Do Electric or Magnetic Fields Cause Adverse Health Effects?

HEI's Research Plan to Narrow the Uncertainties

HEI

Health Effects Institute

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HEI THE HEALTH EFFECTS INSTITUTE

The Health Effects Institute is both an institution and a concept. The Institute itself was established in 1980 as an independent and unbiased source of information on the health effects of motor vehicle emissions. HEI funds research on regulated air pollutants, such as ozone, nitrogen dioxide, and particulate material, and on unregulated pollutants, such as diesel engine exhaust, methanol, and aldehydes. To date, HEI has supported more than 120 studies at institutions in North America and Europe.

The Institute receives half its funds from the U.S. Environmental Protection Agency and half from 28 manufacturers and marketers of motor vehicles and engines in the U.S. However, the Institute exercises complete autonomy in setting its research priorities. An independent Board of Directors governs the Institute. The Research and Review Committees, interdisciplinary groups of basic and environmental scientists, serve complementary purposes. The Research Committee and staff develop and oversee the Institute's research program. The Review Committee evaluates completed studies and publishes each one as a Research Report, which contains both the Investigator's Report and the Review Committee's Commentary on the study.

HEI is also a concept, a particular way of organizing to do research on the health effects of environmental agents, and a particular approach to creating an institutional context for that research. HEI has explored research opportunities in several areas of concern with respect to human health. HEI-Asbestos Research was formed in 1989 to gather and generate reliable and objective information on asbestos exposure and to evaluate the effectiveness of asbestos management and abatement strategies. More recently HEI has been asked to undertake research planning efforts in environmental epidemiology and the health effects of electric and magnetic fields.

Do Electric or Magnetic Fields Cause Adverse Health Effects?

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STATEMENT FROM THE HEI BOARD OF DIRECTORS

The Health Effects Institute is pleased to release the Report of its EMF Planning Committee recommending a coherent five- to seven-year program of coordinated research by physicists, biologists, and electrical engineers designed to answer the questions: "Does exposure to electric or magnetic fields have effects upon human health? If so, what is it about either field that causes the health effects?"

Why the Concern About EMF?

The transportation and use of electricity give rise to surrounding electric and magnetic fields. A number of scientists and many other citizens have become concerned that some such fields may cause cancer or a wide range of other harmful health effects. Because electricity is fundamental to 20th century human activity in all parts of the world, these reports have produced widespread alarm.

Many other scientists, relying on extensive research and reviews supported by public and private institutions, are convinced that there is no reason for concern, and that the studies cited to support the fears are misinterpreted.

So long as the scientific community is divided and uncertain, public worry and the public pressure for some action to reduce any danger—now—are bound to grow.

Why Is the Health Effects Institute Involved?

The growing concern over possible effects of EMF gave rise to calls for a national research strategy, independent of but complementary to existing EMF research. HEI, an organization jointly funded by the U.S. Environmental Protection Agency and the motor vehicle industry to plan and manage studies on the health effects of automotive emissions, had developed new concepts and methods for coordinating specific research projects. In addition, its sister institution, Health Effects—Asbestos Research, had successfully undertaken, at the request of the Congress and EPA, a review of what was known about the scientific issues in the lively controversy over asbestos in buildings—a review that went far to narrow and redirect controversy about these issues. Seeking a new perspective, the EPA and the Large Public Power Council requested that HEI consider the development and management of a research program on the biological and potential health effects of electric and magnetic fields.

HEI then undertook a feasibility study. Concurrently HEI was engaged in a study on EMF epidemiology as part of another program. The combined results led the HEI Board of Directors to three conclusions:

(1) There is a need for an expanded scientific effort to determine whether EMF has effects upon human health;

(2) The only kind of program worth undertaking is one that holds out substantial prospect of providing widely credible answers to that key question;

(3) Such a program must be guided by a rationale that encourages both exploration and sequential testing of well-formed hypotheses and that actively relates the different types of biological studies to each other.

The Institute's EMF Research Planning Committee was then formed, chaired by Dr. Joseph Brain, Chair of the Department of Environmental Health at the Harvard School of Public Health. The Committee was charged:

(1) To devise a coherent research plan that would have the prospect of providing within five to seven years a credible answer to the question, "Does EMF exposure cause human health effects?" and

(2) To determine the best method of carrying out such a program, including the selection of research projects, oversight, and peer review.

The membership of the EMF Research Planning Committee was chosen to achieve a diverse blend of scientific disciplines; it included members with broad experience in current EMF research and leaders in relevant disciplines who had not been involved in the controversy. HEI's staff, particularly Dr. Jane Warren, provided both internal help and reached out to knowledgeable consultants to do the additional staff work. Working in the summer and fall, the Committee developed the program. The winter and early spring were devoted to editing and to seeking reviews of the strategy from a still broader range of reviewers. The very positive general response of those reviewers to HEI's EMF research plan confirms our judgment about the quality of the Committee's work. The Board is very grateful to the Committee and the staff.

Report of the EMF Research Planning Committee

The Report seeks to move the EMF controversy towards a resolution by providing as a national resource a concrete and coherent plan for interdisciplinary research offering a promising prospect of widely credible answers to the critical questions within the next decade.

We think the Committee has been eminently successful. The Report lays out the fundamental questions to be addressed. It takes into account the fact that the resolution of the EMF issues must coordinate the best biological talent in the country with the best talent from physics and electrical engineering. It then develops a sequential approach to utilizing the various types of biological disciplines and processes to begin answering these questions; it also stresses the importance of bringing in physicists and electrical engineers to establishing reproducible exposure parameters and thus enhancing the comparability of different types of research. To give the plan of research specificity and to give impetus to launching the work, the Report takes the unique step of carrying these considerations forward into a sequence of draft Requests for Applications, which a new program on EMF could promptly issue to the scientific community.

The characteristics of the research needed to move effectively towards resolution of the EMF controversy dictate the appropriate institutional arrangements for research selection and oversight.

First, the need for interdisciplinary skills, demonstrated by the Committee's report and draft Requests for Applications, dictates that there should be competitive extramural research grants to solicit and draw in the talent and new ideas of a broader range of scientists than could be found within a single laboratory—or institution.

Second, discipline must be wed to creativity by a judicious degree of continuing oversight. One of the problems of interpreting past EMF research findings from wholly independent projects is that the exposure parameters were very different and sometimes ill-defined.

Third, the program needs to progress in an integrated way. Researchers at work under any one RFA need to be kept well aware of how their work interacts with the other studies chosen. The work emerging from one RFA must guide the research selection in the succeeding set. And, we would especially emphasize, that the program must be driven by the research findings. As stated in the preface, the research strategy "will have the flexibility to change directions as indicated by findings of HEI studies and research supported by other organizations." This report then provides a set of questions arising from past studies, a set of research objectives to initiate the program, and a flexible and coordinated approach to building on the results of the initial studies.

The foregoing needs can be satisfied only by organizing a diverse group of scientists from the relevant fields of scientific expertise who, as standing committees, will arrange the extramural research, provide continuing oversight and coordination, and ultimately review research reports both individually and comprehensively. The Board, based on the work of the EMF Research Planning Committee, believes that the processes and procedures developed by the Health Effects Institute would appear to be capable of clarifying the EMF controversy. And the fact that HEI is experienced in mixing private and public funds is also relevant.

What Lies Ahead?

The Energy Policy Act of 1992 calls for a complex procedure for moving forward on EMF research. It locates responsibility for generation of the program in the National Institute of Environmental Health Sciences (within the context of a larger research effort to be conducted in cooperation between NIEHS and the Energy Department). The Act envisages the additional involvement of several advisory committees.

The Health Effects Institute, as stated above, makes this report available to the public, the scientific community, and especially to those policy-makers responsible for wise resolution of the EMF controversy, believing that the plan developed in the Report is conceptually clear and promises to advance scientific knowledge on precisely the issues that confound scientists and the public today. The research should be done. The plan developed in the Report should be, and is, available publicly. HEI is prepared to do the research, and we think that the HEI methods are well suited to the work. But the important thing is that a carefully formulated strategy for five to seven years of interdisciplinary research be carried out under some central direction. We publish the plan for the relevant community so that those responsible for decision may see what kind of program is required and so that the plan may focus the attention of both the scientific and policy making communities on the research approach and specifics which we believe will be necessary if the EMF controversy is ever to be resolved.

DO ELECTRIC OR MAGNETIC FIELDS CAUSE ADVERSE HEALTH EFFECTS?

