EUROPEAN COMMISSION

Directorate-General for Health & Consumers

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Research needs and methodology to address the remaining knowledge gaps on the potential health effects of EMF

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

SCENIHR adopted this opinion at its 3rd plenary of 6 July 2009

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They are: the Scientific Committee on Consumer Safety (SCCS), 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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SCENIHR

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Scientific Committee members

Anssi Auvinen, James Bridges, Kenneth Dawson, Wim De Jong, Philippe Hartemann, Peter Hoet, Thomas Jung, Mats-Olof Mattsson, Hannu Norppa, Jean-Marie Pagès, Ana Proykova, Eduardo Rodríguez-Farré, Klaus Schulze-Osthoff, Joachim Schüz, Dorothea Stahl, Mogens Thomsen, Theodorus Vermeire

Contact:

European Commission
DG Health & Consumers
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

Sanco-Sc1-Secretariat@ec.europa.eu

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ACKNOWLEDGMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

SCENIHR members:

Prof. Mats-Olof Mattsson (*Chair and Rapporteur)*

Prof. Anssi Auvinen

Prof. James Bridges

Dr. Hannu Norppa

Dr. Joachim Schüz

External experts:

Prof. Jukka Juutilainen, Department of Environmental Science, University of Kuopio, Finland

Dr. Georg Neubauer, Business Unit EMC & Optics, Seibersdorf Laboratories GmbH, Seibersdorf, Austria

Prof. Dr. Myrtill Simkó, Austrian Academy of Science, Institute for Technology Assessment, Vienna, Austria

Dr. Eric van Rongen, Health Council of the Netherlands, The Hague, The Netherlands

All Declarations of working group members are available at the following webpage:

http://ec.europa.eu/health/ph_risk/committees/04_scenihr/scenihr_memberswg_en.htm

ABSTRACT

SCENIHR has been asked to provide more details on the research recommendations presented in the SCENIHR opinion on the health effects of electromagnetic fields (EMF) adopted on 19 January 2009. The present opinion makes specific recommendations regarding research covering several frequency bands (radio frequency (RF) fields, intermediate frequency (IF) fields, extremely low frequency (ELF) fields, static fields) and also considers environmental aspects.

All the studies that are suggested in this opinion are considered very important and given high priority based on their relevance for fundamental understanding of the issue and/or their relevance for public health. However, this opinion strongly suggests that three work packages (WP) are given extra consideration. These work packages are restricted to a specific frequency band and are multidisciplinary.

WP1: RF fields

a. Health effects of RF fields from wireless communication in adults

b. RF field mechanisms and verification of preliminary but important findings

WP2: IF fields

Possible health effects (pregnancy outcome) of IF

WP3: ELF fields

Association between ELF and neurodegenerative diseases

The opinion also identifies separate studies within the three work packages that have the potential to provide relevant results within a time-frame of 2-3 years.

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

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EXECUTIVE SUMMARY

Recently, SCENIHR delivered its opinion on Health Effects of Exposure to EMF where considerable knowledge gaps in a number of areas regarding possible health effects from various frequency bands were identified (SCENIHR 2009). Accordingly, a number of research recommendations were suggested to overcome deficiencies in data necessary for proper risk assessment.

SCENIHR is now requested:

1. To provide more details on the research recommendations presented in the SCENIHR opinion on the health effects of EMF adopted on 19 January 2009. This would include in particular the definition of the main scientific gaps addressed by each recommendation. It should also include methodological guidance on the experimental design, and on the requirements to ensure data quality and comparability as well as the usability of the results for risk assessment.
2. To prioritize these research recommendations.
3. To develop a research strategy based on studies which are feasible and able to deliver results within a reasonable time-frame.

Opinion

1. Research recommendations

Radio frequency fields

- Health effects from RF fields from wireless communication in adults (prospective cohort study).
- Health effects from RF fields from wireless communication in children (interdisciplinary research including dosimetry, epidemiology and animal studies).
- RF field mechanisms and verification of important but preliminary findings (experiments testing the existence of modulation-specific effects or demodulation of RF signals in biological structures; experimental studies on EEG patterns and sleep.

Intermediate frequency fields

Investigation of possible health effects (interdisciplinary research focusing on pregnancy outcome and selected biomarkers in personnel working close to anti-theft devices, including dosimetry, biomarker studies, epidemiology, and in vivo and in vitro studies).

Extremely low frequency fields

- Experimental studies relevant to possible carcinogenicity of ELF fields (laboratory studies using in vitro and/or animal models).
- Studies on the association between ELF magnetic fields and neurodegenerative diseases (epidemiological study (cohort study or register-based case-control study) on Alzheimer's Disease and laboratory study using animal and possibly in vitro models of Alzheimer’s Disease).

Static fields

- Epidemiological studies on patients and workers (feasibility study of pediatric MRI patients; cohort studies on personnel dealing with equipment that generates strong static magnetic fields including biomarker studies of possible cancer risk).
- Experimental studies on possible health effects (experimental animal and in-vitro studies on end-points relevant for human health, including genotoxicity; experimental human and animal studies on possible cognitive effects of exposure to magnetic

gradient fields; experimental human studies on the functioning of the cardiovascular system at flux densities > 3 T).

Additional considerations

Environmental effects (comparison of selected ecosystem(s) before and after the installation of a new facility and/or located at varying field strengths from specific ELF EMF source(s)).

