Proposals for research into health effects of electromagnetic fields (0 Hz - 300 GHz)

Gezondheidsraad
Health Council of the Netherlands

To the State Secretary of Housing, Spatial Planning
and the Environment

Subject	: Presentation of report "Proposals for research into health effects of electromagnetic fields (0 Hz – 300 GHz)"
Your reference	: SAS/2005180309
Our reference	: U531/EvR/IV/673-A11
Enclosure(s)	: 1
Date	: May 30, 2006

Mr State Secretary ,

In your letter of 9 September 2005 you indicated that you would like to start at short notice a research programme on electromagnetic fields and you asked the Health Council to indicate in what areas research might be performed in the Netherlands.

In this advisory report the Electromagnetic Fields Committee of the Health Council proposes research topics, taking account of the Research Agendas drafted by the World Health Organization. The current proposals are in the areas of static, low frequency and high frequency fields and pertain to different types of research: epidemiology, social sciences, experimental studies, measurements and model calculations. For each proposal, the Committee indicates which scientific and social arguments for prioritization are applicable.

The Committee is of the opinion that the current state of knowledge does not allow to indicate which type of research gives the best prospects for health benefits. The Committee does expect, however, that the knowledge the research program will generate, will contribute to forming balanced opinions and to a reduction of anxiety in society.

I herewith present you this report, that has been reviewed by the Health Council's Standing Committee on Radiation Hygiene. I have also presented this report today to the Minister of Economic Affairs, the Minister of Health, Welfare and Sport and to the State Secretary of Social Affairs and Employment.

Yours sincerely,

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to:
the State Secretary of Housing, Spatial Planning and the Environment
the Minister of Economic Affairs
the Minister of Health, Welfare and Sport
the State Secretary of Social Affairs and Employment

No. 2006/11E, The Hague, May 30, 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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This report can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Proposals for research into health effects of electromagnetic fields (0 Hz - 300 GHz). The Hague: Health Council of the Netherlands, 2006; publication no. 2006/11E.

ISBN-10: 90-5549-612-X
ISBN-13: 978-90-5549-612-9

Contents

Summary

At the request of the government, a research programme on electromagnetic fields and health is currently being set up in the Netherlands. The State Secretary for Housing, Spatial Planning and the Environment has asked the Health Council of the Netherlands to indicate what topics could be included in the programme, partly in light of research being conducted in other countries.

In this advisory report, the Electromagnetic Fields Committee proposes topics for inclusion in the research programme. In drawing up the proposals, the Committee has taken account of the expertise present in the Netherlands and of the World Health Organization's recommendations for research in this area (these can be found in annex C). The Committee's proposals are summarized in the table below.

Proposals for research into the effects of electromagnetic fields on health

Epidemiological research
Radio frequencies (RF)
• Prospective cohort study of adult mobile phone users
• Large-scale international case-control study of the relationship between use of mobile phones and the occurrence of brain tumours in children
• Prospective cohort study among children examining the relationship between use of mobile phones and health effects other than brain tumours
• Large-scale studies of health effects in individuals subjected to high occupational exposure

Extremely low frequencies (ELF)

- Further research into the possible link between miscarriage and exposure to ELF magnetic fields
- Further research into the risk of amyotrophic lateral sclerosis in 'electrical' occupations and into Alzheimer's disease in relation to exposure to ELF magnetic fields

Static magnetic fields

- Studies of the long-term effects of static magnetic fields

Social science research

- Research into determinants of perception of risks from electromagnetic fields
- Impact of precautionary measures on risk perception

Human experimental studies

Radio frequencies

- Laboratory studies of the relationship between RF exposure and health problems, and effects on cognition
- Health problems among people living in the vicinity of base stations: research in the living environment
- Laboratory studies into acute effects on cognition and brain activity in children

Extremely low frequencies

- Study of cognitive effects, sleep and brain function in adults (including those with occupational exposure) and children using a range of ELF frequencies and high field strengths

Static magnetic fields

- Effects of strong static magnetic fields on cognition and behaviour
- Effects of strong static magnetic fields on heart function

Animal experimental studies

Various frequencies

- Effects on the development and functioning of the immune and haematopoietic systems
- Effects on the development of the central nervous system
- Effects on the development of cognitive functions
- Effects at molecular level in brain tissue
- Effects on carcinogenesis

Extremely low frequencies

- Development of an adequate animal model for childhood leukaemia

In vitro studies

- Effects of existing and new signal types
- Possible interaction between electromagnetic fields and chemical and physical agents

Characterization of exposure

Research at micro-level

- Research into effects on cellular and subcellular structures, including effects on formation of radical pairs and effects that can influence cellular communication

Research at macro-level

- Characterization of exposure in epidemiological studies: characteristics of exposure and distribution among populations studied; development of methods for valid estimation of exposure resulting, for example, from mobile phone use; measuring exposure to electromagnetic fields in the workplace and the living environment
- Translation of basic restrictions into reference values for near-field exposure
- Calculations for actual exposure situations using recent models: exposure to several sources simultaneously and near-field exposures; development of models for women (and expectant mothers) and children

The Committee has not made any specific proposals for prioritisation. It does, however, present a list of social and scientific arguments that might play a role in prioritisation. The arguments are presented in order of importance, according to the views of the Committee. Relevant arguments are indicated for each of the research proposals. This information can be used by the committee that oversees the research programme, for example, to set priorities for research.

The Committee would reiterate its recommendation made in an earlier advisory report that a group of experts be established in the Netherlands who should at least have an important advisory role in the characterization and measuring of exposure in the various studies. They might also play a role in the implementation of the research.

Great care must be taken in measuring the strength of electromagnetic fields in home and work situations. Inaccurate measurements and interpretation of data could exacerbate public concern about this issue.

The State Secretary has also asked the Health Council to indicate which research areas offer the best prospects for health benefits. The Committee would point out that the indications for short- and/or long-term exposure to electromagnetic fields with strengths commonly found in home and work situations are limited and, to some extent, contradictory, and that causal connections have yet to be found. The Committee therefore believes it is not possible to respond to the State Secretary's question at this time. It does, however, believe that benefit could be derived from reducing public concern, although it is unable to draw any firm conclusions in this matter.

Chapter 1

Introduction

1.1 Reason for this advisory report

On 4 February 2003, at the request of the Minister of Health, Welfare and Sport, the Health Council issued an advisory report containing recommendations for research into the effects of exposure to radiofrequency electromagnetic fields.[22] That report led neither to the establishment of a research programme nor to the funding of individual studies. In late 2004 the House of Representatives urged the government to take steps to allow research to be performed into the health effects of electromagnetic fields. The State Secretary for Housing, Spatial Planning and the Environment then asked the Health Council to update its 2003 advisory report and expand it to include the entire range of frequencies from 0 Hz to 300 GHz. The request for an advisory report is included in annex A.

The President of the Health Council asked the Electromagnetic Fields Committee to draw up this report. Its members are listed in annex B.

1.2 Principles

In his request for an advisory report, the State Secretary requests that it tie in as far as possible with international developments and insights. To this end, the Committee took good note of, among other things, the research recommendations made by the World Health Organization (WHO) as part of the International

EMF Project (see http://www.who.int/peh-emf/en). These recommendations, listed in annex C, form the basis of the proposals in the present report, but they have not all been adopted.

In drafting its proposals the Committee proceeded from the following principles, which are based partly on the State Secretary for Housing, Spatial Planning and the Environment's request.

It is important to consider the fact that, given the growth in wireless applications, the pattern of exposure is changing. Some 20 years ago, radio and television transmitters and the electricity supply network were the main sources of electromagnetic fields. Nowadays there are many new applications, particularly in the radiofrequency part of the spectrum, and more are constantly being introduced. As a result, people are being exposed to all types of new signals. It is not clear whether this has in fact changed the overall intensity of exposure, but the exposure pattern is certainly changing. The question is whether these new types of signal may have an impact on the incidence of health effects. Though there is no scientific evidence for this at present, there is public concern at the possibility, prompted particularly by the findings of a number of studies that are yet to be confirmed by further research, and also by reports of health problems, some serious, in certain individuals. This scientific uncertainty, combined with a high level of public concern, is a key reason behind some of the recommendations in this report.

The Committee's position is that the research:

- must not be an exact repeat of earlier studies, unless there are sound scientific reasons for this, an improved hypothesis has been formed and/or improvements or refinements have been made to the design of the study
- should complement research being conducted in other countries
- should be possible using the expertise present in the Netherlands, possibly in collaboration with research groups in other countries
- should be technically and scientifically feasible
- should be designed in such a way that it produces valid results
    - exposure must be properly measured; good dosimetry is an absolute, fundamental requirement for every study
    - there should be enough contrast in exposure
    - objectively measurable endpoints must be used; in studies examining subjective endpoints such as health problems, the experiment must be designed in a way that allows objective determination
- should help improve our insight into the biological effects of exposure to electromagnetic fields

- should be relevant to society; in other words, it must aim to find answers to relevant questions posed by society about the safety of certain technical infrastructure, such as mobile telecommunications equipment and power lines.

The studies must also be:
- of a high academic standard and the results must be published in internationally cited scientific journals
- independent; in other words, stakeholders must have no influence on the implementation and reporting of the research.

Most of the proposals in the 2003 advisory report have been retained in this report. Some have however been excluded because new scientific insights mean they are no longer relevant.

The Committee would reiterate the recommendation it made in 2003 that a university expertise and research centre be set up to look into the health effects of electromagnetic fields. It should pool and expand the expertise on both biology and dosimetry of electromagnetism in the Netherlands, and play a role in university teaching of this subject.

1.3 Structure

The research has been divided into a number of categories, mainly for practical reasons:
- epidemiological studies (chapter 2)
- social science research (chapter 3)
- human experimental studies (chapter 4)
- animal experimental studies (chapter 5)
- *in vitro* studies (chapter 6)
- dosimetry and model studies (chapter 7).

In risk analyses of exposure to electromagnetic fields carried out by the Health Council, the WHO and other organisations, data obtained from studies involving humans (epidemiological and experimental) carry the greatest weight. However, such findings must be underpinned by more fundamental and mechanistic research.

In several chapters the committee gives separate recommendations for research into exposure to radiofrequency (RF) electromagnetic fields and extremely low

frequency (ELF) or static magnetic fields. There are no reasons to make recommendations into the effects of extremely low frequency or static electric fields.

Most research into the possible health effects of exposure to electromagnetic fields has thus far focused on the most commonly used frequencies, in the ELF and RF range. There are very few data for the intermediate frequency range, defined by the WHO as frequency range between 300 Hz and 10 MHz.[1]

Since applications are increasingly being developed in this range – including anti-theft gates, electronic article surveillance (EAS), metal detectors, radiofrequency identification tags (RFID), induction heating – people are increasingly being exposed to this type of frequency. The exposure limits in this range have been calculated by extrapolating those for the higher and lower frequencies. The uncertainty associated with this could be reduced if more data were collected, in a more targeted manner.

The Committee would therefore make a general recommendation that research be carried out into the effects of exposure to intermediate frequencies.

1.4 Prioritisation

The State Secretary has requested the Committee to indicate which proposals have priority. The Committee has done so by indicating which of the social and scientific arguments listed below apply in each case. The arguments are ranked in order of importance, according to the views of the Committee.