HEI'S RESEARCH PLAN TO NARROW UNCERTAINTIES

June 1993

SECTION 1: MAIN REPORT

SECTION 2: POTENTIAL COMMUNICATIONS TO INVESTIGATORS

SECTION 3: APPENDICES

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CHAPTER 1: PREFACE

Epidemiologic results have raised the possibility that exposure to electric and/or magnetic fields (EMF) associated with electric power distribution and use increases risk for cancer, particularly childhood leukemia and brain cancer. Several studies using surrogate measures of exposure to EMF thought to reflect magnetic field exposure (such as wiring configurations) have reported significant increases in relative risks for childhood leukemia. However, when actual measurements of some magnetic fields were made in homes in the same studies, they were not associated consistently with an increased relative risk. Laboratory studies have provided some evidence of effects on a variety of end points of potential significance, but there has been difficulty in reproducing results and at this time they do not offer strong mechanistic support for effects seen in epidemiologic studies. In addition, many physical scientists question whether EMF exposures from power lines could have effects on cells, tissues, or animals because of the small size of the fields in comparison to the biologically generated fields and physical noise.

The epidemiologic literature, while not entirely coherent, provides enough evidence to require resolution, especially given the fact that exposure to EMF is nearly universal. In addition, the public has strongly held but ill-defined fears about electrical facilities. Research to date has not been able to provide clear answers to concerns about the health effects of EMF. Part of the problem in clarifying questions about the health effects of EMF is ignorance about what components of electric and magnetic fields may be responsible for such effects. The failure to have a biological end point to use in experimental studies that is reproducible and of potential health significance complicates the problem further. Poor reproducibility may be due to failure to replicate experimental conditions adequately or it may mean that there is no EMF effect. To provide stronger evidence for an effect, or to provide convincing evidence against an effect, a systematic and innovative effort is needed that builds on the strongest clues available and attracts the ideas and efforts of the best biologists, including those who have not previously worked on EMF.

The HEI Board of Directors, at a meeting in February 1992, concluded that there is a need for scientific research of high quality to address the public concern about possible health effects of EMF exposure and that HEI, upon receipt of adequate funding, should pursue this area of research. The Board authorized formation of an EMF Research Planning Committee that would complete HEI's EMF research planning effort by defining a five-year research program. This research program is to be directed to the question: "Does EMF exposure cause human health effects?" This decision by the HEI Board of Directors was informed by the findings of two previous complementary studies organized by HEI to investigate the state of knowledge with respect to health effects of EMF. The Feasibility Study Committee emphasized the need to define the active component of EMF in simple biological systems while the EMF Working Group of the Environmental Epidemiology Planning Project described approaches to improve epidemiologic information.

Further information on the history of HEI's EMF research planning effort can be found in Appendix 1.

This report of the HEI EMF Research Planning Committee presents a 5-7 year research plan with an estimated cost of about $60 million. The proposed program is intended to clarify whether or not there are adverse health effects from exposure of the public to EMF from electric power transmission, machinery, or household appliances. The plan encompasses two complementary approaches: 1) improving the information from epidemiologic studies to either identify other explanations for the apparent association of EMF exposure and increased risk for cancer or verify that improved EMF exposure assessment increases the measured relative risk for cancer; and 2) evaluating a variety of end points in diverse biological systems, with the dual goal of elucidating a component of EMF that interacts with cells or tissues and identifying basic biological mechanisms that may be related to cancer or other health effects. In summary, because of the epidemiologic findings, HEI's research strategy has an emphasis on carcinogenic effects, but will also explore other potentially important health and biological effects. It will have flexibility to change directions as indicated by findings of HEI studies and research supported by other organizations.

CHAPTER 2: EXECUTIVE SUMMARY

Designers of a national research program to explore whether there are health effects from electric or magnetic fields (EMF) are faced with a daunting task. On the one hand, the program should be designed to identify the existence of a hazard (an adverse effect causally related to defined exposure parameters) if there is one. On the other hand, if no such effects are found, it should provide some assurance that such a hazard does not, in all likelihood, exist.

Even if evidence from humans linking an adverse effect to an EMF exposure regime is verified, it is likely that the degree of increased relative risk will be modest compared to other hazards such as smoking or driving an automobile. In addition, unless these results can be corroborated in other biological systems and/or a sound mechanistic explanation for the effects can be developed, these modest increases may be caused by other (confounding) factors. Suitable animal models to test for the specific cancer end points suggested by the epidemiological data do not yet exist. Existing animal models represent end points that may not be related to the end points associated with EMF in epidemiological studies and may thus be misleading. The evidence to date for effects of any sort from *in vitro* and animal studies does not present a coherent picture.

We believe that the program proposed in the chapters that follow represents the best effort possible in 1993 to use the tools and concepts available to the scientific community. Our goal is to devise a program which within 5-7 years will have one of two results: 1) it will provide evidence for the existence of a hazard from EMF; <u>or</u> 2) it will have explored such a full range of biological questions without finding effects that scientists can be confident in asserting that EMF is not a public health risk of significance. The following paragraphs outline the proposed three-phase EMF research program.

- Initial program (1993-1994): A modest start-up effort focused on three areas is proposed. They are: a) A set of additional studies in conjunction with the National Toxicology Program (NTP) EMF studies now scheduled for 1993-1994 would be undertaken (if HEI receives EMF funding in time). This program would build on the collaborative working relationship which has developed between the National Institute for Environmental Health Sciences and the Health Effects Institute for NTP's ozone study; b) Methodological studies would be initiated to clarify interpretation of the results of previous epidemiological studies by either strengthening the association with EMF exposure by improved exposure characterization or by providing alternative explanations for the findings. There would be a simultaneous effort to determine whether there are physiological changes or markers that might be related to the diseases associated with EMF in the epidemiological studies; and c) There would be studies to investigate a spectrum of cellular responses and elucidate active components of EMF. Findings in these studies would provide guidance for subsequent animal experiments and for the design of new epidemiological studies as well as aid in the interpretation of existing ones.

This $4.5 million 2-year program would be intended to set tbe stage for a larger research effort.

- Full program (1994-1996): This second phase would utilize human, animal, and *in vitro* systems to explore many hypotheses about end points, to study factors related to development of disease, and to identify EMF exposure parameters associated with adverse effects. Additionally, pilot studies would be initiated to determine whether full studies - either animal or epidemiologic - are warranted. For example, animal models would be developed that are more relevant to types of cancer currently suggested by tbe epidemiological data than currently available animal models. Similarly, pilot studies would be conducted on additional populations whose exposures to EMF might be greater or better characterized or where confounding factors might be minimized.

- Follow-up program (1996-2000): The research in the third phase would be a comprehensive effort involving animal, cellular, and epidemiologic studies and building on results of phase 1 and 2 studies. Animal and epidemiologic studies will utilize information about exposure parameters, mechanisms, and end points resulting from phase 1 and 2 studies. New animal models developed in phase 2 will be used to investigate enhancing effects of EMF on carcinogenesis. This set of studies should provide a sound basis for determining what EMF exposure parameters, if any, constitute a hazard.

The EMF research program is designed to either characterize the hazard from EMF or to show that extensive data do not provide evidence that a hazard related to EMF is likely to exist. If a hazard is identified, the studies will have laid the groundwork for efforts to develop specific dose-response curves and other data needed for more complete risk analysis and assessment.

This proposed program requires two fundamental elements:

- The effort must involve scientists whose prior experience is linked to either innovative biological approaches or to exposure issues related to the physical characteristics of EMF. Any effective program must both recruit and then link these competencies. Only an extra-mural program which self-consciously worked to link previously unassociated researchers would achieve such results.

- The effort must be coherent and integrated internally and with EMF research programs funded by other organizations. We must promote rapid learning about which end points are most relevant, what markers are most useful, and which exposure regimes are most relevant. Hence, while an extra-mural program would spread the net to a wider group of researchers and ideas, the program could well remain diffuse unless a persistent effort is made to link the studies. Although an open-ended extra-mural program of independent studies might eventually provide the same results, the public need for early and definitive results makes it crucial that the program promote the most rapid cross-fertilization of studies. The research program would best be carried out if it were developed through the basic HEI research selection, oversight, and review mechanisms. That is to say, while the studies would be chosen through competitive processes, the selected researchers would be brought together both prior to and during their studies to assure the most productive linkages among the studies. While fostering the development of a cohesive, coordinated, and flexible program, HEI would actively pursue ties with the larger community of EMF research and coordinate its EMF research with other efforts.

