2007 WHO Research Agenda for Extremely Low Frequency Fields

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 October 2005, WHO carried out a health risk assessment of extremely low frequency (ELF) electromagnetic fields up to 100 kHz, which is published as a WHO Environmental Health Criteria monograph[1]. Gaps in knowledge about possible health effects of ELF field exposure are identified in this monograph, and form the basis for research recommendations given in this Research Agenda.

Following a standard health risk assessment process, it was concluded that there were no substantive health issues related to ELF *electric* fields at levels generally encountered by members of the public. Thus this Research Agenda addresses further research concerning the possible acute and long term effects of exposure to ELF *magnetic* fields.

In general, acute effects are known to result from exposure to ELF magnetic field which induces electric fields and currents in the body. These can, at high experimentally induced field strengths (well above 100 μT), cause nerve and muscle stimulation and changes in nerve cell excitability in the central nervous system. Various research recommendations are made which address uncertainty in the threshold levels of these acute effects. With regard to long term effects, epidemiological studies have presented data indicating an association between ELF exposure above approximately 0.3-0.4 μT and an increased risk of childhood leukaemia. Despite several decades of work, however, compelling evidence from experimental studies to support a causal relationship is lacking. In addition, there is no widely accepted mechanism by which ELF fields at normal environmental and occupational exposure levels might affect the incidence of cancer or any other disease in the human population. Therefore, there is a need 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.

Most studies carried out have concerned the possible effects of exposure to power frequency fields. Further research on intermediate frequencies, usually taken as frequencies between 300 Hz and 100 kHz, is required given the present lack of data in this area. For these frequencies very little of the required knowledge base for a health risk assessment has been gathered and most existing studies have contributed inconsistent results, which need to be further substantiated. General requirements for constituting a sufficient intermediate frequencies

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[1] World Health Organization (2007). Extremely Low Frequency Fields. Environmental Health Criteria 238. Geneva, World Health Organization (see: www.who.int/emf).

database for health risk assessment include exposure assessment, epidemiological and human laboratory studies, and animal and cellular (in vitro) studies.

Researchers are encouraged to use the present Research Agenda as a guide to studies that have high value for future 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 timeliest completion of the studies identified as being of high priority for health risk assessment.

This Research Agenda 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, while 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.

Research topics relating to social sciences are included in this Research Agenda because of the need to better understand the perception of risk from the general public and to better communicate with the public on issues relating to ELF field exposure and health.

Each research activity is given a priority as follows:

- **High priority research needs:** Studies to fill important gaps in knowledge that are needed to significantly reduce the uncertainty in the current scientific information relevant to health risk assessment.
- **Other research needs:** Studies to better assist the understanding of the impacts of ELF field exposure on health and that would contribute useful information to health risk assessment.

Epidemiology

Epidemiological studies are of primary importance in health risk assessment. 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:

- **Pooled analyses of existing childhood brain tumour studies**

  Rationale: Brain cancer studies have shown inconsistent results. This was also the case for childhood leukaemia studies and here, pooled analyses have been very informative. Therefore a pooled analysis of childhood brain cancer studies is recommended. Such pooled analysis can inexpensively provide greater and improved insight into existing data, including the possibility of a selection bias, and, if studies are sufficiently homogeneous, provide the best estimate of risk.

- **Update of existing pooled analyses of childhood leukaemia with new information**

  Rationale: Since the pooled analyses have been performed, several new epidemiological studies have been published. The pooled analyses should be updated with the results from these recent studies.

- **Further study of the risk of amyotrophic lateral sclerosis in 'electric' occupations**

Rationale: 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 studies in which sufficient information is collected on ELF magnetic field exposure, electric shock exposure as well as exposure to other potential confounders.

Other research needs:

- **Update of existing pooled and meta-analyses of adult leukaemia and brain tumour studies and cohorts of occupationally exposed individuals**

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

- **Further study of the possible link between miscarriage and ELF magnetic field exposure**

  Rationale: There is some evidence that the risk of miscarriage may be affected by ELF magnetic fields exposure. Taking into account the potentially high public health impact of such an association, further epidemiological research into this hypothesis is recommended.

- **Further study of the risk of Alzheimer's disease in relation to ELF magnetic field exposure**

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

Human volunteer studies

Human laboratory studies allow ELF field effects to be studied on humans with control of experimental parameters, but are confined to investigations of acute, transient effects. For all volunteer studies, it is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration[2].

High priority research needs:

None.

Other research needs:

- **Cognitive, sleep and EEG studies in volunteers, including children and occupationally exposed subjects, using a wide range of ELF frequencies at high field strengths**

  Rationale: Studies of adult volunteers and animals suggest that acute cognitive effects may occur with short-term exposures to intense fields. The characterization of such effects is very important for the development of exposure guidance, but there is a lack of specific data concerning field-dependent effects, particularly in children. It is recommended that

[2] World Medical Association (2004). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. (http://www.wma.net/e/ethicsunit/helsinki.htm, accessed 12-2-2007).

laboratory-based studies of cognition and changes in electroencephalograms (EEG) in people exposed to ELF magnetic fields be performed, including children and occupationally exposed adults.

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.

High priority research needs:

- **Development of transgenic mouse models of childhood leukaemia for use in EMF studies**

  Rationale: Resolving the conflict between epidemiological results and experimental and mechanistic results for childhood leukaemia is the highest priority. It is recommended that epidemiologists and experimental scientists collaborate on this. To this end, the development of transgenic mouse models for childhood leukaemia should be undertaken in order to provide appropriate experimental animal models relevant to the epidemiological data showing an association of EMF exposure with childhood leukaemia.

