of techniques and methods are available, ideally, the used methods should confirm and/or compensate each other. Therefore, it is necessary to prove positive findings by using different techniques (Table 2). In addition, the reproducibility of positive findings has to be shown by independent laboratories.

For non-genotoxic studies the same criteria mentioned above are valid. In vitro studies are very helpful when they are producing specific and reproducible results, however, the biological relevance can be unclear and the extrapolation of data is rather difficult. An isolated finding should not be overestimated; it has furthermore to be proven by independent laboratories. For risk assessment it is useful to consider functional studies that are investigating several cellular processes (and/or alterations in physiological processes). The novel methods that on a large scale (by high-throughput screening; "-

omics") can study e.g. gene transcription, protein expression and modification, and cellular metabolism can be instrumental in elucidating possible mechanistic cellular action of an agent.

**Table 2 Advantages and disadvantages with certain commonly used cyto-/genotoxic assays.**

| | Advantages | Disadvantages |
|---|---|---|
| **MN** | •detection of chromosome and genome mutations<br>•discrimination between clastogen and aneugen effects by using FISH or CREST<br>•co-detection of apoptosis and necrosis possible<br>•no cell type dependency<br>•fast, inexpensive, easy<br>•allow automatic scoring | • cell division is needed<br>• detects only acentric fragments (for structural chromosome aberrations) |
| **MN** with cytochalasin B | •discrimination between cells with and without nuclear division<br>•detection of dicentric bridges as nucleoplasmic bridges<br>•measurement of cell proliferation (% binucleated cells) | • possible interference of cyto-B with test agent; e.g. spindle poisons and other inhibitors of cytokinesis<br>• cytoxicity of cyto-B varies between cell types |
| **CA** | •identification of all chromosome mutation types<br>•co-detection of mitotic indices | • needs cell cultivation (mitosis)<br>• need of highly skilled and experienced personnel<br>• labour and cost intensive<br>• subjectivity<br>• automatic scoring is not possible |
| **SCGE/ Comet assay** | •no cell cultivation<br>•estimation of DNA repair capacity<br>•fast, inexpensive, easy<br>•some indication of apoptosis | • quality of protocol and experimental performance is of crucial importance especially during electrophoresis |
| **SCE** | •co-detection of cell proliferation rate | • does not necessarily indicate mutagenicity<br>• needs cell cultivation (two mitoses and two consecutive S phases)<br>• mechanism unknown<br>• addition of BrdU<br>• time consuming |

## 4. OPINION

As part of its mandate, the SCENIHR is asked to continuously monitor new information that may influence the assessment of risks to human health in the area of electromagnetic fields (EMF) and to provide regular updates on the scientific evidence base to the Commission.

In view of this, the Committee is requested to update the SCENIHR opinion of 21 March 2007 in the light of newly available information.

The Committee should furthermore provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment.

### 1. Update

#### Radio frequency fields (RF fields)

In its opinion from 2007 the SCENIHR concluded regarding Radiofrequency fields:

*"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 longterm 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.*

*RF exposure has not consistently been shown to have an effect on self-reported symptoms (e.g. headache, fatigue, dizziness and concentration difficulties) or well-being.*

*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 limited especially for long-term low-level exposure."*

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

The question receiving most attention is whether RF field exposure is involved in carcinogenesis. The previous opinion stated that, based on epidemiological findings, mobile phone use for less than ten years is not associated with cancer incidence. Regarding longer use, it was deemed difficult to make an estimate since few persons had used mobile phones for more than ten years.

Since then, a few additional epidemiological studies have been published. Unfortunately they do not significantly extend the exposure period. These studies do not change this assessment.

New improved studies on the association between RF fields from broadcast transmitters and childhood cancer provide evidence against such an association.

Animal studies show that RF fields similar to those from mobile phones, alone or in combination with known carcinogenic factors, are not carcinogenic in laboratory rodents. Certain studies have also employed higher exposure levels (up to 4 W/kg), still with no apparent effects on tumor development.