2. Priorities

All the studies that are suggested in this opinion are considered very important and given high priority based on their relevance for fundamental understanding of the issue and/or their relevance for public health. However, this opinion strongly suggests that three work packages (WP) are given extra consideration. These work packages are restricted to a specific frequency band and are furthermore multidisciplinary, including dosimetry and exposure assessment, epidemiological studies, and experimental studies. Taken together, the studies in each work package are also relevant for understanding the issue and for public health.

WP1: RF fields

a. Health effects of RF fields from wireless communication in adults (prospective cohort study).

b. RF mechanisms and verification of preliminary findings.

This WP is assigned a very high priority since exposure to RF fields (from mobile phones and other wireless devices) is ubiquitous in the general population and still on the rise. Although recent studies did not find strong evidence for adverse health effects from RF, the number of studies on longer term exposure (beyond ten years of exposure) is very small and considerable scientific uncertainty remains. Outcomes other than cancer and exposures other than mobile phones have been sparsely studied and a broader approach is recommended.

WP2: IF fields

Possible health effects (pregnancy outcome) of IF fields.

This WP is assigned a very high priority since there are generally few studies on IF field exposures. It is recommended to focus on IF field exposures from e.g. anti-theft devices in shops and pregnancy outcome because of the exposed area of the body, the exposure possibly exceeding reference levels, and the number of young women working in these jobs.

WP3: ELF fields

Association between ELF fields and neurodegenerative diseases.

This WP is assigned a very high priority since especially Alzheimer´s Disease is relatively common and there are some recent studies suggesting an increased risk with higher ELF field occupational and residential exposure. There are, however, also some studies not showing any association and there is no known mechanism how ELF fields could cause neurodegenerative disease. Hence, it is important to conduct further epidemiological and experimental studies to generate more data.

3. Research strategies

Within each of the three work packages, studies are identified that have the potential to deliver relevant results within a time-frame of 2-3 years.

1. BACKGROUND

Council Recommendation 1999/519/EC of 12 July 1999[1] on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz) fixes basic restrictions and reference levels for the exposure of the general public to electromagnetic fields (EMF). These basic restrictions and reference levels are based on the guidelines published by the International Commission on Non Ionising Radiation Protection (ICNIRP)[2].

This Council Recommendation provides the framework that was used to develop EU legislation regarding products that emit EMF (the Low Voltage Directive (LVD) 2006/95/EC[3] and the Radio and Telecommunications Terminal Equipment (R&TTE) Directive 1999/5/EC[4] as well as protection of workers (Directive 2004/40/EC[5]).

Council Recommendation 1999/519/EC also requires that the Commission monitor the state of the science in order to assess whether the proposed exposure limits remain adequate to ensure a high level of protection for the public. The Commission has asked its successive independent Scientific Committees to perform this task (SSC 1998[6]; CSTEE 2001[7]; SCENIHR 2007[8]; SCENIHR 2009[9]).

The opinion delivered by the SCENIHR in January 2009 confirmed the conclusions of the previous assessments, namely that there is so far no scientific evidence that justifies a change in the rationale used to set up the current exposure limits.

However, the SCENIHR also referred to the limited database available to perform this assessment and highlighted again a number of areas characterised by insufficient and contradictory information regarding possible health effects from the various frequency bands and recommended that certain knowledge gaps be filled.

Simultaneously, the issue of the possible health effects of EMF remains a very sensitive political subject. As a result, more research is needed to resolve the uncertainties leading to many scientific debates and unreasonable calls for the application of the precautionary principle. This was one of the main conclusions of a workshop on "*EMF and Health: Science and Policy to address public concerns*" that Directorate General (DG) Health and Consumers (SANCO) organised on 11-12 February 2009 together with DG Enterprise and Industry (ENTR).

There is also a need to support the scientific review of the World Health Organization (WHO) on this topic planned for 2015.

The Commission, through the 7th Framework Programme for Research and Development (FP7), can finance such research through calls for proposals launched on a yearly basis. The calls for 2010 are being finalised in the months of March and April 2009.

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

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

[3] http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_374/l_37420061227en00100019.pdf

[4] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1999:091:0010:0028:EN:PDF

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

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

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

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

[9] http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_022.pdf

2. TERMS OF REFERENCE

As a result, and in order for the Commission to be in a position to propose the most relevant topics on this issue for funding in the next calls of FP7, the Committee is requested:

1. To provide more details on the research recommendations presented in the SCENIHR opinion on the health effects of EMF adopted on 19 January 2009. This would include in particular the definition of the main scientific gaps addressed by each recommendation. It should also include methodological guidance on the experimental design, and on the requirements to ensure data quality and comparability as well as the usability of the results for risk assessment.
2. To prioritize these research recommendations.
3. To develop a research strategy based on studies which are feasible and able to deliver results within a reasonable time-frame.

3. INTRODUCTION

3.1. Preamble

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) presented its opinion on Health Effects of Exposure to EMF in 2009 (SCENIHR 2009). The opinion discussed EMF in separate sub-sections based on frequency bands (radio frequency fields (RF) (100 kHz < f ≤ 300 GHz), intermediate frequency fields (IF) (300 Hz < f ≤ 100 kHz), extremely low frequency fields (ELF) (0 < f ≤ 300 Hz), and static fields (0 Hz) (only static magnetic fields were considered in this opinion). In addition, effects relevant for environmental species were discussed. The opinion noted significant knowledge gaps in all these areas, and, accordingly, made recommendations for research that would be able to cover these knowledge deficiencies. All statements regarding the specific state of knowledge are discussed in detail in the mentioned SCENIHR opinion (2009).