- **Evaluation of co-carcinogenic effects of ELF fields**

  Rationale: For animal studies the weight of evidence is that there are no significant carcinogenic effects of ELF magnetic fields alone. Therefore high priority should be given to studies in which ELF fields are rigorously evaluated as a co-carcinogen.

Other research needs:

- **Studies of pre- and post-natal EMF exposure up to 100 kHz on subsequent cognitive function in animals**

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

- **Further investigation of opioid and cholinergic responses in animals**

  Rationale: There is a need to further investigate potential health consequences suggested by a 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 and the exposure parameters and the mechanistic biological basis for these behavioural responses should be defined.

- **Studies of ELF magnetic field exposure on immune and haemopoietic systems development in juvenile animals**

  Rationale: While changes observed in immune and haematological parameters observed in adults exposed to ELF showed inconsistency, there are essentially no research data available for children. Therefore, the recommendation is to conduct studies on the effects of ELF magnetic exposure on the development of the immune and haemopoietic systems in juvenile animals.

Cellular studies

Studies in tissues, living cells and cell-free systems play a supporting role in health risk assessments and are usually used to investigate mechanisms of interaction with EMFs. However, they are not generally taken alone as evidence of effects *in vivo* (in animals or people).

High priority research needs:

- **Evaluation of co-carcinogenic effects using in vitro studies**

  Rationale: The weight of evidence supports the view that there are no significant carcinogenic effects of ELF magnetic fields alone. Therefore high priority should be given to studies in which ELF fields are rigorously evaluated as a co-carcinogen.

Other research needs:

- **Replication of in vitro genotoxic studies**

  Rationale: With regard to other in vitro studies, experiments reporting the genotoxic effects of intermittent ELF magnetic field exposure should be replicated.

Biophysical mechanisms

If ELF electric or magnetic fields, at very low levels, can adversely affect health, then a biophysical interaction must occur through some mechanism whereby biological changes that are detrimental to health are produced in an exposed person. The experimental evidence concerning particular biological effects would be strengthened by the identification of plausible interaction mechanisms that can lead to such effects.

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

High priority research needs:

- **Determination of threshold responses to ELF-induced internal electric fields on multi-cell systems, such as neural networks, using theoretical and in vitro approaches**

  Rationale: The extent to which multi-cell mechanisms operate in the body, especially in the brain, 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. In addition, 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.

Other research needs:

- **Further study of radical pair mechanisms in immune cells that generate reactive oxygen species as part of their phenotypic function**

  Rationale: The radical pair mechanism is one of the more plausible low-level interaction mechanisms, but it is 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.

- **Further theoretical and experimental study of the possible role of magnetite in ELF magnetic field sensitivity**

  Rationale: Although the presence of magnetic particles (magnetite crystals) in the human brain does not, on present evidence, appear to confer sensitivity to environmental ELF magnetic fields, further theoretical and experimental approaches should explore whether such sensitivity could exist under certain conditions. Moreover, any modification that the presence of magnetite might have on the radical pair mechanism discussed above should be pursued.

Dosimetry

Expert dosimetric support for experimental studies of all types is critical to their proper design and interpretation. Computational dosimetry provides the link between an external magnetic field and the internal electric fields and induced currents in living tissues within the field. Such theoretical techniques allow the fields to be characterized in specific tissues and organs.

High priority research needs:

None.

Other research needs:

- **Further computational dosimetry relating external electric and magnetic fields to internal electric fields, particularly concerning exposure to combined electric and magnetic fields in different orientations**

  Rationale: 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 recently 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.

- **Calculation of induced electric fields and currents in pregnant women and in the foetus**

  Rationale: Very little computation has been carried out on advanced models of the pregnant human 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.

- **Further refinement of microdosimetric models taking into account cellular architecture of neural networks and other complex suborgan systems**

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

Sources, Measurements and Exposures

The identification of sources of ELF electric and magnetic fields, the measurement of fields they emit and the exposure of members of the public and workers to such fields is a primary step in the assessment of the possible health consequences of such exposure.

High priority research needs:

- **Identification of gaps in knowledge about occupational ELF exposure, such as in MRI**

  Rationale: It is suspected that in some cases of occupational exposure the present ELF guideline limits are exceeded. More information is needed on exposures (including 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.

Other research needs:

- **Further characterization of homes with high ELF magnetic field exposure in different countries**

  Rationale: Further characterization 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.

- **Assessment of the ability of residential wiring outside the USA to induce contact currents in children**

  Rationale: 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 positive associations between ELF magnetic field exposure and childhood leukaemia.

Social Issues

The benefits of the use of electric power, and the possible costs to society of any adverse effects on health that might result from exposure to the electromagnetic fields that electrical equipment generates, are important socio-economic issues. In addition, the development of adequate health protection policies for communities and the communication of appropriate information concerning risk also form an important part of the way in which developing technologies are integrated into society.

High priority research needs:

None.

Other research needs:

- **Further research on risk perception and communication focused on ELF magnetic fields**

  Rationale: 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 ELF magnetic fields, or to identify other factors that are specific to the risk perception of these fields. 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.

- **Development of cost-benefit/effectiveness analysis for mitigation of ELF magnetic fields**

  Rationale: 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.

- **Research on the development and implementation of health protection policies in areas of scientific uncertainty**

  Rationale: When there are uncertainties about the potential health risk an agent imposes on society, 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 therefore more research would be useful to policy makers.