Furthermore, the in vitro studies regarding genotoxicity fail to provide evidence for an involvement of RF field exposure in DNA-damage.

It is concluded from three independent lines of evidence (epidemiological, animal and in vitro studies) that exposure to RF fields is unlikely to lead to an increase in cancer in humans. However, as the widespread duration of exposure of humans to RF fields from mobile phones is shorter than the induction time of some cancers, further studies are required to identify whether considerably longer-term (well beyond ten years) human exposure to such phones might pose some cancer risk.

Regarding non-carcinogenic outcomes, several studies were performed on subjects reporting subjective symptoms. In the previous opinion, it was concluded that scientific studies had failed to provide support for a relationship between RF exposure and self-reported symptoms. Although an association between RF exposure and single symptoms was indicated in some new studies, taken together, there is a lack of consistency in the findings. Therefore, the conclusion that scientific studies have failed to provide support for an effect of RF fields on self-reported symptoms still holds. Scientific studies have indicated that a nocebo effect (an adverse non-specific effect that is caused by expectation or belief that something is harmful) may play a role in symptom formation. As in the previous opinion, there is no evidence supporting that individuals, including those attributing symptoms to RF exposure, are able to detect RF fields. There is some evidence that RF fields can influence EEG patterns and sleep in humans. However, the health relevance is uncertain and mechanistic explanation is lacking. Further investigation of these effects is needed. Other studies on functions/aspects of the nervous system, like cognitive functions, sensory functions, structural stability, and cellular responses show no or no consistent effects.

Recent studies have not shown effects from RF fields on human or animal reproduction and development. No new data have appeared that indicate any other effects on human health.

From the risk assessment perspective it is important to recognise that information on possible effects caused by RF fields in children is limited. Furthermore, there is a lack of information on diseases other than those discussed in this report.

**Intermediate frequency fields (IF fields)**

Regarding IF fields, the previous SCENIHR opinion concluded:

*"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."*

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

Occupational exposure to IF fields in certain areas is considerably higher than exposure to the general public. However, very little research on IF and health risks in occupational

settings or for the general public have been presented since the previous opinion and no epidemiological studies have appeared. Consequently, the data are still too limited for an appropriate risk assessment.

In view of the increasing occupational exposure to IF among workers in e.g. security, shops, and certain industries it is important that research in this area is given priority.

**Extremely low frequency fields (ELF fields)**

In its opinion from 2007 the SCENIHR concluded regarding Extremely low frequency fields:

*"The previous conclusion that ELF magnetic fields are a possible carcinogen, chiefly based on childhood leukaemia results, is still valid. There is no generally accepted mechanism to explain how ELF magnetic field exposure may cause leukaemia. Animal studies have not provided adequate evidence for a causal relationship.*

*No consistent relationship between ELF fields and self-reported symptoms (sometimes referred to as electrical hypersensitivity) has 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."*

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

The new information available is not sufficient to change the conclusions of the 2007 opinion.

The few new epidemiological and animal studies that have addressed ELF exposure and cancer do not change the previous assessment that ELF magnetic fields are a possible carcinogen and might contribute to an increase in childhood leukaemia. At present, in vitro studies did not provide a mechanistic explanation of this epidemiological finding.

No new studies support a causal relationship between ELF fields and self-reported symptoms.

New epidemiological studies indicate a possible increase in Alzheimer's disease arising from exposure to ELF. Further epidemiological and laboratory investigations of this observation are needed.

Recent animal studies provided an indication for effects on the nervous system at flux densities from 0.10-1.0 mT. However, there are still inconsistencies in the data, and no definite conclusions can be drawn concerning human health effects.

Very few recent in vitro studies have investigated effects from ELF fields on diseases other than cancer and those available have very little relevance. There is a need for hypothesis-based in vitro studies to examine specific diseases.

It is notable that in vivo and in vitro studies show effects at exposure levels (from 0.10 mT and above) to ELF fields that are considerably higher than the levels encountered in the epidemiological studies (μT-levels) which showed an association between exposure and diseases such as childhood leukaemia and Alzheimer's disease. This warrants further investigations.

