World Health Organization

Children's EMF Research Agenda

http://www.who.int/peh-emf/research/children/en/index.html

Introduction & general comments

The Working Group considered research recommendations for studies relevant to the risk of adverse health effects in children from exposure to electromagnetic fields (EMFs). The issues under consideration reflected and amplified the various suggestions and proposals made by the individual presenters at the preceding WHO Workshop on Childhood Sensitivity to EMFs held in Istanbul on 9 & 10 June 2004. The workshop proceedings are available in a special edition of *Bioelectromagnetics* (in press).

Particular issues included the role of extremely low frequency (ELF) magnetic fields in the development of childhood cancer and possible risks from mobile phone radiofrequency (RF) radiation, especially regarding brain cancer and cognitive function. Less emphasis was given to risks from exposure to static fields and to fields associated with security devices. However, pregnant workers are employed in retail industries with an increasing prevalence of security and identity devices, including devices for electronic article surveillance (RFID/EAS). A better understanding of the dosimetry and possible health effects for this region of the spectrum is needed, since it is not clear that extrapolation from higher and lower frequency regions is sufficient.

Separate breakout groups considered research recommendations for further epidemiological studies, laboratory studies (including those using volunteers, animals and *in vitro* techniques), and dosimetry work which were then discussed in a plenary session. The relevance of these different studies to health risks in people varies. Epidemiological studies of the distribution of disease in populations and the factors that influence this distribution provide direct information on the health of people exposed to an agent and are given the highest weighting. However, they may be affected by bias and confounding, and their observational nature makes it difficult to infer causal relationships, except when the evidence is strong. Experimental studies using volunteers can give valuable insight into the transient physiological effects of acute exposure, although for ethical reasons these studies are normally restricted to healthy people. Recommendations concerning laboratory studies using children are, of course, subject to appropriate ethical approval. Studies of

animals, tissues and cell cultures are also important but are given less weight. Animal studies can often be expected to provide qualitative information regarding potential health outcomes, but the data may not be extrapolated to provide quantitative estimates of risk, largely because of differences between species. Studies carried out at the cellular level are normally used to investigate mechanisms of interaction, but are not generally taken alone as evidence of effects in vivo. Nevertheless, each type of study has a role to play in determining the scientific plausibility of any potential health risk.

Dosimetry provides a precise measure of the interaction of EMFs with people, and exposure assessment provides an estimate of individual and population exposure to EMFs that contributes to the assessment of the likely impact of exposure on health. Each such assessment needs to consider all sources of EMF (low and high frequencies) to which an individual or a population may be exposed.

General recommendations

The Dosimetry Working Group made the following general recommendations:

- A better understanding of foetal and childhood exposure to EMFs is required, including an assessment of exposure to the high static magnetic fields encountered around magnetic resonance imaging (MRI) equipment and the lower static magnetic fields encountered in public transport vehicles, and an assessment of exposure to ELF fields, especially residential exposure from under-floor electrical heating and from transformers in apartment buildings. For RF fields, exposure assessment is particularly weak for base stations and TV and radio towers and needs further exploration. **High Priority**

  Rationale: This information, in combination with dosimetric modelling and an understanding of possible biological effects, is needed to assess the risk to health posed by such exposure.

- More-accurate dosimetric models of pregnant women, of foetuses at various developmental stages (neural tube closure; differentiation and organogenesis; growth) and of children are needed. In addition, an exploration of EMF microdosimetry at the cellular or subcellular levels should be supported. **High Priority**

  Rationale: Dosimetric information regarding pregnancy and the developing foetus is lacking; this information is required for a proper health risk assessment. In addition, exploration of EMF microdosimetry may yield new insights concerning biologically relevant targets.

