2006 WHO Research Agenda for Static 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 December 2004, WHO carried out a health risk assessment of **static electric and magnetic fields**, which was published as a WHO Environmental Health Criteria monograph [1]. One of the objectives of the review was to identify gaps in knowledge about possible health effects of static field exposure. The Task Group conducting the review concluded the following.

- For static electric fields, there appears to be little benefit in continuing research into their health effects. None of the studies conducted to date suggest any adverse health effects, except for possible stress resulting from repeated 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.
- For static magnetic fields, 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 a need to investigate the importance of physical parameters such as field intensity, exposure duration and field gradient on biological outcome. Research recommendations from this review are given below.

Researchers are encouraged to use this Research Agenda as a guide to studies that have high value for health risk assessments. To maximize the effectiveness of 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.

[1] World Health Organization (2006) Static fields. Environmental Health Criteria 232. Geneva: World Health Organization (see: www.who.int/emf)

The Research Agenda defines as "high priority" research whose results would contribute significantly to future health risk assessments of static field 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, 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. Dosimetry is considered separately, but is important for all research.

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 static 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. Particular attention should be paid to the use of adequate estimates of exposure from all relevant sources.

High priority research needs:

- **Nested case-control study of chronic diseases in highly exposed occupational groups**

  Rationale: 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 specific cancers, feasibility studies are needed to identify the highly exposed occupational groups that could be considered for 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 toxic fumes, needs to be obtained. International collaborative studies will probably be necessary to obtain sufficient numbers of exposed subjects.

- **Cohort study of short-term effects in highly exposed occupational groups**

  Rationale: 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.

- **Prospective study of pregnancy outcomes in relation to occupational exposure and MRI examinations**

  Rationale: A prospective study of pregnancy risks associated with static magnetic field exposure is needed because of the increasing number of pregnant women in the workforce (chronic exposure), as well as follow-up studies of outcomes of pregnant women who undergo MRI examinations (acute exposure).

- **Development of dosimeters for obtaining reliable estimates of static fields exposure in epidemiological studies**

  Rationale: 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 field due to motion should be recorded.

Human volunteer studies

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

High priority research needs:

- **Studies on vestibular function, head and eye coordination in a gradient field**

  Rationale: 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, and are consequently exposed to relatively high static magnetic fields, additional studies are needed of head and eye coordination, cognitive performance and behaviour in a static magnetic 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.

Other research needs:

- **Cognitive and behavioural effects of static magnetic fields**

  Rationale: The cognitive and behavioural effects due to exposure to 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.

- **Cardiac function in the routine clinical environment**

  Rationale: Additional studies on cardiac function would be useful and could investigate effects on the cardiovascular system. These studies should also be performed at higher than 3 T to evaluate potential risks beyond those in the routine clinical environment.

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:

- **Long-term (including life-time) studies concentrating on cancer-related effects using both normal and genetically-modified animals**

  Rationale: 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.

- **Developmental and neurobehavioural effects**

  Rationale: 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 long lasting 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.

Other research needs:

- **Effects on cardiac functions under very high field intensity (10-20 T)**

  Rationale: Although there are data indicating that exposure of animals (and humans) 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 to high intensity fields (10-20 T) could usefully be explored in animals.

- **Animal study to cover different endpoints**

  Rationale: 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.

Cellular studies and mechanisms

Studies in tissues, living cells and cell-free systems play a supporting role in health risk assessments. 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.

High priority research needs:

- **Mutagenicity and transformation in primary human cells**

  Rationale: 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.

Other research needs:

- **Interaction mechanisms on radical pair reactions and enzymatic activity**

  Rationale: 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.

- **Gene expression in primary human cells**

  Rationale: 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.

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 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.

High priority research needs:

- **Development of a very fine resolution head-and-shoulder phantom**

  Rationale: 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. Whole-body movement by staff around the interventional system should also be simulated.

- **A detailed model of induced current in the heart**

  Rationale: 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.

- **Dosimetric studies on the fetus under high field MRI**

  Rationale: 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.

Other research needs:

- **Dosimetric studies with male/female/pregnant voxel phantoms.**

  Rationale: There are four 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.