**Static fields**

In its opinion from 2007 the SCENIHR concluded 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."*

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

Although a fair number of studies have been published since the last opinion, the conclusion drawn there stands: there is still a lack of adequate data for a proper risk assessment of static magnetic fields. More research is necessary, especially to clarify the many mixed and sometimes contradictory results.

Short term effects have been observed primarily on sensory functions for acute exposure. However, there is no consistent evidence for sustained adverse health effects from short term exposure up to several teslas.

**Environmental effects**

In its opinion from 2007 the SCENIHR concluded regarding environmental effects:

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

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

The current database is inadequate for the purposes of the assessment of possible risks due to environmental exposure to RF, IF and ELF fields.

**Research recommendations**

The scientific rationale has identified a number of areas characterised by insufficient and contradictory information regarding possible health associated effects from the various frequency bands of the EMF spectrum. It is recommended that certain knowledge gaps are filled as outlined in the following suggestions.

RF fields (primarily frequencies relevant for mobile communication)

- *RF exposure and cancer.* A long term prospective cohort study. Such a study would overcome problems identified in 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 specific study on children exists. One way to address this is by studies on immature animals. This research has to take into consideration that dosimetry in children may differ from that in adults. This can be obtained by using a set of adequate phantoms that represent the variability in morphology and anatomy in the entire population.

- *Assessment of total exposure of individuals to RF.* 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.

- *Confirmation of important but preliminary findings.* There are several experimental studies that need to be replicated and/or extended, in particular, studies on genotoxicity and on nervous system effects involving sleep quality and EEG patterns.

IF fields

- *Investigation of possible health effects.* Data on health effects from IF fields are sparse. In view of the increasing exposure to IF particularly among workers it is

important to remedy this deficiency. Both epidemiologic and experimental studies are needed. Such studies should focus on investigations of the modified exposure conditions of the population in that frequency range.

ELF fields

- *Childhood leukaemia*. The epidemiological studies indicate an increased risk of leukaemia in children exposed to ELF fields. However, there is a lack of supporting evidence for such an effect either in animal models or in vitro studies or mechanistic investigations which must be resolved. One element of this further work should be a thorough follow up of the preliminary findings of gene deficiency and susceptibility.

- *Neurodegenerative diseases*. Further epidemiological and experimental investigations of the apparent association between ELF and the development of Alzheimer's disease should be given priority. It requires a coordinated approach involving epidemiological, in vivo and in vitro studies.

- *Dose response relationships*. Dose response studies in vivo and in vitro for exposures of 100 μT and below are required.

Static fields

- *Effects in workers*. Cohort studies on personnel dealing with equipment that generates strong magnetic fields are recommended, beginning with a thorough feasibility study.

- *Investigation of other potential effects*. Relevant experimental studies on carcinogenicity, genotoxicity, developmental and neurobehavioural effects are desirable.

Additional considerations

- *Mechanistic/mode of action studies*. At sufficiently high intensities, RF fields cause biological effects by tissue heating, while ELF fields excite nerve and muscle cells. However, despite several decades of research into biological effects of EMF, there are still no generally accepted biological effects or interaction mechanisms that would explain human health effects below the thresholds for thermal effects and nerve stimulation. Hypothesis-driven research on plausible mechanisms is necessary for major progress in evaluation of possible health risks of weak EMF.

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

## 2. Methodological Framework

The SCENIHR is asked to provide a methodological framework and corresponding guidelines to evaluate available scientific evidence in order to ensure the best possible quality for risk assessment. The subject is covered in detail in chapter 3.8 of the opinion.

The present opinion provides a methodological framework and guidelines as:

- a general outline of criteria used for making EMF health risk assessment
- a description of the work procedure leading to the overall evaluation
- a specialised section where characteristics and quality criteria regarding dosimetry and exposure assessment, epidemiology, human laboratory studies, in vivo studies, and in vitro studies are presented.