Table 1 Arguments for prioritising research

Social arguments	
M1	There is a great deal of public concern; the risk perception is high
M2	A large population is exposed
M3	The exposed population includes possible risk groups
M4	Exposure is involuntary
M5	Exposure is long-term or continuous
M6	The research proposal aims to identify exposure in the workplace or living environment
M7	Exposure intensity is relatively high in comparison with the average exposure of the public
Scientific arguments	
W1	The proposed research is designed to obtain fundamental insight into mechanisms
W2	There is discrepancy between the results of *in vitro*, *in vivo* and epidemiological studies
W3	Earlier research or – in the case of proposals for an epidemiological study – *in vitro* or *in vivo* studies, have indicated an effect
W4	Results of valid (*in vitro*, *in vivo* or epidemiological) studies are not consistent, or are even conflicting
W5	The proposed research is designed to identify exposure
W6	No relevant research has yet been conducted

Chapter 2

Epidemiological studies

2.1 Radiofrequencies

2.1.1 *Prospective cohort study* of adult mobile phone users*

• M1	Public concern	W1	Fundamental insight
• M2	Large exposed population	• W2	Discrepancies
• M3	Possible risk groups	• W3	Effect indicated
M4	Involuntary exposure	• W4	Inconsistent or conflicting data
M5	Long-term exposure	• W5	Identify exposure
M6	Identify exposure	W6	Lack of research
• M7	High-intensity exposure		

Case-control studies in the INTERPHONE study have produced weak indications of a possible relationship between long-term, regular use of mobile telephones and the incidence of certain (benign) tumours (see *Electromagnetic Fields: Annual Update 2005* [24]). However, possible selection bias and the method used to determine exposure – which was based on the recollections of the individuals studied – were weak points in this study.

* See annex D.

A prospective study allows exposure to be determined more accurately. A range of health effects, including the incidence of cancer, can be studied. Important prerequisites include quantifiable exposure and sufficient differences in exposure within the group studied ('exposure contrast'), adequate duration (since one is studying long-term effects) and availability of data on mobile phone use from telephone companies.

This research could be tied in with ongoing cohort studies in the Netherlands (focusing on other causal relationships). Dutch researchers might also participate in cohort studies into the effects of electromagnetic fields being set up abroad.

2.1.2 *Large-scale international case-control study* of the relationship between use of mobile phones and the occurrence of brain tumours in children*

•	M1 Public concern		W1 Fundamental insight
•	M2 Large exposed population		W2 Discrepancies
•	M3 Possible risk groups	•	W3 Effect indicated
	M4 Involuntary exposure		W4 Inconsistent or conflicting data
	M5 Long-term exposure	•	W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
•	M7 High-intensity exposure		

Children have not been included in the INTERPHONE study because at the time of its launch too few children used mobile telephones for long periods. This has changed. Many children now frequently make long mobile phone calls. Since brain tumours are rare in children, however, a cohort study would not be useful. A case-control study would be easy to set up in the Netherlands, where care of young cancer patients is well organised. However, international collaboration will be needed to bring together enough patients. The establishment of a good control group with a sufficiently high participation rate requires particular attention.

* See annex D.

2.1.3 *Prospective cohort study among children examining the relationship between use of mobile phones and health effects other than brain tumours*

• M1	Public concern	W1	Fundamental insight
• M2	Large exposed population	W2	Discrepancies
• M3	Possible risk groups	W3	Effect indicated
M4	Involuntary exposure	W4	Inconsistent or conflicting data
M5	Long-term exposure	• W5	Identify exposure
M6	Identify exposure	• W6	Lack of research
• M7	High-intensity exposure		

Several reports have been published on effects on cognitive functions and other health effects in young mobile phone users.[18,40] The development of cognitive functions and the capacity to learn are of course essential to a child's development.

A prospective cohort study is the most suitable type of research to determine these effects. Since the parameters studied will differ from those in adults, this study cannot be combined with the cohort study among adult mobile phone numbers discussed at 2.1.1.

In studying health effects other than cancer in children it is particularly important to take account of confounding factors. Socioeconomic factors, in particular, impact both on the use of mobile phones and on other health factors, including the development of cognitive functions.[6,34,36]

2.1.4 *Large-scale studies of health effects in individuals subjected to high occupational exposure*

M1	Public concern	W1	Fundamental insight
M2	Large exposed population	W2	Discrepancies
M3	Possible risk groups	W3	Effect indicated
M4	Involuntary exposure	W4	Inconsistent or conflicting data
• M5	Long-term exposure	• W5	Identify exposure
• M6	Identify exposure	W6	Lack of research
• M7	High-intensity exposure		

Workers in some occupations are exposed to high field strengths, sometimes in excess of the ICNIRP guidelines*, and often over large areas of their body. Obvi-

ously, this situation cannot be allowed to continue. However, the workers in question represent a population ideally suited for researching whether health effects occur as a result of such exposure. The assumption is that the likelihood of effects increases with increased exposure.

The Committee proposes on the one hand to set up, if feasible, (international) cohort studies and on the other to further analyse existing data on occupational exposure from large-scale case-control studies.

2.2 Extremely low frequencies

2.2.1 *Further research into the possible link between miscarriage and exposure to ELF magnetic fields*

	M1	Public concern	W1	Fundamental insight
	M2	Large exposed population	W2	Discrepancies
•	M3	Possible risk groups	W3	Effect indicated
•	M4	Involuntary exposure	• W4	Inconsistent or conflicting data
	M5	Long-term exposure	W5	Identify exposure
•	M6	Identify exposure	W6	Lack of research
	M7	High-intensity exposure		

In *Electromagnetic Fields: Annual Update 2003* the Committee discussed several studies that had found indications of a possible link between miscarriage and exposure to ELF magnetic fields.[23] In those studies, exposure had resulted from the use of electrical equipment in the home and living in proximity to overhead power lines.

The Committee would reiterate its conclusion in the Annual Update 2003 that more prospective studies are needed, with a focus on measuring exposure, to allow final conclusions to be drawn as to whether there is a consistent association. Research into a possible action mechanism for the impact of ELF magnetic fields on pregnancy is also needed.

* In 1988 the *International Commission on Non-Ionizing Radiation Protection* published guidelines for exposure limits in the > 0 Hz – 300 GHz frequency range.[30] The European Union adopted these guidelines in (non-binding) recommendations for exposure limits for the general public [9] and a (binding) directive governing the exposure of workers.[13] The Netherlands has no statutory exposure limits. However, the European Directive protecting workers from exposure must be implemented in Dutch law by April 2008 at the latest.

2.2.2 *Further research into the risk of amyotrophic lateral sclerosis in 'electrical' occupations and into Alzheimer's disease in relation to exposure to ELF magnetic fields*

	M1	Public concern	W1 Fundamental insight
	M2	Large exposed population	W2 Discrepancies
	M3	Possible risk groups	W3 Effect indicated
	M4	Involuntary exposure	• W4 Inconsistent or conflicting data
•	M5	Long-term exposure	W5 Identify exposure
•	M6	Identify exposure	W6 Lack of research
•	M7	High-intensity exposure	

Several studies have found an increased risk of amyotrophic lateral sclerosis (ALS) in occupations with exposure to relatively strong magnetic fields [32,43], while no such association has been found in others.[14,19] Further research is needed into a possible causal link between exposure to ELF magnetic fields and this rare neurodegenerative disease. This will require large-scale studies in which the exposure to ELF fields is established, and also the occurrence of electrical shocks and other possible risk factors.

Exposure to ELF magnetic fields may also contribute to the onset of Alzheimer's disease.[14,19,41] The data available on this are however equivocal and inconclusive. There is a need for well-designed studies examining morbidity rather than mortality.

It is proposed that a major international prospective cohort study be established to examine a number of neurological clinical pictures, including ALS and Alzheimer's. This could be combined with a cohort study such as referred to in 2.1.4.

2.3 Static magnetic fields

2.3.1 *Studies of the long-term effects of static magnetic fields*

	M1	Public concern	W1 Fundamental insight
	M2	Large exposed population	W2 Discrepancies
	M3	Possible risk groups	W3 Effect indicated
	M4	Involuntary exposure	W4 Inconsistent or conflicting data
•	M5	Long-term exposure	• W5 Identify exposure
	M6	Identify exposure	W6 Lack of research
•	M7	High-intensity exposure	

Various occupations involve exposure to relatively high static magnetic fields. These include jobs involving MRI equipment, aluminium forging, chlorine electrolysis and public transport (metros, trams, light rail). Research might indicate whether enough participants could be found internationally for epidemiological studies into chronic diseases such as cancer, ALS and Alzheimer's, and for research into effects on pregnancy. These studies might also establish what other exposures occur in these occupations.

Chapter 3

Social science research

Public concern about sources of radiation is on the increase. The perception of risk is an important factor here. The Committee has therefore made recommendations for social science research related to exposure to electromagnetic fields.

3.1 Risk perception

•	M1 Public concern	•	W1 Fundamental insight
•	M2 Large exposed population		W2 Discrepancies
•	M3 Possible risk groups	•	W3 Effect indicated
•	M4 Involuntary exposure		W4 Inconsistent or conflicting data
•	M5 Long-term exposure		W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
	M7 High-intensity exposure		

People hold a wide range of views on the possible risks from electromagnetic fields. Most have no problem with it, while others – such as those who live near GSM and UMTS masts and power lines – perceive electromagnetic fields as a sometimes major threat to health.[15,16,45]

The Committee believes it is important that research be conducted into the determinants of risk perception in individuals: what factors affect the confidence of stakeholders and the general public in technologies associated with the emission of electromagnetic fields; what impact do various information, risk commu-

nication and risk management strategies have on people's ability to develop an informed opinion on electromagnetic fields and health; what is the role of scientific and other information and the associated uncertainties in these processes? It is recommended that both experimental and field studies look into these issues.

3.2 Precaution

•	M1 Public concern	•	W1 Fundamental insight
	M2 Large exposed population		W2 Discrepancies
	M3 Possible risk groups		W3 Effect indicated
	M4 Involuntary exposure		W4 Inconsistent or conflicting data
	M5 Long-term exposure		W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
	M7 High-intensity exposure		

A recent study in Germany indicated that, contrary to what one might expect, precautionary measures can have an adverse effect on perception of risks from electromagnetic fields. The study found that precautionary measures actually increased risk perception and reduced confidence in the authorities.[50] It should however be noted that the study was limited and that the conclusions certainly cannot be generalised. In the aftermath of the Bijlmer air crash in Amsterdam it was also found that conducting detailed medical examinations did not necessarily put people's minds at rest, particularly since their confidence in the authorities was already at a very low level.[46]

One important question that needs addressing is whether also in the Netherlands precautionary measures have a negative impact on the perception of risk and on confidence in the authorities, and if so, how this can be avoided.

Chapter 4

Human experimental studies

Human experimental studies are useful for gaining more insight into acute effects of exposure to electromagnetic fields; some questions can be answered only through this type of research.

In this section the Committee makes recommendations for research into effects on cognition, among other things. It might be possible to tie this research in with the research programme on cognition recently launched by the Netherlands Organisation for Scientific Research (NWO) *.