- Additional data on the dielectric and thermal properties of human tissues and organs at various developmental stages, including the foetal stage, is needed. **High Priority**

  Rationale: The dielectric constant is a factor that varies with age. Foetal data could be significantly different from data on children or adults, but it may be very difficult to obtain ethical approval to acquire experimental data. Perhaps ultrasonic examinations could provide data on dimensions that may allow estimation of water content, from which dielectric constants can be derived.

Static fields

Static magnetic fields were not specifically addressed at the Workshop. It was recognized, however, that there is also a need to address childhood susceptibility to static magnetic fields because of both developing technologies like magnetic levitation transportation and the ever-increasing use of magnetic resonance imaging techniques. This led to the following recommendation:

- Future laboratory studies of static magnetic fields should consider the effects of prenatal and early postnatal exposures in addition to those of adult exposure. **High Priority**

  Rationale: There are few studies of the effects of prenatal and early postnatal exposure, particularly to very intense magnetic fields (>1 T).

Extremely Low Frequency Fields

1. Epidemiological Studies

Something of an impasse has been reached in designing studies of ELF magnetic fields and childhood leukaemia. While existing epidemiological studies show a consistent association, most of the available studies are of case-control design and are thus potentially subject to selection bias. To move forward we need innovative approaches, which might include (1) designing studies capable of evaluateing selection bias (e.g., by collecting data on magnetic fields and participation) and/or minimizing it (e.g., a cohort study), or (2) identifying large, highly exposed populations (e.g., those living in apartments next to transformers), or susceptible subgroups (e.g., previously initiated populations in which magnetic fields act as a second 'event' in carcinogenesis). In addition, two hypotheses concerning causality (contact current and melatonin) were discussed at the Workshop. All of these approaches and hypotheses pose major challenges.

- Pooled analysis of childhood cancer studies. **High Priority**

Rationale: Pooled analyses of childhood leukaemia studies have been very informative. Although new studies would not fundamentally change the results of the previous pooled analyses, recent studies will add new countries and enough data to probe the results further. It might be possible to further explore the high end of the dose–response curve. Additionally, risk modifiers – for example, age – might be further explored. Brain cancer studies have shown inconsistent results; a pooled analysis of brain cancer studies may also be very informative, may inexpensively provide insight into existing data, including the possibility of selection bias, and, if appropriate (i.e., if studies are sufficiently homogeneous), may come up with the best estimate of risk.

- Further studies of ELF exposure and miscarriage. **Medium Priority**

  Rationale: Two recent California studies have reported an increased risk of miscarriage due to maximum levels of ELF exposure, but the studies have areas of potential weakness in study design that can be improved. First we recommend studies to identify behavioural determinants of maximum fields. Further investigation, focusing on early pregnancy loss and using improved design, would also contribute to this area.

2. Volunteer studies

These recommendations address effects for which there is some supporting evidence in studies using adults.

- Laboratory–based studies of cognition and changes in electroencephalograms (EEGs) in children exposed to ELF fields in the laboratory, if ethical approval is possible. **High Priority**

  Rationale: Studies of adult volunteers and animals suggest that acute cognitive effects may occur with short–term exposures to intense fields. Such effects are very important for the development of exposure guidance (e.g., McKinlay et al., 2004; WHO ELF Research Agenda) but there is a lack of specific data concerning field–dependent effects in children.

3. Animal studies

These recommendations focus on possible carcinogenic effects, particularly in relation to childhood leukaemia, and effects in key tissues and organs regarded as potentially susceptible to EMFs, particularly the developing central nervous system (CNS), haemopoietic (bone marrow) tissue and immune system. Experimental protocols should include prenatal and/or early postnatal exposure to EMFs.

- Further development and experimental investigation using appropriate animal models, including the use of transgenic animals (e.g., Carron et al., 2000), which develop a disease having similarities to childhood acute lymphoblastic leukaemia. (Animal studies carried out to date have not used such models.) Experimental studies to include the effects of prenatal exposure and the combined effects of ELFs and known carcinogens. **High Priority**

  Rationale: The possible role of EMF exposure in childhood leukaemia development is a priority research area (e.g., AGNIR, 2001; WHO ELF Research Agenda). In addition the combined effects of ELF-EMFs and known chemical or physical carcinogens and/or mutagens have been reported in many studies (IARC, 2002).