In order to make specific research recommendations, it is necessary to define the context of the research field and its shortcomings, as well as criteria for the type of studies that the recommendations identify. This is discussed below.

3.2. Strategic Framework

For risk assessment purposes, it is fundamental to have a thorough understanding of the exposure situation, be it for the general public or for specific occupational settings. Regarding RF fields, multiple sources are contributing to exposure (mobile phones and their base stations, DECT telephony, WiFi, Bluetooth, RFiD, DVB-T etc.) which has to be taken into account in future studies. For IF and static fields, occupational exposure in particular is expected to increase and give rise to groups with high exposures. There is a general lack of knowledge regarding these exposures, prompting research efforts to remedy this situation.

A general recommendation is to develop protocols on how emission and exposure should be measured. The applicability of such protocols needs to be tested in samples representative of the general population.

Despite many years of research into biological and health effects of EMF, there are no generally accepted mechanisms that could explain possible effects at levels below those which cause tissue heating (for RF fields) and tissue excitation (for ELF fields). Hypothesis-driven research on plausible mechanisms is thus necessary for major progress in the evaluation of possible health risks of EMF that are below levels of current guidelines (see chapter 1).

Regarding RF fields a potentially important question is the possibility of specific effects due to amplitude modulation (addressed specifically in chapter 4). Concerning ELF fields, three proposed mechanisms stand out as most plausibly operating at low field levels: the radical pair mechanism, the impact of magnetite-containing structures, and the impact of induced electric fields in neural networks. Mechanistic considerations should be integrated in experimental studies evaluating biological effects of ELF fields.

Other considerations focus on taking combinations of exposures into account. Two types of combinations are considered here: 1. Combinations of exposure from different frequency bands. 2. Combinations with other physical or chemical factors. However, it might be premature to investigate combinations of frequencies as long as results from individual frequency bands need confirmation and better understanding. Studies on combinations of EMF and other physical and chemical factors can be integrated in the recommendations presented in the opinion below.

Research is vital in the following overlapping areas to fill the most relevant knowledge gaps for risk assessment:

1. If epidemiological studies have indicated that the incidence of a particular disease / adverse effect / endpoint of high concern is increased by exposure to EMF.
2. If in vitro / animal / human studies with EMF have identified biological changes / mechanisms that suggest an association with a particular disease / adverse effect / endpoint of high concern.
3. If methodology or background data or mechanistic studies need to be established to allow that studies on 1. and 2. are optimised.
4. If exposure to emerging and/or existing EMF technologies is occurring but data regarding the extent of exposure are insufficient for risk assessment applied to humans and the environment.
5. If there is a complete lack of knowledge on specific exposure scenarios.

3.3. Study criteria

3.3.1. Dosimetry

Reliable studies on biological effects of EMF require adequate exposure facilities and exposure assessment procedures.

An exposure set up for experimental studies must allow reproducible and accurate exposure, i.e. the EMF must be well defined at the site of the cell culture or in the specific tissue(s) of animals or volunteers. The variations on the induced fields due to e.g. posture or size of test animals should be minimized. Moreover, environmental conditions such as temperature, humidity, and background electromagnetic fields have to be controlled. Uncertainty analysis is an important part of the study.

To assess exposure both for scientific studies and compliance two approaches are available: measurements and calculations. The adequate selection of the equipment for measurements depends on the type, the magnitude, and the variability of the signals from the emitting sources and the purpose of the study. When performing exposure assessment, ambient conditions and multisource exposure have to be considered. It is furthermore necessary to describe the uncertainty when giving exposure assessment results.

3.3.2. Power calculation

Realistic calculations regarding statistical power (sample size) must be presented. Two-sided testing is preferable to one-sided, unless one direction of effect is logically impossible. Beta level for type II error is conventionally set at 0.1-0.2 (with probability of detecting the effect, given it exists, at 0.8-0.9). The effect size which is used for such calculations have to be justified by e.g. results from other studies. The frequency of occurrence of outcome should be based on a relevant population with a specified age and sex distribution. It is necessary that outcomes are stringently defined based on objective criteria. Comparability of information should be ensured by study design with similar procedures in groups to be compared. Blinding should be used where applicable. The exposure distribution has to be defined and optimally derived from feasibility (pilot) studies. Exposure assessment in non-experimental studies needs to include quantitative assessment of uncertainty, ideally by means of validation studies.

Data analysis has to be based on detailed analysis plans prepared in advance. Exclusion and eligibility criteria should be clearly defined. In grouping by exposure level or other features, selection of cut-points should be justified. Potential confounding factors should be identified in the study protocol as well as valid methods used for their assessment.

3.3.3. Cohort design

In EMF research, cohort studies must be particularly large (as rather small-to-moderate health effects are expected) and long-term (due to outcomes of interest with presumably long induction periods) to deliver meaningful results. Hence, the feasibility of all design features and study procedures has to be demonstrated in advance. This applies to the enrolment of study subjects, exposure assessment, and traceability of subjects over time. The latter includes both follow up of contact data (for repeated exposure assessment), follow up of vital status and emigration (for the calculation of person years under risk), and follow up of the investigated outcomes. For enrolment it needs to be demonstrated that a cohort reflecting a wide range of exposures can be assembled, with sufficient statistical power under the consideration of the age-, gender- and exposure distribution of the cohort. For exposure assessment, it is necessary to show how well the exposure proxy applied to a large cohort represents the actual exposure of interest, and, in this field of rapidly changing technologies, it is necessary to demonstrate how the individual's exposure will be monitored over time.