* One part of this programme concerns *Application Oriented Research Projects*.[2] The goal is described as follows in the call for proposals: 'This specific call focuses on one of the main aims of the NWO Special Programme for the Cognitive Sciences: stimulating the embedding of results from cognitive science in society, by applying the insights gained and achieving a significant improvement of methods, techniques and tools for the acquisition, management and use of knowledge in society, both with respect to natural and artificial intelligence. Utilization of cognitive science in education, pharmaceutical industry, robotics or ICT, for the development of neuroprostheses, or in men-machine interfaces are examples of potential research themes, but these examples are by no means exhaustive. In accordance with STW regulations, proposals with a strong technological component are especially invited.'

4.1 Radiofrequencies

4.1.1 Health problems and cognition: laboratory studies

• M1	Public concern	• W1	Fundamental insight
• M2	Large exposed population	• W2	Discrepancies
• M3	Possible risk groups	• W3	Effect indicated
• M4	Involuntary exposure	• W4	Inconsistent or conflicting data
• M5	Long-term exposure	W5	Identify exposure
M6	Identify exposure	• W6	Lack of research
M7	High-intensity exposure		

A growing number of people are attributing all kinds of aspecific health problems – including headache, sleeplessness and concentration problems – to exposure to electromagnetic fields. They maintain there are major differences between individuals in terms of their sensitivity to electromagnetic fields. Signals from this group of people indicated that, over time, a growing number and range of problems are being attributed to electromagnetic fields. Associations with other disorders such as allergies are also reported.

Research has so far been limited to the effects of ELF fields generated by computer monitors and RF fields from mobile phones.[42] None of the studies published so far has demonstrated a clear link.[24,42] More targeted research is needed under controlled conditions to obtain a clearer picture. It is important that such research be carried out using people who have problems and who have attributed them to exposure to electromagnetic fields.

In its 2003 advisory report the Committee proposed focusing on research into health problems, on condition that they are objectifiable.[23] One good way of doing this is to perform experimental studies in controlled laboratory conditions whereby test subjects do not know whether or not they have been exposed (double-blind studies). However, studies to date have examined only acute effects of short-term exposure, whereas symptoms are in fact more usually ascribed to long-term exposure and often do not set in until some time after exposure begins, according to the individuals in question. A different type of experimental set-up would therefore be needed.

Besides the above-mentioned group experiencing health problems, this kind of research might also be performed with other – possibly sensitive – groups, such as children and people with sleep or other disorders (e.g. concentration problems).

The Committee also believes it is important not only to look at brain functions such as cognition, but also to take into account other factors, such as physiological parameters.

To obtain a good understanding of any causal relationships, it is essential that the effects of various exposure characteristics, including field strength, frequency and pulse form be examined. This should involve simulation of signals not only from mobile telecommunications antennas, but also those from other sources, such as DECT telephones, WiFi equipment and digital radio and television.

It is also recommended that associations and correlations between such aspecific health problems themselves be studied. Electromagnetic fields are not the only possible stimulus for such problems.

4.1.2 *Health problems among people living in the vicinity of base stations: research in the living environment*

•	M1 Public concern		W1 Fundamental insight
•	M2 Large exposed population		W2 Discrepancies
•	M3 Possible risk groups		W3 Effect indicated
•	M4 Involuntary exposure		W4 Inconsistent or conflicting data
•	M5 Long-term exposure	•	W5 Identify exposure
•	M6 Identify exposure	•	W6 Lack of research
	M7 High-intensity exposure		

In the laboratory study recommended above it will not be practically possible to study effects that occur in the longer term. It would however be possible in field research, studies in the living environment to establish whether people living in the vicinity of base stations report symptoms. Studies using questionnaires could be used to correlate symptoms to whether or not a transmitter is on, without local residents knowing. In this type of field study, it is important not to give any indications as to the aim of the research. If the subjects are aware beforehand that the effects of the presence of antennas are being studied, this will certainly influence the results.

Such a study might also be extended to include risk perception, as examined in more detail in chapter 3 on social science research.

4.1.3 *Acute effects on cognition and brain activity in children*

•	M1	Public concern	•	W1	Fundamental insight
•	M2	Large exposed population		W2	Discrepancies
•	M3	Possible risk groups		W3	Effect indicated
	M4	Involuntary exposure	•	W4	Inconsistent or conflicting data
	M5	Long-term exposure		W5	Identify exposure
	M6	Identify exposure		W6	Lack of research
•	M7	High-intensity exposure			

Since children are using mobile telecommunications equipment earlier and earlier, they are increasingly being exposed to the electromagnetic fields they produce. If this has a direct effect on cognitive ability or on brain activity, their development could be hampered.[18,40] However, more data are needed, on children younger than those who have been studied to date. This study should also be performed in the laboratory, under controlled dosimetric conditions.

4.2 Extremely low frequencies

4.2.1 *Study of cognitive effects, sleep and brain function in adults (including those with occupational exposure) and children using a wide range of ELF frequencies and high field strengths*

	M1	Public concern		W1	Fundamental insight
	M2	Large exposed population		W2	Discrepancies
•	M3	Possible risk groups	•	W3	Effect indicated
	M4	Involuntary exposure	•	W4	Inconsistent or conflicting data
	M5	Long-term exposure		W5	Identify exposure
	M6	Identify exposure		W6	Lack of research
•	M7	High-intensity exposure			

Since earlier studies used a variety of methods to examine cognitive functions, it is difficult to compare their results. It is therefore important that research methods be harmonised and standardised as far as possible in future research.

Volunteer and animal studies have indicated that cognitive functions can be affected by short-term exposure to high field strengths.[10,31] More research is needed to establish the nature and scale of these effects and determine whether they have implications for exposure limits. It is particularly important to study

children and the occupationally exposed (because of the possible effect of long-term exposure on sensitivity) and to use frequencies other than 50 or 60 Hz.

4.3 Static magnetic fields

4.3.1 *Effects of strong static magnetic fields on cognition and behaviour*

	M1	Public concern		W1	Fundamental insight
	M2	Large exposed population		W2	Discrepancies
•	M3	Possible risk groups	•	W3	Effect indicated
	M4	Involuntary exposure		W4	Inconsistent or conflicting data
	M5	Long-term exposure	•	W5	Identify exposure
	M6	Identify exposure	•	W6	Lack of research
•	M7	High-intensity exposure			

Several experimental studies have shown that possible effects on cognitive functions and self-reported problems (such as dizziness and a metallic taste) can occur with exposure to strong static magnetic gradient fields, as in the vicinity of MRI equipment.[11,12] There are indications that hand-eye coordination and vision, in particular, can be affected by movement in strong gradient fields. Studies of test subjects exposed to homogeneous magnetic fields in MRI equipment showed clinically insignificant effects on short-term memory.[7]

Since medical staff are increasingly working in the immediate vicinity of MRI equipment, while performing interventional MRI procedures, for example, it is desirable that research be conducted into possible cognitive effects of exposure to magnetic gradient fields.

MRI equipment is available with static magnetic fields varying from less than 1 tesla (T) to more than 8 T, and a similar variation in the strength of the magnetic gradient field. This equipment could be used in the proposed studies to explore dose-effect relationships.

4.3.2 *Effects of strong magnetic fields on heart function*

	M1	Public concern	•	W1	Fundamental insight
	M2	Large exposed population		W2	Discrepancies
	M3	Possible risk groups		W3	Effect indicated
	M4	Involuntary exposure		W4	Inconsistent or conflicting data
	M5	Long-term exposure		W5	Identify exposure
	M6	Identify exposure	•	W6	Lack of research
•	M7	High-intensity exposure			

Model calculations indicate that high magnetic field strengths might affect heart function.[27] It is therefore desirable that research be conducted into the functioning of the cardiovascular system at flux densities > 3 T. These field strengths are higher than those routinely used in clinics. Driven by improvements in image quality, technological developments are moving more and more towards higher field strengths. Indeed, there will soon be three 7-T MRI facilities in operation in the Netherlands.

Chapter 5

Animal studies

5.1 Frequency-independent research

In the case of a number of biological and health effects there is no compelling reason to study exposure only in a certain frequency range. Nothing is known about the occurrence of these effects across the entire range from 0 Hz to 300 GHz. The Committee therefore makes general recommendations for research below, but in some cases also indicates why a certain frequency range should be given priority.

5.1.1 Effects on the development and functioning of the immune and haematopoietic systems

	M1	Public concern	• W1 Fundamental insight
•	M2	Large exposed population	W2 Discrepancies
•	M3	Possible risk groups	• W3 Effect indicated
•	M4	Involuntary exposure	• W4 Inconsistent or conflicting data
•	M5	Long-term exposure	W5 Identify exposure
•	M6	Identify exposure	• W6 Lack of research
	M7	High-intensity exposure	

Indications have been found for effects of ELF magnetic fields on the immune and haematopoietic systems in adult humans and animals.[4,29,31,47,48] The data are

inconsistent, however, and no conclusions can be drawn as to any negative effects. However, a more important question is whether effects on these systems may be caused in developing organisms. It is therefore recommended that research be performed to establish whether exposure to electromagnetic fields with varying frequencies has effects on the development and functioning of the immune and haematopoietic systems of young experimental animals.

5.1.2 *Effects on the development of the central nervous system*

•	M1 Public concern	•	W1 Fundamental insight
•	M2 Large exposed population		W2 Discrepancies
•	M3 Possible risk groups		W3 Effect indicated
	M4 Involuntary exposure	•	W4 Inconsistent or conflicting data
	M5 Long-term exposure	•	W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
•	M7 High-intensity exposure		

Various countries have recommended that the use of mobile phones by children be kept to a minimum, as a precautionary measure.[39,44] The main argument cited is that exposure to the RF electromagnetic fields of telephones might have a greater impact on the brains of children than on those of adults because their head and brain are still developing.

There are no developmental biological reasons for assuming that the sensitivity of the brain to electromagnetic fields is any different from the age of around two to three to that of the adult brain. In two earlier reports the Committee has presented arguments to support this notion.[20,21] Recent publications from an international meeting on children and exposure to electromagnetic fields organised by the WHO support this view.[8,33,37] However, no targeted research has ever been done on the effects of exposure to electromagnetic fields on the development of the central nervous system. The Committee therefore recommends to perform such studies in young animals.

In all cases, both long-term exposure to low field strengths and short-term exposure to high field strengths should be studied. The main goal of this type of research is to determine where the damage is most clearly expressed, so that any effects in humans can be quantified.

5.1.3 *Effects on the development of cognitive functions*

M1	Public concern	• W1	Fundamental insight
M2	Large exposed population	W2	Discrepancies
• M3	Possible risk groups	W3	Effect indicated
M4	Involuntary exposure	W4	Inconsistent or conflicting data
M5	Long-term exposure	W5	Identify exposure
M6	Identify exposure	• W6	Lack of research
M7	High-intensity exposure		

In the previous section the Committee made recommendations for research into cognitive functions in both adults and children. The Committee also believes it is important that any effects of exposure to electromagnetic fields on the *development* of cognitive functions be studied. Such research can only be performed using animals.

5.1.4 *Effects at molecular level in brain tissue*

M1	Public concern	• W1	Fundamental insight
M2	Large exposed population	W2	Discrepancies
M3	Possible risk groups	• W3	Effect indicated
M4	Involuntary exposure	• W4	Inconsistent or conflicting data
M5	Long-term exposure	W5	Identify exposure
M6	Identify exposure	• W6	Lack of research
M7	High-intensity exposure		

A number of studies have found indications of effects on proteins in nerve cells in response to exposure in the ELF and RF range, at field strengths that fall below the current exposure limits, but which are higher than the field strengths in the living and working environment.[31,35,38] Such effects may have an influence on functioning or on health, although no indications of this have been found to date.