- Studies of developmental effects of pre- and postnatal exposure to low-frequency EMFs on immune function and on the induction of minor skeletal variations. Effects of prolonged, intermittent exposure from the early postnatal period on subsequent cognitive function in animals. **Medium Priority**

  Rationale: An increase in minor skeletal anomalies is the only consistent finding from a number of developmental EMF studies in mammals (e..,g Juutilainen, 2003). The immune system continues to develop postnatally; Study of the effects of ELF fields on this system is thus a useful means to evaluate them as possible immunotoxicants. Behavioural studies with immature animals provide a useful and established model for studying possible cognitive effects in children.

- Further study of possible ELF carcinogenic mechanisms, including exposure to intermittent fields and transients, both alone and in combination with known carcinogens. **Low Priority**

  Rationale: The possible carcinogenicity of EMFs remains an issue of concern (e.g., IARC, 2002), although the experimental evidence for carcinogenic effects is weak. However, hypotheses such as those involving the role of signal intermittence, transients or contact currents have not been widely investigated and the possibility for co-carcinogenicity must be clarified.

4. *In vitro* studies

Areas requiring further ELF in vitro study include possible electric field and (contact) current effects on carcinogenic processes, especially pathways involved in haemopoietic cell differentiation and proliferation, and on nerve cell growth and synaptogenesis. In addition, further exploration of the possible role of melatonin in free-radical scavenging is required.

- Studies of ELF magnetic field and induced electric field effects on cell differentiation (e.g., during haemopoiesis in bone marrow) and on nerve cell growth using brain slices or cultured neurons. **High Priority**

  Rationale: As in the recommended animal studies, possible effects on pre- and post-natal cellular differentiation and tissue development are a priority research area. Cell differentiation is inhibited during neoplastic progression; cell orientation and migration are both key processes in development. The developing nervous system and bone marrow are thought to be key tissues in this respect.

- Effect of EMF exposure on the protectiveness of physiological levels of melatonin against oxidative damage from free radicals, reactive oxygen species, etc. during haemopoiesis in foetal and postnatal tissue. **Medium Priority**

  Rationale: Melatonin has been shown to be highly protective against oxidative damage to human lymphocytes in vitro (e.g., Vijayalaxami et al., 1996, 2004) and similar damage to the brain tissue of rat foetuses in vivo (Wakatsuki et al., 1999, 2001), possibly by increasing the concentration of known radical scavengers such as superoxidase dismutase (Okatani et al., 2000). The possibility that EMF exposure may affect the ability of melatonin to suppress oxidative damage in foetal or postnatal tissue should be investigated.

- Further studies of possible carcinogenic mechanisms for ELF fields, particularly in combination with known carcinogens. **Low Priority**

  Rationale: The possible carcinogenicity of EMFs remains an issue of concern (e.g., IARC, 2002), although the experimental evidence for carcinogenic effects is weak. The combined effects of ELF-EMFs and known chemical or physical carcinogens and/or mutagens have been reported in many studies (IARC, 2002). In addition, hypotheses such as those involving the possible role of signal intermittence or transients have not been studied.

5. Dosimetry and exposure assessment

A better understanding of the prevalence of earth leakage currents and the potential consequences of exposure to contact currents in small children (e.g., when bathing), is needed. Work is in progress to examine the prevalence of contact currents in countries other than the United States (e.g., in European and Asian residential electrical systems). If exposure to contact currents is a global issue and some mechanism can be demonstrated, the model should be further examined.

- Dosimetric modelling of the interaction between induced or injected current and juvenile limbs should be undertaken, taking account of reduced surface resistance, lack of bone calcification and the presence of active marrow. **High Priority**

  Rationale: The extent to which electric current flows through the bone marrow of small children as a consequence of contact which allows an earth leakage current to flow through their bodies should be further studied.

