2006 WHO Research Agenda for Radio 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 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[1] 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

[1] 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.

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.

In each section, a brief summary of ongoing research[2] 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).

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

[2] 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).

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.