3.3.4. Biomarker studies

Biomarkers can be used to assess the biological effects of EMF in subgroups of exposed subjects, such as subsamples of cohort studies. Adequate individual exposure assessment and, depending on the end-point, estimation of concurrent and past exposures that could affect the measurements are crucial for biomarker studies. The choice of a proper, unexposed control group, matched to the exposed group as closely as possible for sex, age, and social group is also important. Information should be gathered on various factors that could affect the outcome, such as life-style, medication, and medical history.

3.3.5. Human 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: 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. Such studies should be double blind to prevent expectations of participants or researchers to distort the results, and subjects should be randomly allocated to the different exposure conditions. Before starting the blinded experiments, open provocation may be useful to demonstrate the adequacy of the experimental setting. Sham exposure should also be incorporated. A cross-over design, where the same individuals are exposed to both (or several) conditions in a random order, is preferred but needs to take into account any possible carry-over effects. Habituation sessions during which the participants will be acquainted with the procedures and setups may be useful. Consideration has also to be given to the choice of the study group. A very homogenous group (e.g. with regard to age and sex 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.

If possible, objectively measured data (e.g. heart rate, blood chemistry etc.) are desirable since self-reported effects are more difficult to assess.

3.3.6. Animal studies

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. Extrapolation from animal experiments to humans should always include consideration of the validity of the animal model used – relevant animal models do not exist for a number of human diseases that are of interest from an EMF-perspective. Nevertheless, at a molecular level, many basic processes, such as DNA damage and repair, are similar in animals and humans. Therefore, animal studies have remained a cornerstone in evaluating toxicity of chemical and physical agents.

Properly performed animal studies need to consider the following characteristics: (i) Characteristics of the animal (e.g. sex, age, species, strain) (ii) Number of animals per group (iii) Random group allocation (iv) Appropriate exposure levels and treatment durations (v) Adequate duration of observation with respect to the health endpoint addressed (vi) Identical treatment of exposed and control groups apart from the exposure of interest, (vii) Adequate endpoints and measurements (viii) Dose-response relationships (ix) Negative, sham, and, where appropriate, positive control groups.

3.3.7. In-vitro studies

In-vitro studies investigate toxicological, mechanistic, and other relevant effects to increase understanding of the development of cancer and other diseases. Therefore, the appropriate cell types have to be used for the proper identification of biological effects. It is useful to consider functional studies that are investigating several cellular processes (and/or alterations in physiological processes). The novel methods that act on a large scale (high-throughput screening; "-omics") can be used for studies of e.g. gene transcription, protein expression and modification, and cellular metabolism. Such approaches can be instrumental in providing mechanistic understanding of possible effects of EMF. To provide information about genotoxic capacity, a battery of techniques and methods are available, ideally, the used methods should confirm and/or complement each other.

When performing experiments it is essential to employ accurate control conditions. Both positive and negative controls should be included. 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 and documented conditions regarding field characteristics (e.g. frequency conditions, flux density, SAR-values, modulations), temperature, CO_2, exposure-response relationships, experimental timing etc. 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 ensure reproducibility of findings, harmonization of study protocols by means of "Round-Robin" routines is recommended.

3.4. Priorities

All the research recommendations suggested are important to fill identified knowledge gaps. However, this opinion makes priorities that are based on the suggested study´s relevance for:

- Fundamental understanding of the scientific issues (adding substantially to the existing knowledge base, having relevance for understanding of mechanisms).
- Public and occupational health (taking into account the population affected, size of risk, occurrence and severity of outcome, exposure levels, development of incidence over time, etc.).
- Likelihood of producing the required information within a reasonable time frame.

Furthermore, the suggested studies should not be already the subject of substantial ongoing research activity. It is also advantageous if the studies are multidisciplinary, invoking an integration of high quality exposure and effects methodologies.

4. OPINION

4.1. Reply to Question 1 of ToR – Research Recommendations

4.1.1. Radio frequency Fields

4.1.1.1. Health effects of RF fields from wireless communication in adults

Study type

Prospective cohort study.

Rationale/justification

A long-term prospective cohort study is the next logical step in the hierarchy of evidence following inconclusive results of previous case-control studies. A cohort study overcomes shortcomings of case-control studies, such as recall bias and selection bias, as well as uncertainty due to self-reported retrospective exposure assessment. Such a study would also significantly expand the narrow scope of outcome in previous studies that were mainly limited to intracranial tumours. Additional outcomes include e.g. neurological diseases, cerebrovascular diseases, and other types of cancer. Prospective studies can consider not only the effects of current exposure but also exposure history incurred prior to start of follow-up as well as exposure from new technologies, developed during the course of the study.

Minimum technical requirements to ensure relevance and usability of results

- Feasibility studies are needed to demonstrate availability of traffic records (call-time) from several major network operators.
- Sample sizes should be adequate to show realistic effect sizes.
- An internal analysis within the cohort by amount of mobile phone use and other RF field exposures must be performed.
- Appropriate follow-up needs to be ensured by use of population-based registries for ascertainment of vital status and disease outcomes.
- The study duration should be suitably long to allow for the delivery of reliable results in several outcomes.

Expected impact of results (use for Risk Assessment)

In classifications of level of evidence in evidence-based medicine[10], well-conducted prospective cohort studies are characterized as providing the second strongest evidence for a causal association right after randomized intervention studies, which are not feasible in the field of RF field exposure and risk of chronic diseases. Both positive and negative results have a relevant impact.