## 5. MINORITY OPINION

None

## 6. LIST OF ABBREVIATIONS

| | |
|---|---|
| **µT** | Microtesla |
| **µW** | Microwatt |
| **ALS** | Amyotrophic Lateral Sclerosis |
| **AM** | Amplitude modulation |
| **AP** | Apurinic/apyrimidinic |
| **ATP** | Adenosine triphosphate (?) |
| **BMI** | Body Mass Index |
| **CA** | Chromosomal Aberration |
| **cDNA** | complementary DNA |
| **CENELEC** | European Committee for Electrotechnical Standardization |
| **CFL** | Compact Fluorescence Lamps |
| **CI** | Confidence Interval |
| **cm** | centimeter |
| **$cm^2$** | Square centimeter |
| **CNS** | Central Nervous System |
| **COR** | Interaction odds ratio, Case-only odds ratio |
| **CREST** | Calcinosis cutis Raynaud-Syndrome Esophageal dysfunction Sclerodactylia Teleangiectasia antibodies |
| **CSTEE** | Scientific Committee on Toxicity, Ecotoxicity and the Environment |
| **CW** | Continuous wave |
| **d** | day |
| **DECT** | Digital Enhanced Cordless Telephone |
| **DMBA** | 7,12-dimethylbenz[a]anthracene |
| **DNA** | Deoxyribonucleic acid |
| **DVB-T** | Digital Terrestrial Television |
| **EEG** | Electroencephalogram |
| **E-field** | Electric field |
| **EHS** | Electromagnetic hypersensitivity |
| **ELF** | Extremely low frequency |
| **EMF** | Electromagnetic field |
| **EMS** | Ethylmethanesulfonate |
| **ENU** | Ethylnitrosourea |
| **f** | Frequency |
| **FDTD** | Finite Differences in Time Domain |
| **FEM** | Finite Element Method |
| **FISH** | Fluorescence in situ hybridization |
| **FM** | Frequency Modulation |
| **g** | gram |
| **GHQ** | General health questionnaire |

| | |
|---|---|
| **GHz** | Gigahertz |
| **GSI** | Global severity index |
| **GSM** | Global System for Mobile Communication |
| **H** | Magnetic field strength |
| **h** | hour |
| **hLECS** | Human lens epithelial cells |
| **HSP** | Heat-shock Proteins |
| **Hz** | Frequency in Hertz |
| **IARC** | International Agency for Research on Cancer |
| **ICNIRP** | International Committee on Non Ionising Radiation Protection |
| **IF** | Intermediate frequencies |
| **IL** | Interleukin |
| **kg** | Kilogram |
| **kHz** | Kilohertz |
| **km** | Kilometer |
| **kV** | Kilovolt |
| **m** | Meter |
| **$m^2$** | square meter |
| **MAPK** | Mitogen-activated Protein Kinase |
| **MF** | Magnetic field |
| **MHz** | Megahertz |
| **min** | Minute |
| **MMS** | Methyl methane sulfonate |
| **MN** | Miconucleus (-i) |
| **MOM** | Method Of Moments |
| **MRI** | Magnetic Resonance Imaging |
| **mRNA** | Messenger ribonucleic acid |
| **MS** | Member States |
| **mT** | Millitesla |
| **mW** | milliwatt |
| **MX** | 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanonen |
| **NMR** | Nuclear Magnetic Resonance |
| **nT** | Nanotesla |
| **nW** | Nanowatt |
| **ODC** | Orthinine decarboxylase |
| **OR** | Odds Ratio |
| **RF** | Radio Frequency |
| **ROS** | Reactive Oxygen Species |
| **RR** | Relative Risk |
| **SAR** | Specific Absorption Rate |
| **SCE** | Sister Chromatid Exchange |