CHAPTER 3: HEI'S EMF RESEARCH PLAN

RESEARCH STRATEGY

Overview

HEI's research plan is directed toward clarifying whether or not exposure to extremely low frequency electric or magnetic fields (EMF) from electric power transmission and use causes an adverse health effect. This plan builds on existing pieces of information, following the strongest clues, to try to determine whether they represent real and significant effects. If better evidence that there is a health effect is obtained in this program, then further research will be necessary to determine dose-response relationships. At the end of the 5-7 year research period, an assessment will be made of the state of knowledge, based on results from HEI-funded studies and other research, and recommendations will be made about the need for further research.

The strongest indication of a human health effect of exposure from EMF is from epidemiologic studies reporting an increased incidence of cancer. A report of association of leukemia in children with proximity of residence to "high-current wiring configurations" has spawned many investigations of cancer and wiring configurations or other measures of exposure to EMF. It has been assumed in most studies that the exposure of concern is the magnetic field, rather than electric field, because of the shielding of electric fields by most objects. Results to date have been suggestive, but have not provided conclusive evidence that EMF exposure increases risk for any type of cancer.

A major problem in sorting out whether or not there is an effect of EMF exposure on cancer in children or adults is the fact that EMF is actually a complex and varying mixture, making identification, and measurement, of exposure factors of high relevance to biological effects difficult, given the current state of knowledge. It should be possible to begin to identify at least one biologically effective component of exposure once a biological assay, in which effects can be consistently measured, has been identified. However, there has been great difficulty in repeating effects that have been reported. This may be because the reported effects are not "real" or because of differences in exposure or other experimental conditions among studies, which in the past were often not well defined or well controlled.

There have been some hypotheses generated, based on animal and cellular studies, for possible mechanisms for effects of EMF on carcinogenesis. These need to be followed up and experiments carried out to test them and to perhaps generate additional mechanistic hypotheses. If a reliable bioassay were found that could be used to define biologically active EMF parameters, then it would be easier to carry out studies to define cellular responses to EMF that may provide a mechanistic explanation for an effect of EMF on carcinogenesis or on other diseases or conditions.

There are several questions that arise from this general discussion that are reflected in HEI's research program:

1) Can existing EMF epidemiologic studies be clarified? Can the increased relative risk for certain types of cancer be shown to be due to confounding factors associated with measures of EMF used in prior studies or, on the other hand, can the relevant exposure parameters be better defined and be used to strengthen the epidemiologic evidence?

2) Can effects be consistently demonstrated in animal and *in vitro* models that provide a mechanistic explanation for an effect on cancer? Do effects in cellular studies suggest alternative physiological or health end points to investigate in animal studies?

3) Can a simple biological end point, particularly one relevant to hypothesized health effects, be found in animal or cellular studies and utilized to help determine what aspects of the EMF exposure are biologically active? If so, this finding can be helpful in improving the design of animal and epidemiologic studies of carcinogenic effects of EMF exposure.

Figure 3-1 illustrates how specific facets of the proposed EMF research program, described in the next section and in more detail in the Requests for Applications (RFAs) in Chapter 5, fit into this strategy.

Summary of proposed EMF research program

A key aspect of the proposed program is having the experimental and epidemiologic studies build on each other. Thus, the question of increased risk for cancer raised by epidemiologic studies will be investigated not only in epidemiologic studies, but also in animal and *in vitro* studies, as described below:

Human studies of cancer and other effects

Several approaches will be taken in the HEI research program to improve the information from human studies, as described below. While there is an emphasis on cancer in these studies, investigation of physiological and other end points that may be related to cancer or other health effects is also encouraged.

- Possible problems in epidemiologic studies that might have led to lower or higher relative risks will be investigated (see RFA 1). For example, if the EMF exposure factor represented by "wiring configurations" could be determined, the measured relative risk for cancer would presumably become larger. On the other hand, perhaps wiring configurations could be found to correlate with other factors related to cancer risk that have nothing to do with EMF. There is already ongoing work in this area, which HEI would take into account as it develops its program.

- Biological markers such as changes in levels of hormones, enzymes, or other factors that might be related to mechanisms by which EMF affects cancer will be investigated in human epidemiologic or clinical studies (see RFA 2). These could be based on a theoretical rationale or be suggested by animal or *in vitro* studies. For example, it has been suggested that decreased production of melatonin resulting from EMF exposure could be a factor in increased risk for cancer. If studies of biological markers demonstrate comparable effects in human beings, then human studies investigating whether such effects are linked to increased risk of disease may be undertaken. HEI will encourage discussions among investigators doing animal and cellular studies and those doing human studies to identify markers suitable for human studies.

- There will be investigation of new populations not previously studied that might produce more definitive evidence of whether or not there is an effect of EMF exposure on cancer (see RFA 3).

- Although there is an emphasis on cancer and physiological end points that may be related to the development of cancer in the proposed epidemiologic RFAs, they also offer the opportunity for investigation of other end points, including measures of neurologic function, such as auditory or visual evoked potentials, indices of immune function, alterations in circadian rhythms, and behavioral effects (see RFA 2).

Animal and *in vitro* studies of effects related to cancer

Most of the hypothesized mechanisms by which EMF may increase risk for cancer have involved promotion or growth enhancement rather than initiation. While EMF does not appear to have genetic effects, it has been reported to cause a variety of effects that could have a promoting or growth-enhancing effect on tumor or pre-neoplastic cells. These include: effects on the cell membrane with some evidence of effects on receptor binding or activation; enhancement of DNA synthesis and growth rate in tumor cells; increased activity of ornithine decarboxylase; increased synthesis of some messenger RNAs with appearance of new proteins; and decreases in melatonin levels. It is not clear which of these end points are "real" effects of 60-Hz EMF and which ones, if real, are significant with respect to health effects. Many studies investigating EMF as a tumor promoter in mouse skin and liver have been negative, but a recent study in mouse skin has suggested co-promotional activity of a 60-Hz magnetic field (20 G). The animal and cellular approaches to investigating effects of EMF exposure on cancer are summarized below:

- HEI will support the development of relevant animal models in which promotional and co-promotional effects of EMF could be investigated (see RFA 4). Of particular interest are animal models for investigating tumors that have been linked with EMF exposure in epidemiologic studies, such as childhood leukemia, brain cancer, and perhaps breast cancer. Currently there are not appropriate animal models for testing EMF as a promoter or co-promoter for these types of cancers.

- *In vitro* cellular transformation systems will be used in assessing EMF as a promoter, co-promoter, and carcinogen (see RFA 6). In these systems, cells with tumor-forming capability can be identified by their formation of a focus of piled up cells in a confluent monolayer of cells. This assay is simple enough to enable evaluation of a spectrum of exposure parameters. Biochemical end points showing changes in some earlier studies might also be investigated in these studies.

- HEI and the National Toxicology Program (NTP) may be able to collaborate in investigating the potential health effects of EMF (see RFA 5). NTP will investigate the carcinogenicity of chronic exposure of mice and rats to 60-Hz magnetic fields [10 G continuous, 10 G intermittent (1 hour on, 1 hour off), 2 G continuous, 20 mG continuous]. It will also conduct investigations of effects on reproduction and development. Since the NTP bioassay is investigating EMF as a complete carcinogen, HEI would emphasize studies related to promotional or co-promotional activity. Such studies would determine whether there are physiological or biochemical changes of oncogenic or preneoplastic significance that may not be detected through the standard NTP bioassay protocol, where clinical cancer is the dominant end point. These may include the emergence of preneoplastic cells in blood, bone marrow, or other organs as a function of time and intensity of exposure; depression of homeostatic and immune mechanisms; alterations in the expression of oncogenes or tumor-suppressor genes; long-term perturbations of pineal and endocrine status; and effects on cell kinetics in the bone marrow, central nervous system, endocrine tissues, and other organs.

Mechanistic studies

Besides animal and human studies of the effects of EMF on cancer, other research will focus on finding repeatable effects in relatively simple systems. Several RFAs seeking relatively simple measurements that might be useful both in understanding biological mechanisms relevant to cancer or to other potential health effects and in understanding what component of EMF is detected at the cellular level. These include:

- Effects of EMF exposure on cell processes will be investigated using a variety of cell physiology parameters in mammalian cells, confluent cell populations, and tissue slices (see RFA 8). Parameters may include membrane potential, free calcium, pH, enzyme activities, ion metabolism, receptor organization, and cytoskeletal assembly. In these studies a broad range of exposure variations could be investigated. In addition, these studies can serve as a base for exploring effects on whole animals.