- Assess exposure to the 217–Hz nonsinusoidal magnetic fields from mobile phones. **Low Priority**

  Rationale: The pulsating battery current in a mobile phone generates a low–frequency nonsinusoidal magnetic field (Jokela 2004) in the vicinity of the phone. The field penetrates without any effect on the skin into tissue. Some preliminary estimates show that the resulting exposure to induced currents in the head is not much lower than the ICNIRP limit. Furthermore, it has been suggested that mobile phones are an important source of ELF exposure, particularly to bone marrow in children's hands. More detailed investigation of exposure is necessary to assess exposure quantitatively

Radio Frequency Fields

1. Epidemiological studies

There is little relevant epidemiology at present that examines health effects in children; the following recommendations address general health effects, including cancers in children who use mobile phones or live near base stations or radio or TV towers.

- Prospective cohort study of children mobile phone users and all health outcomes other than brain cancer (see below) but including more general health outcomes such as cognitive effects and effects on sleep quality. **High Priority**

  Rationale: Since many children are heavy mobile phone users and will continue to be in the future, they represent a unique population. The type of mobile use among children (e.g. text messaging), their potential biologic vulnerability and longer lifetime exposure make such a study desirable. Cognitive effects and other general health outcomes have been anecdotally reported in mobile phone users. They can be assessed in a prospective cohort study of children. A separate study of children was found necessary, as it is not possible to just extend the age range of a cohort study of adults because the outcomes have to be assessed by different methods in children and adults, and children's exposure probably

differs from that of adults' (more use of pay-as-you-go SIM-cards, more frequent change of phones and operator).

- Case-control study of children mobile phone users and brain cancer. **High Priority**

  Rationale: Brain cancer is an important end-point to study given the location of the antenna for the phone, but it is rare in children and so this is not likely to be a feasible end-point for a cohort study.

- Nested case control studies of childhood cancer with improved exposure assessment for (1) base stations and (2) TV and radio towers. **High Priority**

  Rationale: There is at present a lack of information concerning health effects associated with living in close proximity to base stations or TV or radio towers. One particular difficulty is exposure assessment. Further investigation into improved measures is a critical step in better capturing exposure from these sources and in determining the feasibility of epidemiological studies of children living in the vicinity of these sources.

2. Volunteer studies

The following recommendations address effects seen in laboratory-based studies using adult volunteers.

- A laboratory-based assessment of effects of RF exposure on cognition, EEGs, and sleep in children is recommended as a part of a larger prospective cohort study (see the Epidemiology section). 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. **High Priority**

  Rationale: Cognitive effects are a priority research area in RF studies. However there is a paucity of data concerning RF effects on children (Goldstein et al, 2003; AGNIR, 2003; WHO RF Research Agenda).

3. Animal studies

A large U.S. National Toxicology Program (NTP) rodent (both rats and mice) study is likely to be funded in the near future. The study will examine the toxicity and carcinogenicity of RF radiation characteristic of mobile phones; animals will be exposed in utero and postnatally. A full histopathology will be carried out, along with assays of endocrine levels, estrus cycling and sperm levels, urinary metabolite patterns (as indicators of physiological perturbation), haematology and

genotoxicity (i.e., micronucleus frequency, DNA-strand breaks, etc.). There will be a particular focus on changes in blood-brain-barrier permeability and any concomitant neuropathology. [Tissue may be made available to other research groups; contact Ron Melnick, email: melnickr@niehs.nih.gov]

The recommendations given below focus on the developing central nervous system, haemopoietic (bone marrow) tissue and immune system. Experimental protocols should include prenatal and/or early postnatal exposure to EMFs.