| | |
|---|---|
| **SCENIHR** | Scientific Committee on Emerging and Newly Identified Health Risks |
| **SCGE** | Single-cell Gel Electrophoresis |
| **SCL** | Symptom checklist |
| **SMF** | Static Magnetic Field |
| **SMS** | Short Message Service |
| **SSC** | Scientific Steering Committee |
| **SSP** | Swedish university Scales of Personality |
| **STROBE** | STrengthening the Reporting of OBservational studies in Epidemiology |
| **T** | Tesla |
| **THz** | Terahertz |
| **TMS** | Transcranial magnetic stimulation |
| **TNO** | Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek (Netherlands Organisation for Applied Scientific Research) |
| **UMTS** | Universal Mobile Telephony System |
| **UNEP** | United Nations Environmental Programme |
| **UWB** | Ultra-Wide Band |
| **V** | Volt |
| **VDT** | Video Display Terminals |
| **VDU** | Video Display Units (for computers, videos, TV and some measurement devices using cathode ray tubes) |
| **VGPC** | Voltage gated potassium channel |
| **W** | Watt |
| **W-CDMA** | Wideband Code Division Multiple Access |
| **WHO** | World Health Organisation |
| **WiMAX** | Worldwide Interoperability for Microwave Access |
| **WLAN** | Wireless Local Area Network |

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## 8. GLOSSARY

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

**Alpha-band/waves:** A specific frequency range (8-13 Hz) of the human EEG activity which is associated with relaxed wakefulness.

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

**Confounding factor (confounder):** A confounding factor in an epidemiological study is a variable which is related to one or more of the variables defined in a study. The confounder may mask an actual association or falsely demonstrate an apparent association between the study variables where no real association between them exists. If confounding factors are not measured and considered, bias may result in the conclusion of the study.

**Contralateral**: On the opposite from another structure.

**Contralateral use of mobile phone**: Preferred side of the head during mobile phone use corresponds to the side of the head opposite to the tumour.

**Crossover design**: A cross over design is a special situation where a separate comparison group is not present. Instead, each subject receives both treatments or is exposed to both sham and active exposure and the outcomes under the two conditions are compared within the same subjects. Thus, the subject serves as his/her own control. Ideally in a crossover design, a subject is randomly assigned to a specific treatment/exposure order.

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

**Double-blind (study):** Blinding is used to prevent conscious as well as subconscious bias (e.g. by expectations) in research. In a double-blinded study the participants as well as the researchers are unaware of (blind to) the nature of the treatment (e.g. a new drug or placebo) or the exposure condition (e.g. the exposure under study or sham) that the participants receive in the study.

**Ecological studies:** An ecological or correlational study is one in which the unit of analysis is an aggregate of individuals and information is collected on this group rather than on individual members. The association between a summary measure of disease and a summary measure of exposure is studied. An error of reasoning occurs when conclusions are drawn about individuals from data that are associated with groups, as relationships observed for groups may not necessarily hold for individuals.

**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).

**Electroencephalogram (EEG)**: Extracellular recording of the electrical activity of the cerebral cortex.

**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.

**Far field:** The far field of an antenna or other source of an electromagnetic field is the field that is at a distance away which is far exceeding the wavelength of the field.

**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.

**Ipsilateral**: On the same side as another structure.

**Ipsilateral use of mobile phone:** Preferred side of the head during mobile phone use corresponds to the side of the head where the tumour is located.

**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 $F = q*(v \times B)$ 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 $H = B/\mu$ 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.

**Near field**: The near field of an antenna or other source of an electromagnetic field is the field in the close vicinity of the source, much less than the wavelength of the field.

**Nocebo** A nocebo effect is an adverse, non-specific effect caused by expectation or belief that something is harmful.

**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 such an unexpected dependence upon an experimental variable that it is difficult to see how heating could be the cause.

**Permeability (μ):** A property of a material 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 watt per square meter ($W/m^2$).

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

**Sham exposure:** A control condition used to simulate the environmental conditions of the exposure under study, but in absence of exposure (Similar to Placebo-controlled, which is a term used to de scribe a method of research in which an inactive substance (a placebo) is given to one group of participants, while the treatment (ususally a drug or a vaccine) being tested is given to another group. The results obtained in the two groups are then compared to see if the investigative treatment is more effective (or has more negative effects) than placebo. Both treatments may also be given in succession to the same subjects, see crossover design.)

**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).

**Static 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.