- Other studies will investigate effects of EMFs on neural systems at a variety of levels in several species (see RFA 9). One important goal is to investigate the hypothesis that the retina is a detector of EMF exposure and that the visual system may mediate effects of EMF exposure on melatonin synthesis by the pineal gland, as it does with light exposure. Studies may include: absolute, color and contrast sensitivity in humans; electroretinographic and other electrophysiological measures in humans and animals; ganglion discharge properties and sensitivity in frog and fish cells; biophysical and biochemical changes in isolated cells. Physiological and biochemical mechanisms underlying changes and their significance for neuroendocrine function that may be related to health effects will be investigated.

- Other research will be directed toward end points in simple systems requiring interactive, cooperative systems of cells. In aggregates of cells or in small organisms in which there is extensive cell-to-cell communication, the calculated background noise would be small compared to possible signals resulting from EMF, whereas this would not be the case for isolated cells. The approaches include:

  - Studies of developmental changes, and mechanisms for any effects seen, will be undertaken using simple multicellular organisms (see RFA 7). Small vertebrates like zebra fish and invertebrates like nematodes (*C. elegans*) or fruit flies (*Drosophila*), which have been well characterized genetically and developmentally, would be appropriate. Even simpler organisms like cellular slime molds (*Dictyostelium*) could be considered. Developmental changes are of interest because of their dependence on cell interaction and communication.

  - Other studies using a system of communicating cells will investigate whether EMF can induce mammalian cell transformation *in vitro* (see RFA 6). If successful, these studies are simple enough to be used to evaluate a series of exposure parameters.

- There is skepticism among some physicists and electrical engineers that ambient EMF exposures could have effects on biological systems because of the small size of the fields in comparison to the biologically generated fields and physical noise. The research plan includes studies to quantify the endogenous electric fields in the human body in order to establish bounds for significant interactions with external electromagnetic fields (RFA 10). One important question to be addressed is whether there are "electrically quiet" sites at which environmental EMF fields can clearly compete successfully with the endogenous fields.

Additional research approaches

An additional facet of HEI's proposed research program on EMF will involve investigator-initiated research on topics beyond those specified in the RFAs developed by the EMF Research Planning Committee (see RFPA 11). While these RFAs define what the Committee presently considers to be the best approaches to clarifying questions about the potential adverse health effects of EMF exposure, it recognizes that there are worthwhile approaches that fall outside the boundaries of these RFAs.

FIGURE 3-1: HEI'S EMF

Does EMF exposure increase risk for childhood

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Methodological issues in epidemiologic studies (RFA 1)
Investigation of methodological issues that could affect interpretation of previous epidemiologic studies. This includes examination of possible biases that might account for the observed associations and development of new methods for characterizing exposure.

Human studies to test biological hypotheses (RFA 2)
Human clinical and field studies will be undertaken to determine whether there are changes in levels of enzymes, hormones or other factors that might affect cancer development. Results from animal and cellular studies will provide new ideas for these studies.

Epidemiologic studies of new populations (RFA 3)
Studies will be undertaken using populations or exposure circumstances not previously explored Populations of interest include those with particularly heavy or otherwise unusual exposure to EMF or those for which there is preliminary evidence of a high incidence of health effects thought to be associated with exposure to EMF.

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Determination of endogenous fields (RFA 10)
Naturally occurring fields within living animals will be determined to establish the bounds for significant interactions with external electromagnetic fields. Electric fields are to be determined in terms of their power spectrum at different sites within the body. That is, what are the voltages at each frequency component of each localized field? One question is: Are there "electrically quiet" sites at which environmental EMF can successfully compete with endogenous fields? Finally, a quantitative assessment of *in situ* magnetic fields, particularly at the microscale of magnetosomes, is sought.

Effects on retina/visual system and their significance for neuroendocrine function (RFA 9)
Investigate effects of EMFs on neural systems at a variety of levels in several species. Studies may include: human absolute, color and contrast sensitivity; electroretinographic and other electrophysiological measures in humans and animals; ganglion discharge properties and sensitivity in frog and fish cells; biophysical/biochemical changes in isolated cells. Physiological and biochemical mechanisms underlying changes and their significance for neuroendocrine function (eg, melatonin synthesis by the pineal gland) will be investigated.

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What biological effects can be consistently measured provide a mechanistic explanation for increased exposure parameter that

leukemia, brain cancer, or other types of cancer?

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<u>Animal studies of promotion and co-promotion</u> (RFA 4)
Animal models for types of cancer showing elevated risks in epidemiologic studies will be developed and used to investigate promotional or co-promotional effects of EMF. Findings in *in vitro* studies of evidence for effects on receptor activation, increases in DNA synthesis, growth rate, and mRNA synthesis, coupled with the absence of genetic effects, have supported a hypothesis of EMF as a promoter or co-promoter rather than initiator. Recently EMF has been shown to be a co-promoter with the promoter TPA in a mouse skin assay.

<u>Studies in collaboration with the National Toxicology Program's EMF studies</u> (RFA 5)
NTP will conduct studies of effects of magnetic fields on reproduction, development, and cancer in mice and rats. Using the same facility, HEI studies will investigate whether there are physiological or biochemical changes of oncogenic or preneoplastic significance from exposure to magnetic fields. The basis for these studies is the hypothesis that EMF, if it affects carcinogenesis, is likely to act via a promotional or co-promotional process.

<u>*In vitro* transformation studies</u> (RFA 6)
Studies of effects of EMF exposure on *in vitro* transformation will be supported. These cell systems have the potential to detect promotional or co-promotional effects on cells that have already been treated with an initiator or promoter. Biochemical changes such as enzyme activities or receptor binding can also be evaluated. Transformation studies could be used to investigate exposure parameters.

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<u>Cell physiology parameters</u> (RFA 8)
Studies of the effects of EMF exposure on fundamental cell physiology parameters in living mammalian cells and tissue slices are emphasized. Parameters to be investigated include membrane potential, free calcium, pH, enzyme activities, ion metabolism, receptor organization, and cytoskeletal assembly. Besides adding to understanding of biological effects of EMF, such studies can help to define the biologically active EMF parameters, which can then be used in designing human and animal studies.

<u>Developmental effects</u> (RFA 7)
Studies of effects of EMF on development in simple multicellular organisms. Such changes are of interest because of their dependence on cell interaction and communication. If such effects are found, then the biological mechanism and the exposure parameters responsible can be explored. This better understanding of exposure could then be used in designing human and animal studies.

⇑ ⇑ ⇑

in cellular and simple animal studies? Can they risk for cancer? Can they be used to define an EMF is biologically active?

TIMING AND COSTS OF PROPOSED EMF RESEARCH PROGRAM

The EMF research program described in the previous section can be viewed in three phases:

1) A first phase (1993-1994) with three components: animal studies in collaboration with the National Toxicology Program, methodological studies to clarify the meaning of results of previous epidemiological studies, and *in vitro* studies to investigate a spectrum of cellular responses and elucidate active components of EMF. This program, estimated at a cost of $4.5 million, would set the stage for a larger research effort. Use of the NTP facility would only be possible if HEI received funding very soon and initiated its EMF program promptly.

2) A second-phase full program (1994-1996) as depicted in Figure 3-1. We envision a multifaceted effort to continue investigation of possible biological mechanisms for cancer or other health effects and to understand what EMF parameters may interact with cells and tissues. This information should enable better design and interpretation of epidemiologic studies. New animal models will be developed for evaluation of EMF as a promoter, co-promoter, or other type of enhancer for the kinds of cancer that epidemiologic studies have suggested may be affected by EMF.

3) A third phase follow-up program (1996-2000), involving animal, cellular, and epidemiologic studies that build on information from earlier studies. These studies should complete a comprehensive and systematic exploration of exposure parameters, biological mechanisms, and health effects of EMF. When this program is completed, it should either provide good evidence for the existence of a hazard from EMF or, if there is no evidence for an effect, will have explored such a full range of biological mechanisms and systems that the likelihood that there are adverse effects of EMF is significantly reduced.

Figure 3-2 provides more detailed information on studies to be carried out in the three phases, including projected costs. Figure 3-3 illustrates the flow of information among the various types of studies in the three program phases.