Given this possible effect on health or well-being, the Committee recommends that further research be done into the effects of exposure to electromagnetic fields at the membrane and molecular level in the brain. It is important that the influence of exposure parameters such as intensity, duration and, for example, specific stimulus patterns, be determined and that the research focus on underlying biological mechanisms.

5.1.5 *Effects on carcinogenesis*

•	M1 Public concern	•	W1 Fundamental insight
•	M2 Large exposed population	•	W2 Discrepancies
	M3 Possible risk groups	•	W3 Effect indicated
•	M4 Involuntary exposure	•	W4 Inconsistent or conflicting data
•	M5 Long-term exposure		W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
	M7 High-intensity exposure		

Numerous studies have found no direct effect of exposure to electromagnetic fields on the onset and progress of cancer.[23,28,31] There are however a few indications that the carcinogenic effect of certain chemicals is enhanced, though this has only been found with exposure to ELF magnetic fields.[31] It is therefore recommended that further research be performed into the effects of exposure to ELF and static magnetic fields, in particular, on the consequences of exposure to known carcinogens.

5.2 Extremely low frequencies

5.2.1 *Development of an adequate animal model for childhood leukaemia*

•	M1 Public concern	•	W1 Fundamental insight
	M2 Large exposed population	•	W2 Discrepancies
•	M3 Possible risk groups	•	W3 Effect indicated
•	M4 Involuntary exposure	•	W4 Inconsistent or conflicting data
•	M5 Long-term exposure		W5 Identify exposure
	M6 Identify exposure		W6 Lack of research
	M7 High-intensity exposure		

Epidemiological studies have revealed an association between exposure to ELF magnetic fields and enhanced risk of childhood leukaemia.[3,17] The many data produced in experimental research do not indicate a causal link, however. The Committee believes more insight is needed into this relationship before more definitive conclusions can be drawn. It is therefore important that a animal model be developed for childhood leukaemia to allow a possible causal link between exposure to ELF magnetic fields and this disease to be studied. A recent publication describes such a model [5], but its scientific value is at present uncertain.

Chapter 6

In vitro studies

The Committee regards it as generally important that research using *in vitro* techniques be conducted to establish the effects of existing and new signal types.

•	M1 Public concern	•	W1 Fundamental insight
	M2 Large exposed population		W2 Discrepancies
	M3 Possible risk groups	•	W3 Effect indicated
	M4 Involuntary exposure		W4 Inconsistent or conflicting data
	M5 Long-term exposure		W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
•	M7 High-intensity exposure		

It is theoretically possible that certain types of signal and/or sequences cause biological effects, including effects on the functioning of membrane proteins (which play a role in the interaction between cells and their environment) and on cell differentiation. Research into these effects related to the frequency and intensity of electromagnetic fields might yield information on these mechanisms.

Some of the results of the REFLEX research programme point to possible impacts on DNA damage and repair.[24] Although several replication studies are underway or have been completed, there remains a need for more and better information. More research is required in particular into the questions of why the effect is strongest in the event of a certain on/off sequence, and why it is found only in certain cell lines.

The Committee reiterates the recommendation made in its 2003 advisory report [23], that *in vitro* studies should be performed in the Netherlands into the possible interaction between electromagnetic fields and chemical and physical agents. Combined exposure often occurs, particularly in occupational settings. Better knowledge of interactions at the molecular level would help to give better insight into the biological implications.

If *in vitro* studies find indications of more than additive effects of certain combinations of electromagnetic fields and agents, *in vivo* studies should be performed to establish whether this type of exposure leads to adverse health effects.

The Committee makes no specific recommendations for the study of certain combinations. It leaves it up to other parties to form plausible hypotheses and identify potentially harmful exposures.

Chapter 7

Characterisation of exposure

In its 2003 advisory report [23] the Committee stated that a specialised group of experts should be set up in the Netherlands who would at least play an important advisory role in the characterisation and measuring of exposure in the various studies in the programme, and might also have a role in implementing the research. The Committee still regards it as highly important that these elements of the research be performed by well-trained experts.

Measurements of the strength of electromagnetic fields in homes and work-places must be taken in an expert manner. Experience has shown that inaccurate measurements and interpretation of data can lead to public concern.

7.1 Research at micro-level

M1	Public concern	•	W1	Fundamental insight
M2	Large exposed population		W2	Discrepancies
M3	Possible risk groups		W3	Effect indicated
M4	Involuntary exposure	•	W4	Inconsistent or conflicting data
M5	Long-term exposure		W5	Identify exposure
M6	Identify exposure	•	W6	Lack of research
M7	High-intensity exposure			

In most cases it is not clear what biological mechanisms play a role in the way cells or organisms respond to electromagnetic fields. One way of providing a better theoretical basis would be to model cell tissue and cell processes more effectively. This would require collaboration between experts from various disciplines. The results of these activities would generate hypotheses for verification by means of *in vitro* and *in vivo* experiments.

The Committee recommends that research be conducted at micro-level into effects on cellular and subcellular structures, including effects on the formation of radical pairs and effects that may influence cellular communication.

7.2 Research at macro-level

7.2.1 Characterisation of exposure

•	M1	Public concern	•	W1	Fundamental insight
	M2	Large exposed population		W2	Discrepancies
•	M3	Possible risk groups		W3	Effect indicated
•	M4	Involuntary exposure		W4	Inconsistent or conflicting data
•	M5	Long-term exposure	•	W5	Identify exposure
	M6	Identify exposure	•	W6	Lack of research
	M7	High-intensity exposure			

The characterisation of exposure in epidemiological studies is often unclear, incomplete or inaccurate. Research is needed to give a better insight into what characteristics of exposure are important and how they are represented in the populations studied.

The Committee believes it is important that exposure in the living and working environment be researched. Better methods must be developed to produce valid estimates of, for example, exposure due to mobile phone use. Exposure to electromagnetic fields in the workplace and the living environment in general as a result of the presence of base stations and other sources should also be established by measurement and/or calculation.

7.2.2 *Near-field: deriving reference values*

•	M1 Public concern	•	W1 Fundamental insight
	M2 Large exposed population		W2 Discrepancies
•	M3 Possible risk groups		W3 Effect indicated
•	M4 Involuntary exposure		W4 Inconsistent or conflicting data
•	M5 Long-term exposure	•	W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
•	M7 High-intensity exposure		

The current exposure limits refer to exposure in the far field, at some distance from the source. In practice, however, exposure increasingly occurs in the near field, as a result of mobile phone use or work with equipment that generates electromagnetic fields, for example. The Committee therefore repeats its 2003 recommendation [23] that basic restrictions* be translated into reference values for near-field exposure.

7.2.3 *Calculation of realistic exposures*

•	M1 Public concern	•	W1 Fundamental insight
	M2 Large exposed population		W2 Discrepancies
•	M3 Possible risk groups		W3 Effect indicated
•	M4 Involuntary exposure		W4 Inconsistent or conflicting data
•	M5 Long-term exposure	•	W5 Identify exposure
	M6 Identify exposure	•	W6 Lack of research
	M7 High-intensity exposure		

* The exposure limits proposed by the Health Council of the Netherlands [25,26] and the Council of the European Union [9] distinguish between two types of limit. The basic restrictions are the actual exposure limits. These are values for variables that directly relate to processes in an organism that can be harmful to health. The current density induced in the body is the basic restriction for the ELF range. In the radiofrequency range, the basic restrictions are the Specific Absorption Rate (SAR) for frequencies up to 10 GHz and the power density of the electromagnetic field for frequencies in the range 10 to 300 GHz. The relevant biological effect is the warming of the organism. The SAR is a measure of the speed with which the body absorbs electromagnetic energy, and thus a measure of the conversion of this energy into heat, leading to a rise in body temperature. Current density and the SAR are difficult to measure directly, however. Therefore from the basic restrictions 'reference values' have been dereived. These are values for the electrical and magnetic field present at the exposure location in the absence of the exposed object. These field strengths are relatively simple to measure. The reference values are a tool for determining compliance with the actual exposure limits, the basic restrictions.

The conversion from basic restrictions to reference values for the current exposure limits was made using very simple models of the human body (ellipsoids with homogeneous electromagnetic properties) and in relation to exposure to single sources. Major developments have since led to the development of better and more accurate models. MRI scans have allowed realistic models to be developed, showing different tissues and their specific electromagnetic properties. The Committee believes it is important that the conversion from basic restrictions to reference values be performed using these detailed models. They can also be used to calculate the effects of external electromagnetic fields in realistic exposure situations, such as exposure to several sources at once, and near-field exposure.

The models currently available are virtually all of adult males. It is however important that these calculations also be performed using electromagnetic models of women, particularly women in various stages of pregnancy, with particular emphasis on the modelling of the foetus, and with models of children of various ages. Such models are being developed on a limited scale.

Chapter 8

Responses to questions

In this chapter the Committee responds to the questions in the State Secretary's request for advice.

What is the general international EMF research agenda with regard to health effects for the coming years? What are the key questions awaiting answers?

The answer to the first part of the question can be found in the current WHO research agendas, which are included in annex C. The answer to the second part has been presented in the form of the research recommendations in this advisory report.

What useful contribution could the Netherlands make to this, given the expertise available here? In what areas should the Netherlands seek to tie in and collaborate with research groups in other countries? What research activities would help strengthen the research infrastructure in this field of study in the Netherlands?

The recommendations that the Committee sets out in this report could all make a useful contribution to this field of research, and could be performed using the expertise present in this country. Only in the case of epidemiological studies does the Committee feel it is necessary to collaborate with researchers in other countries. In other studies, this decision will be left to the researchers themselves,

partly because only limited scientific expertise available here relates directly to work on the effects of electromagnetic fields. One side effect of the research programme will be the development of new expertise in the Netherlands on the biological and health effects of electromagnetic fields. Each part of the programme will also strengthen the existing knowledge infrastructure in this country.

Which research deserves priority? This decision should take into account both scientific and social factors, as well as the desire to optimise the deployment of the resources available, and scheduling issues.

All the proposals in this report are accompanied by an indication of which social and scientific factors are at stake. These factors are noted in order of importance. The questions regarding priority, optimisation of the deployment of available resources and scheduling will be answered by the programme committee established by ZonMw.

I should also be pleased to see in your report one or more research areas highlighted where a specific focus in the Netherlands might be expected to yield the most 'health benefit' within the foreseeable future. However, if considering this matter is likely to delay the rest of the report, I request that you focus on this issue in a later advisory report.

Indications of short- and/or long-term health effects of exposure to electromagnetic fields at strengths commonly found in the living and working environment are scarce, and to some extent conflicting. No causal links have been found to date. It is not possible, given the current scientific insight, to make a useful estimate of the qualitative or quantitative effect on public health of enhancing the scientific knowledge. The Committee does however believe that benefit might be derived from reducing public concern, though it is unable to draw any firm conclusions on this matter.