[10] See e.g. http://www.cebm.net/index.aspx?o=1025 and http://www.cochrane.org/consumers/sysrev.htm

4.1.1.2. Health effects of RF fields from wireless communication in children

Study type

Interdisciplinary research including dosimetry, epidemiology, and animal studies.

Rationale/justification

Children are exposed to RF fields from mobile telecommunications equipment earlier and thus have longer life-time exposure than present day adults. They may also be more susceptible than adults due to anatomical and morphological differences and as they are exposed during development. Available and ongoing research is mainly limited to case-control studies on childhood brain tumours.

Hardly any research has been done on the effects of exposure to EMF on the development of the central nervous system, on cognitive functions in children, and on behaviour.

More data are also needed on children younger than those who have been studied to date.

Animal experiments on early brain and behaviour development can answer some of the questions related to effects on children.

Minimum technical requirements to ensure relevance and usability of results

The dosimetry study should consider:

- The relation between exposure and SAR (to ensure protectiveness of reference levels).
- Both near field and far field exposure, and partial and whole body exposure.
- Use available sets of phantoms.
- Moreover, exposure patterns typical of children and adolescents should be investigated, and thus not only the exposure arising from mobile phone use in the talk mode (e.g. SMS or use of RF field transmitting toys etc.).

For epidemiological studies in children (different age groups), the following features have to be considered:

- Feasibility studies need to be performed initially due to a lack of adequate study set-ups for children.
- Exposure assessment is more difficult than in adults as children are not the owners of their mobile phones.
- When a broad age range is covered, questionnaires must be both applicable to young and older children and, most likely, interviews have also to be performed with the parents.

It is furthermore recommended that an epidemiological study should focus on both behavioural problems and cognitive development in children, especially since the on-going case-control studies MOBIKIDS[11] and CEFALO[12] already address the question of cancer.

[11] http://mbkds.com/

[12] http://childhoodcancerregistry.ch/index.php?id=2283

Most chronic diseases in children are very rare, making it more difficult to achieve sufficient statistical power to detect reasonable effect sizes. To achieve sufficient power is even more hampered by the fact that many diseases as well as amount of mobile phone use are age-dependent and sufficient variability of exposure in the age strata needs to be demonstrated. For cognitive outcomes, reverse causation is a concern.

Experimental animal studies on brain functions and on early brain and behaviour development should be performed in young animals of several species with life-long exposure (daily exposure in animals from early age throughout immaturity).

In addition, experiments on human volunteers as well as in vitro studies should be considered since they would provide data on possible acute cognitive effects and on mechanisms, respectively.

Expected impact of results (use for Risk Assessment)

It has been suggested that children are more sensitive than adults to RF fields since they exhibit different dosimetry properties and have organ systems, including the nervous system, that are undergoing development. To what extent this is true is unclear at present. This study would fill several of these knowledge gaps and provide a foundation for risk assessment of children's exposure to RF fields.

4.1.1.3. RF field mechanisms and verification of important but preliminary findings.

Study type

a) In vitro, animal or human experiments testing the existence of modulation-specific effects or demodulation of RF signals in biological structures.

b) Experimental animal and human studies on EEG patterns and sleep parameters.

Rationale/justification

There are no generally accepted interaction mechanisms that would explain human health effects below the thresholds for well-known effects that serve as the basis for current exposure limits: thermal effects at high RF field levels and nerve stimulation at lower frequencies. An interesting and potentially important question is the possibility of specific effects from amplitude-modulated RF fields. Hypothesis-driven research on the most plausible mechanisms is necessary for evaluating the possibility of any biological effects from RF EMF below recommended limits.

There is some evidence that RF field exposure influences brain activity as seen by EEG studies in humans where exposure has caused amplification of the so-called alpha-band. 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 nervous system processes such as sleep and EEG.

Minimum technical requirements to ensure relevance and usability of results

Knowledge regarding dose-relationships and/or threshold levels for effects is essential.

Expected impact of results (use for Risk Assessment)

The results of the proposed mechanism studies would be helpful in evaluating the plausibility of any biological or health effects from low-level modulated RF fields. Amplitude-modulated signals are commonly used in mobile communication systems.

The studies on nervous system function would have high impact on the evaluation of potential effects of RF fields, in particular from mobile communication technologies, on user's cognitive capabilities.

4.1.2. IF fields

4.1.2.1. Investigation of possible health effects

Study type

Interdisciplinary project on health effects in specific occupational settings.

This should examine pregnancy outcome and selected biomarkers in personnel working close to anti-theft devices. This would include dosimetry, biomarker studies, epidemiology, as well as experimental in vivo and in vitro studies.

Rationale/justification

In contrast to the large amount of evidence available on ELF and RF fields, studies on health effects from IF fields are sparse, and inadequate for risk assessment. 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. 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). Depending on the type of system, these applications are operated at very different frequencies ranging from some tens of Hz to a few GHz although the majority of these applications operate in the intermediate frequency range. It is known that under worst case conditions, the so-called reference levels (used in relevant legislation and guidelines – see chapter 1) can be exceeded when in close proximity to some systems.

There is a general lack of studies in the IF range, comprising all major outcomes such as cancer, neurological disease, and cardiovascular disease. However, there is currently no strong evidence why IF studies on these endpoints should be started as long as there is scientific uncertainty in the RF and ELF range that needs to be resolved. An exception is pregnancy outcome and IF, e.g. from anti-theft devices in shops, because of the exposed area of the body, the exposure possibly exceeding reference levels, and the number of young women working in these jobs.