Figure 3-2: Phases of the EMF Research Program

PHASE 1: INITIAL PROGRAM 1993-1994

Epidemiologic studies ($1 million)
- Methodological investigations to clarify whether EMF affects cancer risk (RFA 1)
- Assessment of biological effects in clinical or epidemiologic studies (RFA 2)

Animal and *in vitro* studies ($3.5 million)
- Studies of oncogenic and preneoplastic changes in rats using NTP's EMF facility (RFA 5)
- Studies of cell physiology parameters (RFA 8)

PHASE 2: FULL PROGRAM 1994-1996

Epidemiologic studies ($6 million)
- Continuation of methodologic and marker investigations

Animal and in vitro studies ($10 million)
- Studies to investigate mechanisms and to identify reproducible effects that can be used to explore exposure parameters
  - Cell physiology parameters (continuation of initial program)
  - *In vitro* transformation studies (RFA 6)
  - Reproductive and developmental effects (RFA 7)
  - Effects on the retina and visual system (RFA 9)
  - Determination of endogenous fields (RFA 10)

Pilot studies ($4 million)
- Identification of new populations/exposure circumstances for epidemiologic studies (RFA 3)
- Development of new animal models for studying EMF as a promoter or co-promoter (RFA 4)

PHASE 3: FOLLOW-UP PROGRAM 1996-2000

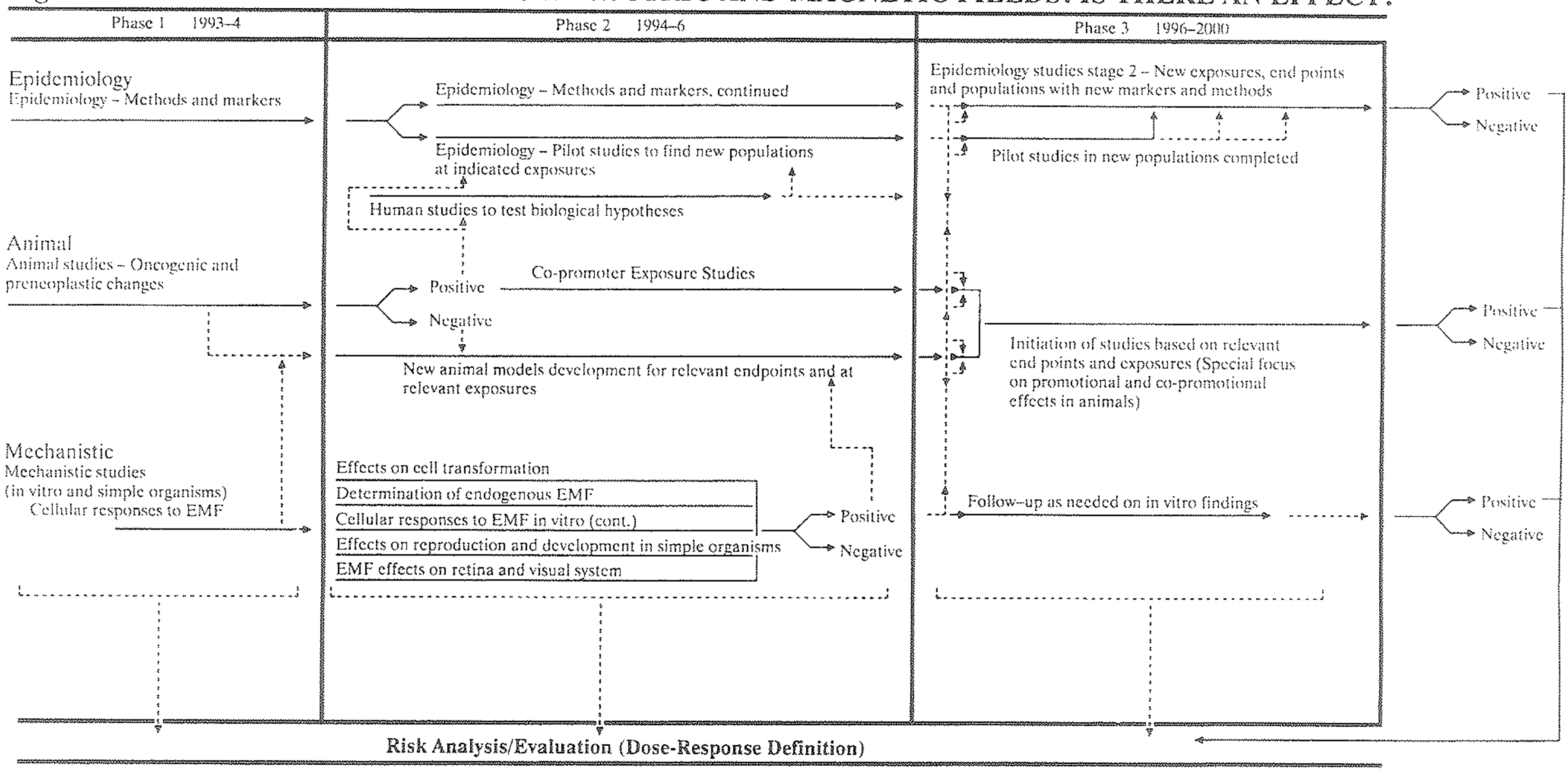
Additional RFAs will be issued, as appropriate, to build on findings. Exactly where the results of the first studies will lead the program, of course, cannot be predicted. Some possible later directions include:

Epidemiologic studies ($20 million)
- Epidemiological studies with "new" exposure measurements based on improved understanding of exposure from earlier studies
- Epidemiological studies of new populations identified as promising in pilot studies
- Clinical and epidemiological studies of biological markers based on findings in animal and *in vitro* studies

Animal studies ($12 million)
- Use of exposure protocols based on improved understanding of exposure from earlier studies
- Investigations of promotional and co-promotional activity of EMF using new models developed in pilot studies
- Investigations of biological end points based on findings in *in vitro* studies

***In vitro* studies ($3 million)**
- Further investigation of mechanisms in *in vitro* studies

Figure 3-3 A RESEARCH PROGRAM FOR ELECTRIC AND MAGNETIC FIELDS: IS THERE AN EFFECT?



RESEARCH APPROACH

Despite a great deal of research, the answer to the question of whether there are any biological or health effects of EMF from electrical power transmission and use has remained elusive. In order to investigate the potential effects of EMF, in a way that negative results will be meaningful, and positive results can be replicated and extended, we need an organized and innovative approach to both the effect and exposure components of experiments as described earlier in this section. Monitoring of research results and flexibility to modify plans based on those results will be essential in developing a comprehensive set of investigations of both exposure and biological components.

Over the past ten years HEI has developed a unique way of overseeing its research program on the health effects of motor vehicle emissions that appears also to be suited to developing and overseeing a program on EMF. In carrying out this EMF research program the same general methods and approach will be utilized. A new EMF Research Committee (separate from that for motor vehicle emissions) with responsibility for the research program would be created. HEI's Research Committee generally issues Requests for Applications to the scientific community that describe research objectives for which HEI would like to receive applications. It defines the research goals broadly, rather than outlining specific studies, in order to take advantage of the vast knowledge and ingenuity of the scientific community. HEI also draws on the scientific community to form *ad hoc* expert panels that review applications for scientific merit. The HEI Research Committee then considers those applications ranked highest by the review panel. From these applications, a set of studies is selected that, together, best address the goals of the RFA. These studies may be modified to exclude parts that are not relevant to HEI's goals, to improve the design, or to minimize the overlap with other studies. This flexible mode of operating encourages creative scientific thinking among applicants and, at the same time, produces a set of studies that addresses HEI's current problems. As with the research related to motor vehicle emissions, an opportunity for investigator-initiated research, outside areas defined by RFAs, will be included in this research program.

One of the major strengths of HEI's research approach is that it creates coherent groups of related studies. Investigators performing related studies are brought together at workshops where an understanding of the scope of the program and each study's contribution to it is developed. Continuing from these initial interactions, HEI Research Committee and staff members keep in close touch with each study through semi-annual progress reports and sometimes through site visits. Increasingly, efforts have been made to identify deficiencies and, as appropriate, to recruit the expertise needed for investigators to solve any problems that emerge.

HEI's Review Committee, whose role is to critically evaluate each completed study and final report, has now begun to look at studies in clusters. Thus, the Review Committee considers the combined efforts of several investigators, along with other research findings.

It then formulates a picture of the current state of knowledge, key uncertainties, and research needs of that area.

This approach of developing sets of coordinated studies approaching a question in different ways is well suited to the EMF research area, where there have been problems with reproducing results. There needs to be an organized, sequential effort made to identify biological effects of significance and to dissect the important components of the exposure. HEI has experience in coordinating a variety of types of studies and recognizes the importance of flexibility in allowing modifications in research plans if findings indicate new directions.