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Annexes

Annex **A**

Request for advisory report

In a letter of 9 September 2005, ref. SAS/2005180309 the State Secretary for Housing, Spatial Planning and the Environment wrote as follows to the President of the Health Council of the Netherlands:

Dear Mr Knottnerus,

At the meeting to discuss national antenna policy with the joint permanent committees on Economic Affairs and on Housing, Spatial Planning and the Environment on 7 December 2004, a request was made for further research into the health effects of radiofrequency electromagnetic fields. The Minister of Economic Affairs and I undertook to seek out possibilities for expanding the research effort, bringing in a greater private-sector contribution. The intention is to launch a research programme in the near future to coordinate and finance the research. This research programme will cover the entire range of electromagnetic fields (EMF), from 0 Hz to 300 GHz.

To achieve such an effort in an efficient and effective manner, insight is needed into ongoing international studies and the possibilities for the Netherlands to make a contribution to such studies. The Health Council has already published a report entitled ‘Health effects of exposure to radiofrequency electromagnetic fields: Recommendations for research’. However, given the time elapsed since publication of the report and the many developments in this area in recent years, it is desirable that it be revised and amended. The recommendations must also be extended to the entire frequency spectrum.

In light of the above, I hereby request you to issue an advisory report addressing the following questions:

1 What is the general international EMF research agenda with regard to health effects for the coming years? What are the key questions awaiting answers?
2 What useful contribution could the Netherlands make to this, given the expertise available here? In what areas should the Netherlands seek to tie in and collaborate with research groups in other countries? What research activities would help strengthen the research infrastructure in this field of study in the Netherlands?
3 Which research deserves priority? This decision should take into account both scientific and social factors, as well as the desire to optimise the deployment of the resources available and scheduling issues.

I would urge you not to limit your recommendations to biological and technological fields of research, but to consider also sociological and psychological research that would enhance our awareness and understanding of the social factors associated with this issue.

I should also be pleased to see in your report one or more research areas highlighted where a specific focus in the Netherlands might be expected to yield the most 'health benefit' within the foreseeable future. However, if considering this matter is likely to delay the rest of the report, I request that you focus on this issue in a later advisory report.

Yours faithfully,
(Signed)
State Secretary for Housing, Spatial Planning and the Environment
P.L.B.A. van Geel

Annex **B**

The Committee

The Electromagnetic Fields Committee was established by the President of the Health Council of the Netherlands on 6 March 2004, with a mandate for four years. Its mandate was extended on 1 January 2004 and on 1 January 2006, on both occasions for a further two years.

The Committee has been charged with the task of producing regular reports on scientific developments in its area of focus and dealing with requests for advice on the matter. If necessary, it will comment on important scientific developments in the interim.

The membership of the Committee that drafted this advisory report was as follows:

- Dr GC van Rhoon, *chair*man
  physicist; Erasmus University Medical Centre, Rotterdam
- Dr LM van Aernsbergen, *advisor*
  physicist; Ministry of Housing, Spatial Planning and the Environment, The Hague
- Prof. G Brussaard
  Professor of Radio Communications (emeritus); Eindhoven University of Technology
- Dr J Havenaar
  psychiatrist; Buitenamstel Mental Health Service, Amsterdam

- Dr H Kromhout
  occupational hygienist/epidemiologist, Institute for Risk Assessment Sciences, Utrecht University
- Prof. FE van Leeuwen
  Professor of Cancer Epidemiology; Free University, Amsterdam (VU), epidemiologist; Dutch Cancer Institute, Amsterdam
- Dr HK Leonhard, *advisor*
  physicist; Ministry of Economic Affairs, Groningen
- Dr MM Sitskoorn
  neuropsychologist/cognitive scientist; University Medical Centre, Utrecht
- Prof. WJ Wadman
  Professor of Neurobiology, University of Amsterdam (UvA)
- DHJ van de Weerdt, MD
  medical environmentalist; Central Gelderland Health Service / GGD
- Prof. APM Zwamborn
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Annex C

WHO research agendas

Static fields

The proposals below are taken from *Environmental Health Criteria 232: Static Fields.*[49]

1.2 Recommendations for further study

Identifying gaps in our knowledge of the possible health effects of static field exposure is an essential part of this health risk assessment. The following recommendations for further research have been made.

1.2.1 Static electric fields

There appears to be little benefit in continuing research into the effects static electric fields have on health. None of the studies conducted to date suggest any untoward health effects, except for possible stress resulting from prolonged exposure to microshocks. Thus, there are no recommendations for further research concerning biological effects from exposure to static electric fields. In addition, there is only limited opportunity for significant exposure to these fields in the workplace or living environment and this therefore does not warrant any epidemiological studies.

1.2.2 Static magnetic fields

In general terms, research carried out to date has not been systematic and has often been performed without appropriate methodology and exposure information. Coordinated research programs are recommended as an aid to a more systematic approach. There is also a need to investigate the importance of physical parameters such as intensity, duration and gradient on biological outcome.

Following a discussion of the limitations of existing studies, further research is recommended covering epidemiology, volunteer studies, animal and in vitro biology, studies into mechanisms of interaction, and theoretical and computational investigations.

1.2.2.1 Theoretical and computational studies

Computational dosimetry provides the link between an external static magnetic field and the internal electric fields and induced currents caused by movement of living tissues in the field. Such theoretical techniques allow the fields to be characterised in specific tissues and organs. There are 4 fine resolution, anatomically realistic, voxel phantoms of adult men available, and these have been widely used in studies with time-varying electromagnetic fields. However, very little work has been done with static fields, and further work is considered necessary using these models. In particular, the use of different sized phantoms, and the use of female phantoms, is considered important, as is the use of pregnant phantoms with fetuses of differing ages. Similar studies could be performed with phantoms of pregnant animals to aid interpretation of the results of developmental studies with these models. (*Medium priority*)

A very fine resolution head-and-shoulder phantom should be developed and used to investigate the electric fields and currents associated with visual phosphenes and vertigo. This model could also be used to investigate the fields and currents generated by head and eye movements in a static magnetic field. The latter is considered of particular relevance to interventional MRI procedures where reduced head movements of surgeons and other clinical staff may necessitate increased movement of the eyes. Gross body movement by staff around the interventional system should also be simulated. (*High priority*)

Computations using a detailed model of the heart and modelling of common cardiac pathologies are considered important. This model should include the micro-architecture of the heart as well as the smaller blood vessels within the heart that might produce fields and currents that could have some influence on pacemaker rhythm generation and the propagation of depolarisation. In addition, calculations are necessary to estimate the magnitude and spatial distribution of currents that are induced in the heart as a consequence of field and field gradient exposure. Multiple orientations to the field should be studied. These would allow comparison with the currents that have been calculated to

induce cardiac effects. Supportive experimental and laboratory studies are recommended. (*High priority*)

Although there is a reluctance to use high field MRI on pregnant women at the moment, it is acknowledged that this situation may change. It would therefore be advisable to carry out modelling studies investigating the currents induced in a fetus by maternal or intrinsic fetal movement in a high field. These calculations (and similar studies with gradient and radiofrequency fields) would allow an estimate to be made of the likelihood of possible effects on the fetus. (*High priority*)

1.2.2.2 In vitro studies

Static magnetic fields may interact with biological systems in a number of ways, although the most likely means of causing health effects are via field-induced effects on charged molecules and alterations in the rate of biochemical reactions.

Further studies are needed on possible mechanisms and targets for biological effects of static magnetic fields. It is recommended to investigate the effects of static magnetic fields of 0.01 - 10 T on interaction of ions (e.g. Ca^{2+} or Mg^{2+}) with enzymes and radical pair formation. Although it is considered difficult to do, there is merit in searching for more enzymatic reactions that proceed through radical pair mechanisms in model systems that are relevant for human health. Another suggestion is to concentrate on toxic radical species, such as the superoxide, which are known to be damaging and are produced by free radical mechanisms. (*Medium priority*)

Reports of a co-mutagenic effect in various cells are of particular interest concerning the carcinogenic potential of static magnetic fields. This type of study should be performed using human primary cells and extended to include transformation and genetically-modified systems. (*High priority*)

Static magnetic fields might affect gene expression and relevant functions in human and mammalian cells under specific conditions of exposure, but there is only little information available on this. Studies with techniques such as proteomics and genomics should be performed with primary human cells to search for possible molecular markers for effects of static magnetic fields relevant to human health issues. (*Low priority*)

1.2.2.3 Animal experimental studies

The effects of long-term exposure to static magnetic fields can be addressed using animal models. In the absence of specific information regarding the carcinogenic potential of static magnetic fields, long-term (including life-time) studies are recommended. Both normal and genetically-modified animals could be used. For example, if an amplification of free radicals was considered a possible route

whereby cancer risk may be increased, a mouse model with deletion of the superoxide dismutase gene could be used. The susceptibility to tumours and other free radical related diseases is greatly enhanced in this model. The use of microarray techniques allows the effects of many different exposure parameters to be readily assessed and quantified on the genome and proteome. (*High priority*)

The possibility of increased risk of developmental abnormalities and teratological effects needs to be addressed in a systematic fashion. The developing brain may be particularly susceptible to the effects of movement-induced currents since orientation effects are very important for guiding the normal growth of neuronal dendrites. It is also possible that longlasting changes could be induced by relatively short exposures. The study of neurobehavioural parameters can provide a rapid and sensitive assay to explore the effects of exposure on developing brain function, and such studies are recommended. Studies to chart the subtle morphological changes that occur during development of specific regions of the brain, such as the cortex or hippocampus, are also of value. The use of appropriate transgenic models should be considered. (*High priority*)

Although there are data indicating that exposure of animals (and human) to fields of around 2 T does not cause electrophysiological effects, it would be useful to know the effects of higher fields. Thus the effects of exposure up to and above 10 T could usefully be explored in animals. (*Medium priority*)

A variety of other endpoints have been investigated in animals that have so far provided only limited information. While a series of single studies for each of those endpoints might not be cost-effective, a broad animal study to cover different endpoints might be worthwhile. (*Low priority*)

1.2.2.4 Human experimental studies

The cognitive and behavioural effects of static magnetic fields should be investigated further. However, the available data do not suggest particular risks to specific aspects of cognition nor do they suggest which parameters should be tested in the laboratory. In the absence of a clear direction, a possible approach would be to investigate the effects of exposure on the performance of a battery of cognitive tasks that encompass standard tests of attention, reaction time and memory, if only to act as an initial screen pending more focused work. The initial work could be done with volunteers as part of experimental studies. (*Medium priority*)

With a wider utilization of MRI studies where support staff are in close proximity to patients within a magnet, such as in MRI interventional procedures, additional studies are needed of head and eye coordination, cognitive performance and behaviour in a gradient field. Further investigation of mechanisms and intensity of field-induced vestibular dysfunction including vertigo is considered of special interest because of the increasing likelihood that medical staff will be performing complicated tasks for extended periods of time within a magnetic field. (*High priority*)

Similarly, additional studies on cardiac function would be useful and could investigate effects on the cardiovascular system. These studies may also need to be performed at higher than 3 T to evaluate potential risks beyond those in the routine clinical environment. (*Low priority*)