Minimum technical requirements

- The exposure in the chosen setting has to be characterised taking into account whether ELF and/or RF frequency components may dominate.
- The epidemiological part of the study needs to identify large enough populations with sufficient occupational exposure to IF fields to detect realistic effect sizes. Appropriate control groups should be chosen for the biomarker studies.
- In the laboratory studies, appropriate exposure systems have to be developed that should correspond to real-life human exposure.

Expected impact of results (use for Risk Assessment)

Current exposure limits for IF fields are based on extrapolation from the known effects of short-term exposure to ELF and RF fields. The proposed studies would produce specific data for evaluating the adequacy of the exposure limits and for well-founded assessment of health risks that might result from long-term exposure to IF fields.

4.1.3. ELF fields

4.1.3.1. Experimental studies relevant to possible carcinogenicity of ELF fields

Study type

Laboratory studies using *in vitro* and/or animal models.

Rationale/justification

The fact that the epidemiological 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. Both some earlier and more recent in vitro studies have 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. It is unlikely that exposure to ELF fields induces direct damage to DNA, therefore alternative mechanisms must be hypothesised.

Minimum technical requirements

- Hypothesis-driven experiments should be based on experimental models that have shown responses to ELF magnetic fields.
- Threshold levels and dose-response relationship below 100 μT should be addressed.

Expected impact of results (use for Risk Assessment)

The proposed studies will potentially help to resolve the current uncertainty concerning existence of adverse health effects from weak (below 1 μT) environmental ELF magnetic fields. The results may have important consequences for risk assessment and management and may have impact on understanding the interaction mechanisms between cells and ELF fields.

4.1.3.2. Studies on the association between ELF magnetic fields and neurodegenerative diseases

Study type

a) Epidemiological study (cohort study or register-based case-control study) on Alzheimer's Disease. Residential exposure or clearly defined occupational groups are preferable. Data on other neurodegenerative diseases (such as Parkinson's Disease or ALS) can be included, although the evidence is weaker than for Alzheimer’s disease.

b) Laboratory study using animal models (and possibly additional in vitro models) of Alzheimer’s disease.

Rationale/justification

Some recent epidemiological studies have shown indications of an association between long-term ELF exposure and an increased risk of Alzheimer's disease in occupational settings and also among people residing in the proximity of power lines. However, the evidence is inconclusive and further epidemiological and also laboratory studies are needed to provide adequate data for evaluating a possible causal relationship behind the associations reported.

Minimum technical requirements

- Epidemiological studies: A reliable estimate of magnetic field exposure needs to be available. The sample size needs to be adequate to show realistic effect sizes.
- Laboratory studies: Appropriate experimental model for Alzheimer's disease; the dose-response relationship should be addressed (including levels relevant for human exposure).

Expected impact of results (use for Risk Assessment)

The impact would be high as neurodegenerative diseases such as Alzheimer´s disease are relatively common.

4.1.4. Static fields

4.1.4.1. Epidemiological studies on patients and workers.

Study type

a) Feasibility study of pediatric MRI patients. The first stage in preparing a study is a pilot phase that evaluates the feasibility of a full study. As for the eventual full study, a retrospective cohort study has the advantage of allowing future extension of follow-up and incorporation of several end-points. Internal comparison between patients with different levels of exposure (number of examinations, various body parts examined) would be the most appropriate design.

b) Cohort studies on personnel dealing with equipment that generates strong static magnetic fields. The cohort could preferably be used for biomarker studies of possible cancer risk.

Rationale/justification

a) MRI is increasingly used in pediatric imaging diagnostics. Both patients and staff are exposed to static fields up to several Tesla, but patients are also exposed to some extent to RF fields (MHz range) and gradient fields around 1 kHz during imaging. It is commonly used in imaging of the head, spine and joints, as well as the heart and abdominal area.

b) Various occupations involve exposure to relatively high static magnetic fields. Very little data exist for risk assessment related to occupational long-term exposure to these fields. It has been suggested that movement in a static field of 2 T or more may induce various sensations including vertigo and nausea, possibly related to the induction of electric fields and currents in the head. Relatively high long-term exposure to static and ELF magnetic fields may occur, e.g. among personnel operating MRI devices. Patients examined by MRI constitute a group with high short-term exposure. Nothing is known about possible risks of such exposures for cancer, neurological diseases (ALS, Alzheimer's disease) and effects, or pregnancy outcome. Neurological effects could be studied in workers that during development of MRI equipment as volunteers have undergone numerous exposures during testing.

Minimum technical requirements

a) Identification of patients from hospitals or registries may be difficult, as electronic databases have been established typically in the late 1990's or after. Pertinent issues to be addressed in the feasibility studies include the size of the potential study cohort, establishing collaboration between multiple centers and researchers from various disciplines (e.g. radiology, physics, epidemiology), the number of patients with

multiple examinations and distributions of body sites and indications.

A protocol needs to be developed defining e.g. minimal data required for exposure assessment by body part/organ. Completeness of follow-up for both vital status and health outcomes needs to be evaluated. In analyses of health outcomes, confounding by indication needs to be addressed.

b) A feasibility study needs to be performed also for the occupational study whether enough participants can be found internationally for epidemiological studies into chronic diseases such as cancer, ALS and Alzheimer's, and for research into effects on pregnancy outcome. Proper control groups and adequate group sizes are required for biomarker studies of cancer risk.

For both studies, exposure assessment has also to take into account other frequencies than static fields since the MRI-environment is very complex and includes also RF and gradient fields.