In its research program on motor vehicle emissions, HEI has already developed experience in bringing together individuals with exposure expertise and those with advanced biological techniques. This will be a particular challenge in EMF studies, where the exposure is even less well understood than for air pollutants. Also, there are many other issues to consider in conducting experiments. For example, we must ensure that the exposure is not altered by any EMFs from nearby equipment and that confounding exposures to heat, light, noise, and vibration are controlled. HEI is developing plans for providing assistance to investigators who have little understanding of or research experience with electric or magnetic fields. HEI will work with funded investigators to ensure that exposure parameters are addressed consistently and reliably among studies. Because of the complexities of the exposure scenarios, HEI expects physicists, electrical engineers, and other experts on the nature of electric and magnetic fields to have significant input in all applications and throughout the course of the studies. More detailed discussion of HEI's approach with respect to EMF exposure in experiments is discussed in Chapter 6. Chapter 7 provides basic information on the nature of electric and magnetic fields; Chapter 8 outlines possible mechanisms for interaction of EMF with biological material.

CHAPTER 4: ORGANIZATIONAL CONSIDERATIONS

The Role of the Federal Government

The manner in which the federal government will organize itself to carry out a major research program to determine the human health effects of electric and magnetic fields remains somewhat unclear. A number of federal departments and agencies have substantial research and program interests associated with electric and magnetic fields; among these departments and agencies are, at a minimum, Health and Human Services, Energy, Transportation, Defense, Housing and Urban Development and Labor Departments and the Environmental Protection Agency.

Several of these federal departments and agencies have developed their own research approaches on this issue; several have been given appropriations by the Congress and provisions that would suggest coordination roles. Passage in October, 1992 and Presidential approval at the end of that month of the 1992 Energy legislation (which contains specific provisions related to the federal research program on electric and magnetic fields) has to some extent narrowed the range of federal entities given the congressional authorization to pursue a major program.

This most recent legislation (for which there is not yet a corresponding appropriation) authorizes a major research and communications program (of $65 million dollars), 50% funded by non-federal sources and 50% funded by the federal government. Some of the responsibilities for the organization and oversight of the program have, in the Energy bill, been given to the Secretary of Energy, others to the Secretary of Health and Human Services (and specifically the Director of the National Institute of Environmental Health Sciences). Formation of an Electric and Magnetic Fields Interagency Committee with representatives from nine separate federal agencies is the responsibility of the President.

It is clear that more clarification of the roles of the Secretary of Energy, the Director of NIEHS and other federal officials will evolve in 1993 under the new Clinton administration.

The Health Effects Institute and EMF Research

As discussed in Appendix 1, the Health Effects Institute has developed its approach to EMF research with the support of funds from the Environmental Protection Agency and several private sector organizations.

The proposal of the HEI Board of Directors in this report is that HEI seek interim NIEHS funding now (to be matched with private sector funds) to undertake a limited research program, including the collaborative NTP project described elsewhere (see Chapter 3 and Chapter 5, RFA 5) in 1993-4. If the NIEHS provides funds currently designated for allocation by EPA in fiscal 1993, HEI would seek to match those funds and carry out an initial $4.5 million program as outlined in phase 1.

For this initial program, the EMF Research Planning Committee proposes that, after consultation with our Research and Review Committees, the HEI Board of Directors appoint an HEI EMF Research Committee (comparable to in stature, responsibilities and reporting relationships to the HEI Research Committee) to oversee the final definition, selection and oversight of this research program. It also recommends that the Board of Directors appoint an HEI EMF Review Committee to review (in a manner similar to current HEI Review Committee processes) the research generated by this initial EMF research program.

During the period of this initial research, the EMF Research Planning Committee recommends that the Board of Directors determine whether the provisions of the new Energy legislation are compatible with the principles for research and review of HEI and whether it should seek to implement the full program described in this report. More specifically the Committee recommends that the Board of HEI authorize the management of HEI to enter into discussions with the Director of NIEHS (who has, under the new Energy legislation, "sole responsibility under the program for research on possible human health effects") to determine whether the Director desires HEI to develop a mechanism to undertake the full and follow-up (1994-2000) programs outlined in this report <u>and</u> with the Secretary of Energy (who has the responsibility for solicitation of private sector funds and may not obligate federal funds unless funds for the program have been received from non-federal sources and to transfer funds to the Director to carry out the Director's responsibilities) to determine whether the Secretary wishes HEI to develop mechanisms to provide for shared public and private funding through arrangements which, like HEI's current arrangements with the EPA and the automotive industry, assure that no contributor may control the HEI program.

If these discussions result in a request that HEI develop such a mechanism and pursue the development of a complete multi-year research program on EMF, it is likely that other longer-term organizational issues will emerge.

Two possible options may emerge in these discussions:

1) That the specific provisions of the Energy legislation will require that HEI form a separate corporate unit (with procedures and format specifically designed to accommodate the input of the mandated Interagency Committee on Electric and Magnetic Fields and the mandated National Electric and Magnetic Fields Advisory Committee). Such a new organization would be constructed as a sister institution to HEI and would follow, within the overall framework of the mandated interactions with the Interagency and Advisory Committees, the research and review procedures developed by HEI. HEI has had successful experience in developing a sister institution, HEI Asbestos Research. The organization would be expected to draw on, to the extent possible and consistent with the purposes of both HEI and the new

organization, the experience of HEI scientific committees and staff in conducting high quality, independent research in environmental science; or

2) That the provisions of the Energy legislation can be met within a structure compatible with the Health Effects Institute's current procedures and obligations. In that case, HEI itself would be the corporate unit undertaking EMF research. The responsibilities of HEI's Board, scientific committees and staff would need to be defined to assure that both HEI's existing responsibilities for developing data on the health effects of automotive emissions and its new responsibilities for the development of data on EMF effects would be met.

It may be that HEI's contribution to resolving the questions about EMF health effects will not be to develop its own research program, but to provide a strategy for EMF research for other organizations. In that case, HEI's Board of Directors will distribute this report broadly to ensure that the research approach and plan developed by HEI's Committee are well utilized. This willingness to share HEI's EMF research strategy with other organizations should not be interpreted as an indication that HEI is not enthusiastic about undertaking the program itself. It is simply a path that HEI would follow if it were not able to obtain sufficient funding to carry out the program described in Chapter 3.

CHAPTER 5: DRAFT REQUESTS FOR APPLICATIONS FOR EMF RESEARCH PROGRAM

INTRODUCTION

The EMF Research Planning Committee has developed a set of draft Requests for Applications (RFAs) showing our present understanding of what research is needed. Final versions of these RFAs would be used to carry out the research strategy described in Chapter 3. If HEI receives funding for this EMF research program, an EMF Research Committee would be formed, with responsibility for development and oversight of the research program.

The draft RFAs are listed on the next page and the draft RFAs themselves are included on the following pages. As the program is viewed at this time, several of the RFAs (marked with an asterisk) would be issued in the first phase of the planned program, which is described in Chapter 3. The remainder would be issued in the second phase. The research goals defined in these RFAs are based on findings in a wide variety of studies. Summaries of the literature in these RFAs are intended to provide the basis for the objectives of the RFAs rather than to give a balanced, complete assessment of the literature.

When the EMF program is initiated, the EMF Research Committee will have freedom to reconsider the strategy of the phases of the program and to modify RFAs based on the current state of knowledge and ongoing work and to add additional RFAs. Given the active research program by other organizations, HEI will need to be in close contact with them to avoid unnecessary duplication of effort and to take into account new findings when making funding decisions.

Please note: Applications are not being sought at this time for the Draft RFAs that follow.

PROPOSED REQUESTS FOR APPLICATIONS

Human studies

Animal and cellular studies

Mechanistic studies

Investigator-initiated studies

*Phase 1 studies

DRAFT RFA 1: RESEARCH TO ADDRESS METHODOLOGIC ISSUES IN EPIDEMIOLOGIC STUDIES OF EMF HEALTH EFFECTS

Please note: Applications are not being sought at this time for the RFAs.

Goal

The aim of this RFA is to evaluate various methodologic issues that could affect the interpretation of previous epidemiologic studies and the design of future studies. Specifically, it is of interest to examine possible biases that might account for some of the observed associations, or lack thereof, and to develop improved methods for characterizing exposure that might improve prospects for demonstrating a causal association, if it exists.