1.2.2.5 Epidemiological studies

There are a number of categories of workers with elevated exposures to static magnetic fields, including MRI technicians, workers at aluminium smelting plants, and certain transportation workers (those on subways, MagLev trains, commuter trains, and light rail). For rare chronic diseases such as cancer, feasibility studies are needed to identify the highly exposed occupational groups that could be assessed for participation in epidemiological studies. Feasibility studies also need to determine which other exposures are present in these occupations. If sufficient numbers of workers can be identified, then a nested case-control approach is probably the most appropriate, since detailed information about the exposure and important confounding variables, such as ionizing radiation, needs to be obtained. International collaborative studies will probably be necessary to obtain sufficient numbers of exposed subjects. (*High priority*)

For other more common health outcomes with short latency periods, specific highly exposed occupational groups (for example, workers in industries where MRI systems are manufactured) can be identified and followed over time. Information about different health outcomes may already be available from routinely performed health examinations of these workers, but this can only be used if similar information is also available for a comparable unexposed group. A health survey of surgeons, nurses and other workers using interventional MRI would provide useful information as to levels, durations and frequency of exposures of workers to static fields in these systems. Similarly, patient records may exist in some hospitals from which it might be possible to obtain data on people who were exposed, but whose condition was subsequently found to be benign. (*High priority*)

There is also merit in performing a prospective study of pregnancy risks associated with occupational static magnetic field exposure, as well as follow-up studies of pregnancy outcomes of pregnant women who had to undergo MRI examinations. (*High priority*)

Experience with other frequencies has shown that obtaining reliable estimates of exposure to electromagnetic fields for use in epidemiological studies can be very difficult, and surrogate measures of exposure, such as job title or distance from a particular source, may not always provide sufficiently accurate assessments. The use of specific instruments is thus required to measure exposure. Relatively small personal dosimeters have proved very useful in research on ELF fields. Personal dosimeters would therefore greatly improve exposure assessment in epidemiological studies. Numerical and experimental validation of the dosimeters should be performed. Magnetic field strength, magnetic

field gradients, exposure durations and, ideally, the rate of change of the magnetic due to motion should be recorded. (*High priority*)

Low frequency fields

The proposals below are taken from a draft version of the WHO *Environmental Health Criteria* document on low frequency fields, dated 24 March 2006.

1.2 Recommendations for research

Identifying gaps in knowledge of the possible health effects of ELF exposure is an essential part of this health risk assessment. This results in the following recommendations for further research.

1.2.1 Sources, measurements and exposures

Further characterisation of homes with high ELF exposure in different countries to identify relative contributions of internal and external sources, the influence of wiring/grounding practices and other characteristics of the home could give insights into identifying a relevant exposure metric for epidemiological assessment. An important component of this is a better understanding of foetal and childhood exposure to EMFs, especially from residential exposure to under-floor electrical heating and from transformers in apartment buildings.

It is suspected that in some cases of occupational exposure the present ELF guideline limits are exceeded. More information is needed on exposures (including to non-power frequencies) related to work on, for example, live-line maintenance, work within or near the bore of MRI magnets (and hence to gradient switching ELF fields) and work on transportation systems. Similarly, knowledge should be increased about general public exposures which could come close to guideline limits: examples are sources such as mobile phone handset pulsed power supplies, security systems, library degaussing systems, induction cooking and water heating appliances.

Exposure to contact current has been proposed as a possible explanation for the association of magnetic fields with childhood leukaemia. Research is needed in countries other than the USA to assess the capability of residential electrical grounding and plumbing practices to give rise to contact currents in the home. Such studies would have priority in countries with important epidemiological results with respect to ELF and childhood leukaemia.

1.2.2 Dosimetry

In the past, most laboratory research was based on induced electric currents in the body as a basic metric and thus dosimetry was focused on this quantity. Only recent work started to explore the relationship between external exposure and induced electric fields. For a better understanding of biological effects and for the development of exposure guidelines, more data on internal electric fields for different exposure conditions are needed.

Computation should be made of internal electric fields due to the combined influence of external electric and magnetic fields in different configurations: vectorial addition of out-of phase and spatially varying contributions of electric and magnetic fields is necessary to assess basic restriction compliance issues.

Very little computation has been carried out on advanced models of the pregnant woman and the foetus with appropriate anatomical modelling. It is important to assess possible enhanced induction of electric fields during foetal life in relation to the childhood leukaemia issue. Both maternal occupational and residential exposures are relevant here.

There is a need to further refine micro-dosimetric models to take into account the cellular architecture of neural networks and other complex sub-organ systems identified as being more sensitive to induced electric field effects. This modelling needs to take into account influences in cell membrane electrical potentials and on the release of neurotransmitters.

1.2.3 Biophysical mechanisms

There are three main areas where there are obvious limits to current understanding of mechanisms: the radical pair mechanism, magnetic particles in the body and signal-to-noise ratios in multi-cell systems such as neuronal networks.

The radical pair mechanism is one of the more plausible low level interaction mechanisms, but it has yet to be shown that it is able to mediate significant effects in cell metabolism. It is particularly important to understand the lower limit of exposure at which it acts, so as to judge whether this could or could not be a relevant mechanism for carcinogenesis. It is recommended that cells of the immune system that generate reactive oxygen species as part of their immune response be used as cellular models for investigating the potential of the radical pair mechanism, given recent studies in which reactive oxygen species were increased in immune cells exposed to ELF.

Although the presence of magnetic particles (magnetite crystals) in the human brain does not, on present evidence, appear to confer a sensitivity to environmental ELF magnetic fields, further theoretical

and experimental approaches should explore whether such sensitivity could exist under certain conditions. Moreover, any modification the presence of magnetite might have on the radical pair mechanism discussed above should be pursued.

The extent to which multi-cell mechanisms operate in the body, especially in the brain, so as to improve signal-to-noise ratios should be further investigated in order to develop a theoretical framework for quantifying this or for determining any limits on it. Further investigation of the threshold and frequency response of the neuronal networks in the hippocampus and other parts of the brain should be examined using *in vitro* approaches.

In addition, there are two other mechanisms, contact currents and effects on airborne pollutants, that are potentially relevant to cancer and should be further investigated.

1.2.4 Neurobehavior

It is recommended that laboratory-based volunteer studies on possible effects on sleep and mentally-demanding task performance be carried out using harmonised methodological procedures. There is a need to identify dose-response relationships at higher magnetic flux densities than used previously and a wide range of frequencies (i.e. in the kilohertz range).

Studies of adult volunteers and animals suggest that acute cognitive effects may occur with short-term exposures to intense fields. The characterisation of such effects is very important for the development of exposure guidance but there is a lack of specific data concerning field-dependent effects in children. It is recommended to perform laboratory-based studies of cognition and changes in electroencephalograms (EEGs) in people exposed to ELF fields in the laboratory, including children and adults that are regularly subjected to occupational exposures.

Some recent data suggest that further research of the relationship between EMF exposure and depressive symptoms or suicide is warranted.

Behavioural studies with immature animals provide a useful model for studying possible cognitive effects in children. Possible effects of pre- and post-natal exposure to ELF magnetic fields on the development of the nervous system and cognitive function should be studied. These studies could be usefully supplemented by investigations of the effects of exposure to ELF magnetic fields and induced electric fields on nerve cell growth using brain slices or cultured neurons.

There is a need to further investigate potential health consequences suggested by the considerable body of experimental data showing opioid and cholinergic responses in animals. Studies examining

the modulation of opioid and cholinergic responses in animals should be extended: the exposure parameters and the mechanistic biological basis for these behavioural responses should be defined.

1.2.5 Neuroendocrine system

The existing database on neuroendocrine response does not indicate that ELF exposure would have adverse impacts on human health. Therefore no recommendations for additional research are given.

1.2.6 Neurodegenerative disorders

Several studies have observed an increased risk of amyotrophic lateral sclerosis in 'electric occupations'. It is considered important to investigate this association further in order to find whether ELF magnetic fields are involved in the causation of this rare neurodegenerative disease. This research requires large prospective cohort studies with information on ELF magnetic field exposure, electric shock exposure as well as exposure to other potential risk factors.

It remains questionable whether ELF magnetic fields constitute a risk factor for Alzheimer's disease. The currently available data are not sufficient, and this association should be further investigated. Of particular importance is the use of morbidity rather than mortality data.

1.2.7 Cardiovascular disorders

Further research of the association between ELF magnetic fields and risk for cardiovascular disease is not considered a priority.

1.2.8 Immunology and haematology

Changes observed in immune and haematological parameters in adults exposed to ELF magnetic fields showed inconsistencies, and there are essentially no research data available for children. Therefore, it is recommended to conduct studies for effects of ELF exposure on the development of the immune and haematopoietic systems in children.

1.2.9 Reproduction and development

There is some evidence for an increased risk of miscarriage associated with ELF magnetic fields exposure. Taking into account the potentially high public health impact of such an association, further epidemiological and experimental research is recommended.

1.2.10 Cancer

Epidemiological data show an association between ELF magnetic field exposure and an increased risk of childhood leukaemia which is not supported by experimental and mechanistic data. Resolving this conflict is the highest research priority in this field. For new epidemiological studies to be informative they have to focus on new aspects of exposure, potential interacting factors and on high exposure groups, or otherwise be innovative in this area of research. In addition, it is also recommended that the existing pooled analyses be updated, by adding data from recent studies and by applying new insights on the analysis.

Childhood brain cancer studies have shown inconsistent results. As with childhood leukaemia, a pooled analysis of childhood brain cancer studies should be very informative and is therefore recommended. Such pooled analysis can inexpensively provide more and better insight into the existing data, including the possibility of selection bias, and, if the studies are sufficiently homogeneous, provide the best estimate of risk.

For adult breast cancer the more recent studies have convincingly shown no association with exposure to ELF magnetic fields. Therefore further research into this association is not recommended.

For adult leukaemia and brain cancer it is recommended to update the existing large cohorts of occupationally exposed individuals. Occupational studies and pooled and meta-analyses for leukaemia and brain cancer have been inconsistent and inconclusive. However, new data have subsequently been published and should be used to update these analyses.

It is a very high priority to support the epidemiological evidence by establishing an *in vitro* cell response or animal model response to ELF fields that is widely transferable between laboratories, if indeed such responses occur. Priority should be given to reported responses (i) for which there is at least some evidence of transferability, (ii) that are potentially relevant to carcinogenesis (e.g. genotoxicity), (iii) that are strong enough to allow mechanistic analysis and (iv) that occur in mammalian or human systems.

Transgenic mouse models for childhood leukaemia should be developed in order to provide appropriate experimental animal models to study the effect of ELF magnetic field exposure. Otherwise, for existing animal studies, the weight of evidence is that there are no carcinogenic effects of ELF magnetic fields alone. Therefore high priority should be given to studies in which ELF magnetic fields are rigorously evaluated as a co-carcinogen.

As a separate area of mechanistic investigation it would be of interest to take reported responses relevant to cancer (e.g. genotoxicity) at very high ELF magnetic fields and determine systematically the

field strength-response profile. These studies would establish whether the profiles are consistent with the theoretical predictions for the free radical mechanism.

1.2.10 Protective measures

Research on the development of health protection policies and policy implementation in areas of scientific uncertainty is recommended; specifically on the use of precaution, the interpretation of precaution and the evaluation of the impact of precautionary measures for ELF magnetic fields and other agents classified as "possible human carcinogens". When uncertainties as to the potential health risk an agent imposes on society exist, precautionary measures may be warranted in order to ensure appropriate protection of the public and workers. Only limited research has been performed on this issue for ELF magnetic fields and more research is therefore necessary. This may assist countries to integrate precaution into their health protection policies.