Expected impact of results (use for Risk Assessment)

The feasibility study of pediatric MRI patients will indicate if it is possible to perform a full scale study into effects of MRI exposure on children.

The results from the occupational study will allow better risk analysis of frequent occupational exposure to static fields.

4.1.4.2. Experimental studies on potential health effects

Study type

a) Animal and in-vitro studies on end-points relevant for human health, including genotoxicity.

b) Human and animal studies on possible cognitive effects of exposure to magnetic gradient fields.

c) Human studies on the functioning of the cardiovascular system at magnetic flux densities > 3 T.

Rationale/justification

The number of artificial sources of static magnetic fields is small but there is a rapid development of technologies using such fields. Such fields are also present in occupational settings, where the exposure situation is unclear.

Although quite a large number of studies have been published, there is 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. Replication and extensions of previous findings on nervous system function, blood flow and vessel growth, and genotoxicity and gene expression in this area are needed.

Studies on possible cognitive effects of exposure to magnetic gradient fields are particularly relevant as medical staff is increasingly working in the immediate vicinity of MRI equipment, for example while performing interventional MRI procedures.

Studies on effects of higher flux densities on the functioning of the cardiovascular system are particularly relevant for patients' safety and are thus an issue related to medical device safety. Mentioned field strengths (> 3T) are higher than those routinely used in present clinical settings. Driven by improvements in image quality, technological developments are moving more and more towards higher field strengths.

Minimum technical requirements

- The studies need adequate exposure systems and well-defined exposure, where field characteristics should correspond to real-life human exposure.
- MRI equipment is available with static magnetic fields varying from less than 1 T to more than 8 T. This kind of equipment could be used in the proposed studies to explore dose-response relationships.

Expected impact of results (use for Risk Assessment)

The proposed studies would produce data for evaluating the adequacy of the exposure limits and for improved assessment of any health risks that might result from current and new technologies using static magnetic fields.

4.1.5. Additional considerations

4.1.5.1. Environmental effects

Study type

Comparison of selected ecosystem(s) before and after the installation of a new facility and/or located at varying field strengths from specific ELF EMF source(s) and/or other EMF sources.

Rationale/justification

There are two reasons why such studies are required:

a) Although exposure of environmental species/ecosystems to important point's sources of EMF is increasing continuously there is inadequate data to identify whether important adverse effects on the environment are occurring.

b) The identification of particularly susceptible species/ecosystems to ELF EMF would enable their use as a surrogate for human exposure.

If effects are clearly demonstrated in one or more species this could provide an important model(s) for detailed exposure-effects studies. This is expected to inform investigations of possible effects of ELF EMF in humans.

Minimum technical requirements

The main challenge is to identify the most appropriate ecosystem(s) to study. However, the criteria for the selection of such a system(s) can be identified:

- The ecosystem needs to be terrestrial and relatively common.
- The majority of the animal species in the system should stay within a limited area (so that their exposure to the ELF from the fixed point source is rather constant).
- The system should include some species whose navigation has been shown to be affected by magnetic fields.
- It needs to be accessible for a period of at least five years, and to be largely free from other major external influences, e.g. pesticide spraying.

Two complementary approaches can be used:

- Assessment of an ecosystem prior to and following the establishment of a power line/ transmitter facilities at several sites.
- Examination of similar ecosystems at varying distances from existing facilities.

Expected impact of results

A new approach is needed to identify whether or not there are significant adverse effects from the ELF from overhead power lines and transmitter stations. Provided an appropriate ecosystem(s) can be identified it could result in the identification of animal/plant species that can be considered as environmental markers.

4.2. Reply to Question 2 of ToR – Prioritization of Research Recommendations

All the studies that are suggested in this opinion are considered very important and given high priority based on their relevance for fundamental understanding of the issue and/or their relevance for public health. However, due to constraints such as financing limitations, this opinion strongly suggests that three work packages (WP) are given extra consideration. These work packages are restricted to a specific frequency band and are furthermore multidisciplinary, including dosimetry and exposure assessment, epidemiological studies, and experimental studies. Taken together, the studies in each work package also have relevance for understanding the issue and for public health. The studies are furthermore not covered by ongoing research projects and can deliver results within a reasonable time frame.

Table 1 Summary of all studies suggested in this opinion.

Study	**Study type**	**Expexted time until result delivery**
Health effects of RF from wireless communication in adults	Epidemiology (prospective cohort study)	First results within 5 years
Health effects of RF from wireless communication in children	Interdisciplinary (dosimetry, epidemiology, experimental (animals))	Dosimetry 2-3 years Other studies 3-5 years
RF mechanisms and verification of preliminary findings	1. Experimental study (modulation/demodulation dependency) 2. Experimental study (EEG, sleep in humans and animals)	1. 1-2 years 2. 2-3 years
Possible health effects of IF	Interdisciplinary (dosimetry, biomarkers, epidemiology, experimental)	Dosimetry 2 years Other studies ≥3 years
Possible carcinogenicity of ELF fields	Experimental study (in vivo, in vitro)	2-3 years
Association between ELF and neurodegenerative diseases	1. Epidemiological study 2. Experimental (in vivo, in vitro)	1. Years – decades 2. ≥2 years
Static fields and patients and workers health	1. Feasibility study of pediatric MRI patients 2. Epidemiological study (cohort) and biomarker study	1. 1-2 years 2. 3-5 years
Potential health effects of static fields	1. Experimental study (health related end-points, in vivo, in vitro) 2. Experimental study (cognitive effects, humans, animals) 3. Experimental study (cardiovascular effects, humans)	1. 2-3 years 2. 2-3 years 3. 1-2 years
Environmental effects	Ecosystems comparison	3-5 years

The following WPs all contain several studies and will, when seen as comprehensive units, provide substantial improvements in the foundation needed for proper risk assessment on various EMFs.