Background

A series of residential and occupational studies have demonstrated associations between indirect markers of EMF exposure and various cancers, but clear associations with direct EMF measurements have been elusive. In residential studies, leukemia and brain cancer in children have been linked with wiring configuration and electrical appliance use in several studies (Wertheimer and Leeper 1979; Savitz *et al.* 1988; London *et al.* 1991). Here, "wiring configuration" refers to a summary variable characterizing the electric power delivery system in the immediate neighborhood of a child's residence (usually within about 50 meters), designed to be a surrogate for the magnetic fields that might be generated inside the house by these wires (see Chapter 7 for more detailed discussion). In occupational studies, various categories of "electrical workers" (*i.e.*, those thought likely to be exposed to relatively high EMF) have been found in numerous studies to have elevated rates of leukemia, brain cancer, and other types of cancer (Savitz and Calle 1987; Pearce *et al.* 1985; Lin *et al.* 1985; Coleman and Beral 1988; also see Chapter 7 for more detailed discussion). In both residential and occupational studies, the surrogate variables (wiring configurations and job titles) have been shown to be related to magnetic fields. However, in neither case has it yet been demonstrated convincingly that the magnetic or electric fields were related to the cancer outcomes or could account for the observed associations with the surrogate variables. This part of the hypothesis has been better studied in the residential setting, where the published studies that have reported on measurements of electric and magnetic fields in the homes of cancer cases and controls have not found consistently greater associations with measured fields than with wire codes.

This apparent paradox suggests two basic interpretations. First, it is possible that magnetic fields are indeed the causal agent that are responsible for the observed associations. Under this interpretation, the failure to demonstrate associations with measured fields may reflect major differences between current fields and historic ones. In particular, wire codes may provide a more accurate summary of past exposure. Thus, the most appropriate exposure metric would need to reflect long-term exposure, which might not be expected to correlate well with short-term, contemporary measurements. The relatively weaker association of leukemia or brain cancer with measured fields may also be due to measurement of the wrong aspect of the field and/or inadequate precision of the measurements. It is presently not known whether the etiologically relevant measure of exposure is the mean intensity or some measure describing EMF variability, harmonics, polarization, resonances, etc.

The second possible interpretation is that the observed associations between disease and these surrogate variables do not represent causal effects but rather some methodological artefact. Possibilities that have been suggested include selection bias in the choice of controls in the residential studies (Poole and Trichopoulos 1991), perhaps as a consequence of the random digit dialing method of control selection (Hartge *et al.* 1984), and confounding by some non-EMF exposures or other variables (Savitz *et al.* 1989). Similarly, studies that indicate no effect of exposure on disease may also be biased, obscuring a real effect of exposure. Clearly, the same diligence with which the search for alternative explanations is conducted for apparently positive studies will need to be applied to the search for error in apparently negative studies.

Resolution of these conflicting interpretations would be aided by further research aimed at elucidating the possible biases and better characterizing the biologically relevant exposure and its relationship to these surrogate variables.

Examples of appropriate research areas

1) **Evaluation of the adequacy of the methods of control selection in case-control studies of residential EMF exposure and cancer.** This could include reanalyses of completed studies to look for evidence of bias, expansion of on-going studies to incorporate comparisons with alternative methods of control selection or to collect additional data to investigate the possibility of bias, or specially designed surveys to investigate the relationship between wiring and characteristics that might relate to participation rates.

2) **Examination of possible confounding variables in relation to wiring configurations or job classifications.** Ideally, this would be done in the context of studies of exposure-disease relationships, so that the association of the posited confounders to both exposure and disease could be assessed. However, more limited studies of the relationships of potential confounders to wiring configurations or job titles in the general population might be worthwhile. Possible confounders could include various cancer risk factors as well as carcinogenic exposures.

3) **Analyses of the relationship of surrogate exposure variables (e.g., wire codes) to EMF fields.** For residential studies, the differences in mean magnetic fields among wiring categories are relatively modest. It would be helpful to describe the characteristics

of the fields that differ between high and low current configuration homes in more detail, and determine whether such characteristics can account for the association with cancer risk. This might entail construction of alternative metrics for summarizing extended EMF measurements. It would also be helpful to develop improved wiring models to predict indoor fields for use in dose-response modeling. In a similar way, occupational studies could investigate the characteristics of EMF fields that best discriminate between high- and low-risk occupations, or identify jobs that have unusual EMF characteristics. Characterization of the fields generated by various household appliances would also be helpful. Such investigations could be done using existing data sets, by the addition of further measurements to on-going studies, or through specially-designed studies.

4) **Approaches to the problem of missing data on exposure.** In several of the better studies of residential exposure and childhood cancer, measurements of magnetic fields have proven considerably more difficult to obtain than wire codes (Savitz *et al.* 1988; London *et al.* 1991), resulting in a high proportion of subjects with missing data and the attendant possibility of biased relative risk estimation if the prevalence of missing data is related to disease status. Methods for ensuring more complete data acquisition, at best, or estimating the direction and magnitude of potential bias are needed.

5) **Methods for assessment of total exposure to EMF.** Exposure to EMF is ubiquitous; no one in modern societies is unexposed. Furthermore, exposure occurs in diverse locales: at home, at work, and in transit. Most epidemiologic studies have addressed particular sources of EMF exposure without taking explicit account of the contribution of other sources. Even if one were truly interested in the contribution of exposure from a particular source (e.g., transmission lines) to human disease, one would need to consider EMF exposure from other sources as a potential confounder. Information is needed on exposure in various microenvironments and on time activity patterns so that complete exposure estimates can be constructed. Ideally, such estimates should refer to the appropriate time period with respect to the hypothesized induction period.

Because much of the current research has addressed the issue of EMF and cancer this area offers specific examples for methodologic work. However, prospective investigators should not restrict themselves to cancer end points; the methodologic issues are general and may apply to other putative health effects of EMF.

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DRAFT RFA 2: HUMAN STUDIES TO TEST BIOLOGICAL HYPOTHESES ABOUT EMF EFFECTS

Please note: Applications are not being sought at this time for the RFAs.

Goal

The purpose of this RFA is to solicit observational or experimental research in human subjects to explore the biological effects of EMF suggested by epidemiologic or laboratory experiments.

Background

Most research in human populations exposed to EMF has focused on clinically apparent health outcomes such as cancer, reproductive loss, or depression. At present, the mechanisms proposed by which EMF might act to produce them are largely speculative; however, clues regarding possible mechanisms and effects of EMF are beginning to emerge from theoretical and experimental work in the laboratory. Some laboratory studies suggest consequences of exposure to EMF that might participate in causal mechanisms, including reduction in pineal and serum melatonin levels and concomitant effects on circadian rhythms, and changes in immune function.

Possible research areas and approaches

The end points to be measured are parameters that might be affected by EMF and could be hypothesized to play a role in the genesis of some health effect. Examples of end points that could be measured in human subjects exposed to EMF include measures of neuroendocrine function, including, but not limited to, pineal melatonin synthesis, pineal gland alterations and their association with menstrual function and levels of reproductive hormones. Studies could also focus on mood or other behavioral factors, indices of immune function, and alterations in normal circadian rhythms. Other areas of potential interest include human perception of EMF, and the effects of EMF on indices of neurologic function, such as auditory or visual evoked potentials or EEG. Given the current undeveloped state of the field, speculation and exploration are to be encouraged; however, prospective investigators should offer rational arguments for their choice of study end points.

Study designs could be either observational or experimental. An observational approach to the study of these end points might include studies of new hirees in jobs or occupations that entail exposure to EMF. Various physiologic parameters could be measured in blood and/or urine before employment begins and then remeasured at appropriate intervals. Either cross-over designs or contrasts with an unexposed cohort could be employed. Such studies might ideally be nested in, or otherwise directly related to, a larger epidemiologic study. Volunteers could also be exposed to EMF under laboratory conditions which either mimic real world exposures or are relevant for other reasons (see Chapter 6 on Exposure Resources and Strategy). Then exposure levels could be rigorously controlled and participants could be studied for their ability to "perceive" EMF; resulting endocrine changes and neurophysiologic responses, such as evoked potentials, could also be examined. Investigators may also wish to consider storing part of the blood or urine sample for analysis at some future date when additional hypotheses could be tested.

Proposals in this area should represent planning by researchers collectively skilled in physiology and endocrinology with some familiarity with epidemiology as well. We wish to encourage epidemiologists and clinical researchers to cooperate with laboratory scientists in the exploration of mechanisms that might underlie observed human health effects, and to develop hypotheses based on experimental observations that could be tested in human subjects. This collaboration could be particularly useful at the planning stage, when the program can be structured to enhance the elucidation of possible mechanisms, but it should continue through the execution, analysis, and interpretation of the results.