Further research on risk perception and communication specifically focused on electromagnetic fields is advised. Psychological and sociological factors influencing risk perception in general have been widely investigated. However, limited research has been carried out to analyse the relative importance of these factors in the case of EMF, or to identify other factors that are specific to EMF. Recent studies have suggested that precautionary measures, conveying implicit risk messages, can modify risk perception by either increasing or reducing concerns. Deeper investigations in this area are therefore warranted.

Research on the development of cost-benefit/effectiveness analysis for mitigation of ELF magnetic fields should be carried out. The use of cost-benefit and cost-effectiveness analysis for evaluating whether a policy option is beneficial to society has been researched in many areas of public policy. The development of a framework that will identify which parameters are necessary in order to perform this analysis for ELF magnetic fields is needed. Due to uncertainties in the evaluation, quantifiable and unquantifiable parameters will need to be incorporated.

High frequency fields

In early 2006 the WHO published the following *2006 WHO Research Agenda for Radio Frequency Fields* on its website.

Introduction

In 1997, the WHO International EMF Project developed a Research Agenda in order to facilitate and coordinate research worldwide on the possible adverse health effects of electromagnetic fields (EMF). In subsequent years, this agenda has undergone periodic review and refinement.

In June 2003, a major update to the radiofrequency (RF) section of the Research Agenda was undertaken with the input of an ad hoc committee of invited scientific experts. Since then, several of the research needs have been addressed and a revision was therefore deemed necessary. Also, three specialized workshops* have been held since 2003, where research needs in the RF range were determined. These have been consolidated in October 2005, by an ad hoc committee of scientific experts, into the present RF Research Agenda, which supersedes all previous RF Research Agendas.

The specialized workshops pointed out the need for focused research on children especially regarding brain cancer and cognitive function. The workshop on EMF hypersensitivity (EHS) indicated that there should be further research to characterize EHS but did not recommend further studies on the relationship between EMF and EHS since, from the studies completed so far, there was no substantiated evidence for a causal relationship. Research on potential health effects from base station RF fields was deemed of low priority since studies of cancer risk related to such exposure are unlikely to be feasible and informative because of the difficulty of reconstructing adequately long-term historical exposures.

Researchers are encouraged to use the Research Agenda as a guide to studies that have high value for health risk assessments. To maximize the effectiveness of large research programs, government and industry funding agencies are encouraged to address the WHO Research Agenda in a coordinated fashion. Such coordination will minimize unnecessary duplication of effort and will ensure the most timely completion of the studies identified as being of high priority for health risk assessment.

The RF Research Agenda defines as “high priority” research whose results would contribute significantly to future health risk assessments of RF exposure. The document is ordered in successive sections according to the weight each research activity carries in human health risk assessment: epidemiology, laboratory studies in humans, animals, cellular systems, and mechanisms. It should be recognized that, whilst epidemiological and human laboratory studies directly address endpoints related to human health, cellular and animal studies are of value in assessing causality and biological plausibility. Dosimetry is considered separately, but is important for all research.

Research topics relating to social sciences are included for the first time in this Research Agenda because of the need to better understand the perception of risk from the general public and to better communicate on the RF and health issue.

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* These workshops were “Sensitivity of children to EMF exposure” held in Istanbul, Turkey in June 2004, “EMF hypersensitivity” held in Prague, Czech Republic in October 2004; and “Base stations and wireless networks: Exposure and health” held in Geneva, Switzerland in June 2005.

In each section, a brief summary of ongoing research* is provided along with relevant overarching issues that should be kept in mind when designing and analysing experimental or epidemiological studies. Each research activity is given a priority as follows:

High priority research needs: Studies to fill important gaps in knowledge focused on health risk assessment that are needed to significantly reduce the uncertainty in the current scientific information.

Other research needs: Studies to better assist the understanding of the impacts of RF field exposure on health and that would contribute useful information to health risk assessment.

Guidelines regarding the quality of EMF research can be found at:

- www.who.int/peh-emf/research/agenda/en/index2.html
- www.icnirp.org/documents/philosophy.pdf (Appendix)

Epidemiology

Epidemiological studies are of primary importance in health risk assessment. A number of epidemiological studies of health effects of RF exposure are currently under way. They include:

- INTERPHONE – An international case-control study of brain tumours and tumours of the parotid gland is conducted in 13 countries. Some results of national analyses have been published and the international analyses are expected in 2006. Information about occupational exposures to RF fields has been collected within the study.
- An international cohort study of mobile phone users is starting with partial funding in a few European countries.
- Case-control studies of brain cancers in children and adolescents are being set up in some European countries.
- Development and pilot testing of a personal dosimeter for population-based assessment of exposure to RF fields in different frequencies (including base stations and mobile phones).
- A case control study of childhood cancer, nested within a cohort of children living near fixed sources (TV and radio towers) is under way in Germany, while a similar study around base stations is ongoing in the UK.
- In Australia, a cohort study will follow 13-year olds for 3 years and look for relations between their mobile phone usage patterns and a number of endpoints (such as cognitive and hearing function).

* More information regarding ongoing and recently completed studies is available on the WHO research database (http://www.who.int/peh-emf/research/database/en/index.html).

The INTERPHONE study is expected to provide key data in determining whether there is a relationship between mobile phone use and head and neck cancers. As a case-control study, it is very powerful for the study of rare diseases, such as brain tumours, since about 6000 cases were collected among persons aged 30-59 in 13 countries, covering a population of several million persons. This type of study allows the statistical power for rare diseases to be maximized at relatively low cost and to collect detailed information about exposure history and possible confounding factors. However, only pre-defined endpoints can be studied.

To alleviate this restriction, large-scale cohort studies can be conducted that allow the study of a wide range of health endpoints (e.g. brain and other cancers, and neurodegenerative diseases). Moreover, in a cohort study, new endpoints brought up by other research activities can be included even during the conduct of the study, and the effects of evolving technologies (e.g. digital, 3G, and new modulation patterns) can be naturally integrated (or tracked). Prospective cohort studies therefore provide a "surveillance" tool and have the advantages of avoiding the recall and selection biases common to case-control studies.

When planning epidemiological studies, investigators should consider international coordination and collaboration to maximize statistical power to estimate small risks and to evaluate the role of exposure patterns in different countries. Studies should focus not only on cancer but also on non-cancer endpoints (e.g. chronic diseases such as neurodegenerative diseases, sleep disturbances). Particular attention should be paid to the use of adequate estimates of exposure from all relevant sources.

High priority research needs:

- A large prospective longitudinal cohort study of mobile telephone users that includes incidence as well as mortality data.

Rationale: A prospective cohort study is being recommended to build on the results of case-control studies, such as the INTERPHONE study, which examines cell phone use for periods of < 10 years, and for which it is not possible to rule out health effects that might appear after a greater latency period or longer exposure.

The high priority given to the cohort study on adults reflects the recent findings from case-control studies indicating some risk increases for certain tumours, but where recall bias or selection bias may have affected the results. Non-cancer endpoints (e.g. sleep, headache) for adults are of interest because some studies have suggested these endpoints may be related, and because they can be evaluated concurrently in a cohort study.

Note: Though such a study is being established in Europe, it could be significantly strengthened by increasing the size of the cohort through broader international collaboration and additional funding.

- A large-scale multinational case-control study of brain cancer risk in children in relation to mobile phone use, following a feasibility study.

Rationale: Few relevant epidemiological or laboratory studies have addressed the possible effects of RF exposure on children [INTERPHONE study did not include children as the number of long term users among children at the start of the study was too low for such a study to be informative]. Because of widespread use of mobile phones among children and adolescents and relatively high exposures to the brain, investigation of the potential effects of RF fields on the development of childhood brain tumours is warranted. The uncertainty about the recent findings in adults also applies to children. Because brain cancer in young people is quite rare, a case-control study is recommended as the most appropriate and cost-effective approach.

Other research needs:

- Large-scale studies of subjects with high occupational RF exposure, including cohort studies as well as the use of the RF occupational exposure data within large scale existing case-control studies.

Rationale: Workers exposed to RF fields in some occupations receive high exposure levels (often to large areas of the body, and sometimes exceeding ICNIRP guidelines). Thus these populations may be well-suited to assess whether a health impact of RF exposure exists. However particular attention needs to be paid to the exposure metric.

- Prospective cohort study of children and adolescent mobile phone users and all health outcomes other than brain cancer such as cognitive effects and effects on sleep quality.

Rationale: Cognitive effects and other general health outcomes have been anecdotally reported in mobile phone users. These endpoints are critical for children because of the importance of cognitive abilities and learning in early development. The outcomes can be assessed in a prospective cohort study of children.

A separate study of children is necessary and cannot be combined with a cohort study on adults for several reasons. Both the endpoints and tools used would be different, so there would be no gain in coordinating the studies. A study on children and adolescents would focus on outcomes such as sleep, headaches etc., while a cohort study of adults would also include outcomes that are more common in older ages such as cancer, neurodegenerative disease, outcomes that cannot be studied in a young population unless the cohort is extremely large (not very efficient, and very costly). The tools (e.g. questionnaires) will also vary according to age and endpoints, and so would the recruitment of subjects (e.g. adults identified through subscriber lists and children through schools).

- Surveys to characterize population exposures from all RF sources.

Rationale: Such surveys need to be conducted as collaboration between epidemiologists, physicists and engineers. The studies should focus on the general population and should include for instance, the relative contribution of occupational and residential exposures, and the impact of age, gender and mobility. Regional variations also need to be assessed. These studies will inform the feasibility of future epidemiologic studies and, if appropriate, the proper design of residential epidemiological studies.

Human & Animal studies

Human studies

Human laboratory studies allow RF effects to be studied on humans with control of experimental parameters but are confined to investigations of acute transient effects.

Studies that were recently completed or are ongoing include:

- Effects of RF exposure on reaction times and on memory performance in children (two studies completed)
- Two studies on cognition and thermophysiology in adults (UK, Finland) and children (Australia, Finland)
- Several studies performed at Uppsala University in Sweden, on subjective symptoms, physiological reactions, alertness, performance and sleep
- A study on EEG, regional cerebral blood flow and sleep in adults in Switzerland
- Four studies on cognition and well-being in adults with and without self-reported symptoms, including replication of the TNO study, in the UK, Switzerland, Denmark and Japan
- Studies on hearing and auditory function in Finland, Germany, UK, Turkey, Italy, France, Russia, Poland, Greece, Lithuania and Japan
- Several studies in adults using the Tetra signal in the UK and Denmark
- EMF perception in adults by subjects with self-reported symptoms in Germany (completed).

When designing human laboratory studies of RF exposure, special consideration should be given to establish protocols that avoid design flaws that may have affected some published studies. The experimental design for human laboratory studies should also consider testing parameters such as volunteer age and the temporal pattern of exposure. Exposure should represent the worst case scenario (highest SARs) and be applied under double blind conditions. Possible heat or acoustic sensations from the exposure by subjects must be assessed and mitigated or eliminated. The setup design must be well characterized to ensure reproducible and quantifiable exposure.

High priority research needs:

- If ethical approval can be obtained, acute effects on cognition and EEGs should also be investigated in children exposed to RF fields in the laboratory.