WP1: RF fields

a. Health effects of RF fields from wireless communication in adults (prospective cohort study).

b. RF field mechanisms and verification of preliminary but important findings.

The rationale for assigning this package a very high priority is that exposure to RF fields (from mobile phones and other wireless devices) is ubiquitous in the general population and still on the rise (including young, elderly or sick persons, many widespread non-occupational exposures). Although recent studies did not find strong evidence for adverse health effects from RF field exposure, the number of studies on longer term exposure (beyond ten years of exposure) is very small and considerable scientific uncertainty remains. Other outcomes than cancer and other exposures than mobile phones have been sparsely studied and a broader approach is recommended. Many of today's young adults have already been exposed as children, and the advantages of studying adults are a more objective exposure assessment and the higher frequency of most outcomes. A promising concept for WP1 would be a prospective cohort study with high-quality dosimetry, with nested studies of biomarkers in affected subjects and recruitment of appropriate sub-samples for studies on cognitive effects. In parallel, human and animal studies should focus on the possibility for nervous system effects and the importance of modulation/demodulation of RF signals.

WP2: IF fields

Possible health effects (pregnancy outcome) of IF fields

The rationale for assigning this package a very high priority is that there are generally few studies on IF field exposures. To recommend a focus on IF field exposures (but not necessarily restricted to IF) such as from anti-theft devices in shops and pregnancy outcome is because of the exposed area of the body, the exposure possibly exceeding reference levels, and the number of young women working in these jobs. A promising concept for WP2 would be dosimetry with a good description of exposure in real-life situtations and a respective development of exposure simulations for experimental studies, and studies investigating in parallel two lines of evidence, namely in vivo studies and epidemiology.

WP3: ELF fields

Association between ELF fields and neurodegenerative diseases

The rationale for assigning this package a very high priority is that especially Alzheimer Disease is relatively common and there are some recent studies suggesting an increased risk with higher ELF field occupational and residential exposure. There are, however, also some studies not showing any association and there is no known mechanism how ELF fields could cause neurodegenerative disease. Hence, it is important to conduct further studies to have more data available. A promising concept for WP3 is to conduct epidemiological studies to see whether findings of increased risk are confirmed and, in parallel, conduct experimental studies to gain insight into possible mechanisms.

4.3. Reply to Question 3 of ToR – Research Strategy

The suggested studies will have different time-spans before completion, and before they deliver publishable sets of data. In general, pure dosimetry and exposure assessment studies reach completion in the shortest time period. In certain instances, these studies are also prerequisites for other types of studies. Conversely, prospective cohort studies will go on for the longest time period, although such studies can deliver results within a few years, depending on cohort size and outcome incidence. Nevertheless, effects of longer term exposure are of high interest, as most chronic diseases occur only after relatively long induction periods. Experimental studies fall normally in between, but will mostly need at least 2-3 years before delivery of data.

As seen in Table I, also certain other studies that are not included in the WPs can deliver results within 2-3 years time.

Within the three work packages proposed in ToR2, the following studies will give results within a reasonable time-frame (2-3 years):

WP1:

- Feasibility study within the cohort study
- Experimental study on RF field mechanisms
- Experimental study on EEG and sleep in humans and animals

WP2:

Dosimetry

WP3:

Experimental in vivo and in vitro studies on neurodegenerative diseases

5. MINORITY OPINION

None

6. LIST OF ABBREVIATIONS

µT	Microtesla
ALS	Amyotrophic Lateral Sclerosis
CO_2	Carbon dioxide
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
DECT	Digital Enhanced Cordless Telephone
DG	Directorate General
DNA	Deoxyribonucleic acid
DVB-T	Digital Terrestrial Television
EEG	Electroencephalogram
ELF	Extremely low frequency
EMF	Electromagnetic field
ENTR	European Commission Directorate General Enterprise and Industry
f	Frequency
FP7	Framework Programme 7
GHz	Gigahertz
Hz	Frequency in Hertz
ICNIRP	International Committee on Non Ionising Radiation Protection
IF	Intermediate frequencies
kHz	Kilohertz
LVD	Low Voltage Directive
MHz	Megahertz
MRI	Magnetic Resonance Imaging
mT	Millitesla
RA	Risk Assessment
RF	Radio Frequency
RFID	Radio-frequency identification
R&TTE	Radio and Telecommunications Terminal Equipment
SANCO	European Commission Directorate General Health and Consumers
SAR	Specific Absorption Rate
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SMF	Static Magnetic Field
SMS	Short Message Service
SSC	Scientific Steering Committee
T	Tesla
THz	Terahertz
ToR	Terms of Reference
WHO	World Health Organisation
WP	Work Package

7. REFERENCES

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). Health Effects of Exposure to EMF. 19 January 2009
(http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_022.pdf)

8. GLOSSARY

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

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.

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

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

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

Round-Robin (protocol): A way to calibrate the specific technical performance of a laboratory activity. Several laboratories follow an identical protocol for a given experiment and compare the obtained results, which ideally should be the same for all participants. This approach will make certain that it is possible to replicate the findings of one laboratory also in other laboratories.

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.)

Static electric field: Static fields produced by fixed potential differences.

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