- Studies investigating the effects of prolonged exposure of immature animals to RF fields on the development and maturation of the CNS, using behavioural, morphological (e.g., synapse formation) and molecular (e.g., using gene microarrays) endpoints. **High Priority**

  Rationale: Possible RF effects on children were specifically raised by the UK's Independent Expert Group on Mobile Telephones (IEGMP, 2000); the CNS was considered potentially one of the most susceptible of the various organs and tissues that continue to develop during childhood.

- Effects of prenatal exposure to RF fields on the development and maturation of the blood-brain barrier. [Note that funded work is likely to begin on this topic in the near future; see above.] **High Priority**

  Rationale: Possible effects on the adult blood-brain barrier and the potential for resulting neuropathology have long been a controversial issue in RF research (e.g., IEGMP, 2000; WHO RF Research Agenda). These studies should be extended to cover pre- and postnatal development of the blood-brain barrier. (In humans, this development is complete at approximately 6 months [Rodier, 2004].)

- Studies investigating the effects of prolonged exposure of immature animals to RF fields on the development of the immune system, including microglia cells (resident macrophages) and induction of autoimmunity in the brain. **Medium Priority**

  Rationale: The immune system also develops during early childhood and is a critical tissue with regard to possible effects of RF exposure. Studies performed in the former USSR showed induction of autoimmunity after exposure to RF fields (Vinogradov, 1993).

4. *In vitro* studies

Studies of possible RF effects on carcinogenic processes, particularly effects on differentiation pathways and haemopoietic tissue, continue to be of interest. In addition, effects on nerve cell

growth and synaptogenesis are considered worthy of further research. The possibility that biological tissue can somehow demodulate modulated RF signals to produce biologically significant ELF electric fields and currents has long been a controversial area. Research into this area, based on a recently proposed, very sensitive method of detection, is being funded in the UK (Challis, in press). If real, this effect could have important implications for both childhood and adult exposure. Other mechanistic studies were also recommended.

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

  Rationale: Cancer cells are generally locked into a rapidly dividing and relatively undifferentiated state, and the possibility that haemopoietic and/or neuronal tissue shows a growth response to EMF exposure was considered to be an important area for further investigation.

- Continued studies of possible mechanisms of RF interaction. **Medium Priority**

  Rationale: Research hypotheses based on plausible interaction mechanisms are a key part of the design and execution of animal and epidemiological studies carried out in order to evaluate possible risks to health. There are two hypotheses that are worthy of further investigation (Challis, this issue): (1.) Whether the mechanism leading to an increase in free-radical concentrations that has been demonstrated at frequencies below 80 MHz might also apply at higher frequencies. 2. Whether the above-average temperature rises that might be expected to occur in electrically conducting regions within thermally insulated parts of the body, such as the cochlea and vestibular apparatus, are large enough to cause concern.

5. Dosimetry and exposure assessment

A key issue in this area has been the development of a personal dosimeter in order to greatly improve exposure assessment (for example, around base stations) for epidemiological studies (Wiart, in press). Recommendations were made for improved childhood exposure assessment and dosimetric and thermal modelling.

- Research is needed to document rapidly changing patterns of phone use (SMS, email, classical phone communication, etc.) and exposure of different parts of the body for children and foetuses. **High Priority**

  Rationale: This research would be required to complement epidemiological studies.

Exposure surveys (in contrast to simple source evaluations) to assess children's exposure are lacking, but urgently needed. Service providers are important sources of information regarding exposure and should be encouraged to participate in exposure surveys and epidemiological studies.

- Dosimetric models of RF energy deposition in children and foetuses, combined with appropriate models of human (childhood) thermoregulatory responses, should be developed. **High Priority**

  Rationale: These dosimetric and thermoregulatory models are required in order to predict potential hazards associated with specific RF exposure conditions (Goldstein et al., 2003; WHO RF Research Agenda). Dosimetric calculations and realistic modelling of exposure to the foetus under various exposure scenarios (e.g., with and without a hands-free device) are needed.

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