Rationale: Possible RF effects on children were specifically raised by the UK's Independent Expert Group on Mobile Telephones (IEGMP, 2000) and the Istanbul WHO workshop (Kheifets et al. Pediatrics. 2005 116: 303-313). Cognitive effects are a priority research area in RF studies. However there are only a few results concerning RF effects on children.

Other research needs:

- None, awaiting the outcome of current human and animal studies.

Animal studies

Animal studies are used when it is unethical or impractical to perform studies on humans and have the advantage that experimental conditions can be rigorously controlled, even for chronic exposures.

There are many recently completed and ongoing studies, which include:

- Two large-scale rodent bioassay studies in Europe (Perform A), one from the U.S. (NIEHS) and one from Japan (completed or ongoing).
- One multigenerational study in Germany with multiple endpoints (ongoing).
- New and replication studies using rodent models of carcinogenicity and cocarcinogenicity (i.e., Pim1, DMBA, ENU) (completed or ongoing).
- Assessments of effects of GSM (published) and UMTS exposure on the inner ear of rats.
- Replication studies of effects on behaviour (e.g., maze performance) (published).
- Confirmation studies to Russian immune system studies that suggest an effect of RF exposure (ongoing).
- Studies to assess the reproducibility of published RF effects on the permeability of the blood-brain barrier and other neuropathologies (e.g. dark neurones) (ongoing).
- Study in Finland investigating the effects of prolonged exposure of young animals on the development of the CNS using behavioural and morphological endpoints (ongoing).
- There are many more ongoing projects on animals in the WHO database with immunological endpoints, with young animals, etc.

Where practical, animal studies should be designed to include information on the potential impact of animal age on RF responses (i.e. comparing foetus and juvenile to adult). The potential role of the exposure regimen (including intermittency, duration) should be considered in experimental design.

High priority research needs:

- Studies investigating effects from exposure of immature animals to RF fields on the development and maturation of the CNS, and on the development of the haemopoietic and immune systems using functional, morphological and molecular endpoints. Genotoxic endpoints should also be included. Experimental protocols should include prenatal and/or early postnatal exposure to RF fields.

Rationale: In both the UK's Independent Expert Group on Mobile Telephones (IEGMP, 2000) and the Istanbul WHO workshop (Kheifets et al. Pediatrics. 2005, 116: 303-313) the central nervous system (CNS), and the haemopoietic and immune systems were considered potentially the most susceptible of the various organs and tissues that continue to develop during childhood.

Other research needs:

- None, awaiting the outcome of ongoing animal studies.

Cellular studies and mechanisms

Cellular studies

Studies in tissues, living cells and cell-free systems play a supporting role in health risk assessments. Cellular model systems are excellent candidates for testing the plausibility of mechanistic hypotheses and investigating the ability of RF exposures to have synergistic effects with agents of known biological activity. They are critical to the optimal design of animal and epidemiology studies (e.g. cellular studies have the potential to identify clear responses to RF exposures and thus can be used in studies of new RF signals).

There are several recently completed or ongoing studies (genotoxicity, apoptosis, etc.) mostly reporting no effects. There have been a large variety of exposure and growth conditions which makes it difficult to compare the data. Most of the recent controversy is related to some genotoxicity investigations that are presently under replication.

A WHO co-sponsored workshop on Genomics and Proteomics was held in Helsinki in late 2005. It was noted that these methods can determine, on a genome-wide and proteome-wide scale, what biological responses may be induced by environmental stressors (e.g. EMF). However, these methods are still under development and are not relevant to evaluate or predict potential health risks. They may be used as a research tool to identify target molecules (genes, proteins) affected by EMF and to provide molecular end-points for formulation of research hypotheses.

High priority research needs

- Independent replication studies of recently reported findings on HSP and DNA damage using low level (below 2 W/kg) and/or modulation- or intermittency-specific signals. The dependence of the effects on SAR levels and frequency should be included.

Rationale: The most useful contribution of in vitro studies is to establish whether there are any reproducible biological effects at low level that are signal and/or cell specific, especially those relevant to cancer (e.g. genotoxicity) or affecting the nervous system. Therefore, in view of some recently published results (e.g. REFLEX), there is a need to ascertain the validity of the findings, possibly via a multicentre study.

Other research needs

- Studies of RF effects on cell differentiation, e.g., during haemopoiesis in bone marrow, and on nerve cell growth using brain slices/cultured neurons.

Rationale: Cancer cells are generally locked into a rapidly dividing and relatively undifferentiated state. The possibility that haemopoietic and/or neuronal tissue might show an abnormal growth response to RF exposure would be important because of lack of investigation in this area.

Mechanisms

The only established mechanisms that relate to health consequences are caused by temperature elevation and induction of electric currents and fields. Other mechanisms exist but there is no evidence that they lead to any health effects.

There are a few ongoing experimental projects on mechanisms. One is exploring the possibility that biological components exist whose response to RF is sufficiently non-linear to demodulate RF signals and hence produce ELF electrical currents. This could be significant if it occurred in the central nervous system (Universities of Bradford and Maryland, and the UK Health Protection Agency). Others are exploring the movement of subcellular calcium ions. There has also been recent theoretical interest in a number of areas. These include the possibility that RF could affect the concentration of free radicals through the radical pair mechanism, excite molecular vibrations or modify the conformation of proteins.

High priority research needs

- None, awaiting the outcome of ongoing studies.

Dosimetry

Expert dosimetric support for experimental studies of all types is critical to their proper design and interpretation.

- Research is active in designing free-running animal exposure systems to ensure that the large scale, rodent bioassay studies, when taken collectively, are able to optimally address the requirements for signal intensities and amount of time per day that the animals are RF exposed.
- Several ongoing studies are adding to the database of dielectric properties of tissues to include age dependency and therefore improving the quality of the numerical modelling.
- Modelling of SAR distribution in children and pregnant women is also being pursued in many countries.

High priority research needs

- Research is needed to document rapidly changing patterns of wireless communication usage and exposure of different parts of the body (especially for children and foetuses), including multiple exposure from several sources.

Rationale: Experimental exposure conditions need to be based on information gathered from exposure surveys (in contrast to simple source evaluations), especially for children. Little information on individuals' exposure in the general population is available which makes it problematic to estimate the exposure from all radio frequency emitting sources. Due to advancing wireless communication technology, communication devices used in close proximity to the body are getting popular in the general public including children and pregnant women; however dosimetry of different parts of the body in each organ is still limited.

- Further work on dosimetric models of children of different ages and of pregnant women. Improvement in dosimetric models of RF energy deposition in animals and humans combined with appropriate models of the human thermoregulatory responses (e.g. inner ear, head, eye, trunk, embryo, and foetus).

Rationale: The relationship between SAR and temperature elevation should be better modelled to predict potential hazards associated with specific RF exposure conditions and improve the quality of the exposure systems.

Other research needs

- Micro-dosimetry research (i.e., at the cellular or subcellular levels) that may yield new insights concerning biologically relevant targets of RF exposure.

Rationale: Little is known about the field distribution at the micro-scale and consequences of non-uniformity of fields on sub-cellular structures and molecules in terms of mechanisms of bioeffects.

Social issues

There are public concerns about possible adverse health effects of RF fields from mobile communications technology. These concerns influence risk management and public acceptance of scientific health risk assessments. Rational risk management should build on evidence stemming from both scientific risk assessments and insights from social studies that investigate this concern through well formulated research.

Relatively few studies exist on RF risk perception and risk communication. The published studies have investigated impacts of risk management and risk communication strategies on conflict resolution, individual risk perception, including risk ratings, perceptions of policy measures (e.g. precautionary principle), and social and psychological determinants of risk perception. Current research includes:

- National surveys on the perception and evaluation of RF risks by the general public (ongoing in several countries)
- Comparative analyses of national risk perception and risk regulation surveys
- Investigations into the determinants that drive risk perceptions, including studies on the role of scientific evidence and scientific uncertainty
- Cognitive mapping of beliefs and attitudes associated with RF risk appraisals
- Assessment of stakeholder participation strategies and risk communication strategies for conflict management.

All the studies described below are needed and no specific priority is given.

- Risk perception of individuals, including studies on the formation of beliefs and perceptions about the relationship between RF exposure and health.

Rationale: To adequately communicate research results, and to contribute to an informed public debate about RF exposure and health, more knowledge about the prevalence of perception patterns, and the concerns shaping these patterns and their diffusion, is needed.

- Studies that analyse, if possible, in an international perspective, conditions of trust and confidence of stakeholders and the general public in technologies, policies, and risk communication and management strategies associated with RF applications.

Rationale: This would contribute to a general framework of analysis that helps to understand the responses of various stakeholders and experts to public concerns and to increase the effectiveness of communications, and institutional responses to those concerns.

- Assess impacts of precautionary measures on public concern and the adoption of voluntary or mandatory policies.

Rationale: There is scientific evidence that precautionary measures can increase public concern. This evidence is preliminary and needs to be confirmed. In addition, studies should investigate the relevant motives and mechanisms in order to enhance our understanding about impacts of precautionary measures on policy.

- Assess the role of health definitions (well-being) and other important concepts in RF risk communication on risk perception and risk management policies.

Rationale: In order to effectively inform stakeholders, and society at large, there is a need to tune the relevant information to target groups. There is an urgent need to know what role key concepts routinely used in RF risk communication (e.g. “well-being”, “significance”, etc.) play and their relevance for risk perception and risk framing.

- Quantify the health related beneficial effects of wireless communication.

Rationale: An informed health assessment has to value both possible health risks as well as health opportunities associated with wireless communication (e.g. increased security, decreased feelings of anxiety, etc.).

- Evaluate the success of programmes for public and stakeholder participation in various countries.

Rationale: In order to increase trust in national and international risk management, citizens and stakeholder involvement in risk management has to be secured. In Europe, such programs could be carried out in association with the European program Trustnet.

Annex **D**

A note on epidemiological studies

Cohort studies

A cohort study is an epidemiological study in which exposure serves as the starting point. A group of exposed individuals and an equivalent control group of unexposed individuals are put together for a particular exposure factor. The incidence of disease in both groups is observed for a certain length of time. A raised incidence of a particular disease among the exposed group may indicate a causal link with the exposure factor in question.

A cohort study may be prospective or retrospective. In a prospective study the groups are monitored for a certain period (often decades) from the moment they are chosen. One advantage of prospective cohort studies is that exposure is determined prior to the occurrence of the disease. However, the time it generally takes for results to become available, particularly if the disease(s) in question has a long latency period, is a drawback.

Retrospective studies look at exposure and the incidence of disease from a certain time in the past to the time of the study. One key disadvantage of this is that it is not possible to accurately determine past exposure, as in case-control studies.

Cohort studies are not well suited to the study of rare disorders.

Case-control studies

In a case-control study a group of individuals suffering from a particular disease is compared with a control group of subjects who do not have the disease, but are similar to the patients in as many other respects as possible. It is then investigated whether, in a relevant period of the past, they experienced different exposure to a certain factor. If so, this can be an indication that that factor may be a contributing factor in the disease.

One major drawback of this kind of study is that exposure is determined in retrospect, after the onset of the disease, and so is surrounded by uncertainty. There is also often a large difference in the percentages of patients and control subjects willing to take part in the study, with controls generally being less willing to participate.