DRAFT RFA 3: IDENTIFICATION OF POPULATIONS FOR FUTURE EPIDEMIOLOGIC STUDIES

Please note: Applications are not being sought at this time for the RFAs.

Goal

The goal is to advance the epidemiologic study of populations or exposure circumstances, hitherto unexplored, that may offer the potential for addressing potential health effects of electric and magnetic fields. Suitable populations would be those with particularly heavy or otherwise unusual exposure to EMF or populations for which there is preliminary evidence of a high incidence of health end points thought to be associated with exposure to EMF. Depending on the current state of knowledge, proposals may include pilot studies to assess exposure, addition of information on EMF exposure to completed studies, or the actual conduct of epidemiologic studies where sufficient evidence is available to document the feasibility and value of such efforts. Our understanding of whether EMF exposures cause adverse health effects may be improved. by evaluating a greater diversity of populations and exposures than has previously been considered.

Background

Epidemiologic research on health effects, particularly cancer, related to EMF has concentrated on two areas: (1) Residential exposure from power lines in relation to childhood cancer and (2) Exposures of male electric utility workers in relation to leukemia and brain cancer. Other avenues such as residential exposure and adult cancers have been pursued to a limited degree, with studies of occupational exposure to females, for example, not undertaken at all. Since there is substantial uncertainty about issues such as which field attributes, if any, might give the greatest hazards and which groups are most vulnerable, further studies are needed.

The potential for selection bias, misclassification, and confounding is likely to vary across populations and sources of exposure. Opportunities to conduct studies that minimize one or more of these threats to validity would be especially attractive. Also, studies that can address exposure circumstances that are likely to be "potent" based on theory, laboratory studies, or prior epidemiologic studies would be especially useful. Exposure diversity could take a variety of forms, for instance: notably high amplitudes or magnetic frequencies not commonly studied, isolated electric or magnetic fields, and/or temporal patterns of particular interest.

Examples of appropriate research areas

1) **Pilot studies to assess the feasibility of conducting full-scale epidemiologic studies of previously understudied exposure circumstances or populations.** Investigators would need to document that an adequate number of exposed persons are available to address the health effect of concern, that exposure actually occurs and can be

captured for the population of interest, and that there is the potential for linking the exposure to the health effect. For example, children's and teachers' exposures in schools from power distribution or other sources, exposures to appliances, occupations outside the electric utility industry, and regular, daily commuters on electric trains would be potentially informative. Exposed populations need not be restricted to the United States; for example, rail commuters may be more common in Europe or Japan.

2) **Extensions of completed studies that include potentially exposed populations could have an EMF exposure component added to them.** Illustrative candidates would be aluminum workers, Department of Energy employees, and nurses (e.g., at MRI facilities). The development of EMF job-exposure matrices (Hoar *et al.* 1980) for particular industries would allow reanalysis of existing cohort studies to be done at relatively modest cost. The possibility of a population-based occupational EMF exposure assessment for application to cancer registry data might also be considered.

3) **Full-scale epidemiologic studies could be considered for populations that have not been evaluated previously when a pilot study has already been completed or the necessary logistical details have been addressed through some other means.**

4) **Studies to test hypotheses about particular patterns of exposure suggested by laboratory results would also be in order, including reanalyses of existing epidemiologic data.** For example, calcium efflux experiments (Lednev 1991) suggest the possibility of "resonance-like" phenomena involving an interaction between geomagnetic and AC fields. Hypotheses about such interactions could be tested in epidemiologic studies by stratifying the AC dose-response relations on the basis of the geomagnetic field (Bowman *et al.* 1991). Also, data from studies of RNA transcription (Goodman *et al.* 1989) have been used to develop a mathematical model for dose-response relations for time varying EMF (Litovitz *et al.* 1990). Such models could be used to construct alternative exposure metrics for the reanalysis of occupational and residential studies.

5) **Methods for assessment of total exposure to EMF are needed.** Exposure to EMF is ubiquitous; no one in modern societies is unexposed. Furthermore, exposure occurs in diverse locales: at home, at work, and in transit. Most epidemiologic studies have addressed particular sources of EMF exposure without taking explicit account of the contribution of other sources. Even if one were truly interested in the contribution of exposure from a particular source (e.g., transmission lines) to human disease, one would need to consider EMF exposure from other sources as a potential confounder. Information is needed on exposure in various microenvironments and on time activity patterns so that complete exposure estimates can be constructed. Ideally, such estimates should refer to the appropriate time period with respect to the hypothesized induction period.

Investigators should be encouraged to consider novel designs for these studies. One of the difficulties of studying EMF effects in the general population is that both exposure and disease are rare. (Admittedly, EMF is ubiquitous, but *high* exposures, such as electrical occupations or very high current configuration wiring, are much less common. This is one reason why the only major study of occupational exposures to date is limited to utility workers.) Thus, neither the standard cohort or case-control designs are particularly efficient. Alternatives that might be considered are the two-stage (White 1982; Cain and Breslow 1988) or randomized recruitment (Weinberg and Sandler 1991) designs. For, example, one might consider doing an occupational study by selecting a first stage sample of cases and controls from a cancer registry, stratifying on electrical vs. non-electrical job title at time of diagnosis. In the second stage, one could collect detailed occupational histories for these selected subjects and develop a job-exposure matrix to assign EMF exposures and covariates to these individuals. (The analysis would then need to take into account the biased sampling fractions.) Similar approaches might be explored for conducting studies of residential exposures, stratifying a first-stage sample on wiring configuration, which can be more easily obtained than extended indoor measurements.

A number of the health end points associated with EMF in prior studies occur with low frequency in human populations, e.g. cancers of the central nervous and hematopoietic systems. Prospective investigators will need to pay particular attention in their proposals to the expected precision of their results under plausible study scenarios.

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DRAFT RFA 4: RELEVANT ANIMAL MODELS FOR EVALUATING THE EFFECTS OF EMF ON CARCINOGENESIS

Please note: Applications are not being sought at this time for the RFAs.

Goal

The goal of this RFA is to develop appropriate animal models to be used in investigating whether electric and/or magnetic fields* (EMF) have carcinogenic, co-carcinogenic, promoting, or co-promoting activity.

Background

Interest in the health effects of electric and magnetic fields (EMF) associated with power distribution and use was spurred by Wertheimer and Leeper's 1979 publication of an epidemiologic study that showed an association between childhood cancer and certain "wire codes" (utility-wire configurations outside the home). Although epidemiologic studies suggesting an association between exposure to EMF and the incidence of certain cancers, such as brain cancer (Savitz *et al.* 1988, Bates 1991), childhood leukemia (Wertheimer and Leeper 1979; Savitz *et al.* 1988; London *et al.* 1991), and possibly breast cancer (reviewed in Stevens *et al.* 1992) have produced statistically significant increases in relative risk, the relative increases have not been large and the results are not entirely consistent. It is therefore important to use animal models relevant to the human EMF-cancer association to examine this association more closely and on a mechanistic level (Poole and Trichopoulos 1991).

There have not been many epidemiologic studies of the association between EMF and breast cancer (reviewed in Stevens *et al.* 1992). However, some studies report a weak association of EMF with premenopausal breast cancer (Wertheimer and Leeper 1987) or male breast cancer (Matanoski *et al.* 1991; Demers *et al.* 1991; Tynes and Anderson 1990; Loomis 1992). EMF can suppress pineal function and decrease production of melatonin in experimental animals (Reiter *et al.* 1988). Lower melatonin output could lead to increased prolactin release by the pituitary and increased estrogen and testosterone release by the gonads (Reiter 1981), and may stimulate growth of breast tissue (Cohen *et al.* 1978). Low levels of melatonin may be associated with the occurrence of several types of cancers, including breast cancer, prostate cancer, ovarian cancer, and melanoma (Gupta *et al.* 1988). Taken with the epidemiologic evidence, these observations have led to the hypothesis that exposure to EMF may be related to breast cancer (Stevens *et al.* 1992), or possibly other hormone-responsive cancers such as prostate cancer.

* Please see Chapter 6 for a description of the range of EMF exposures of potential interest.

Cell culture studies investigating EMF exposure suggest that EMF can cause a slight increase in cell growth and proliferation in normal and tumor-derived cells (Byus *et al.* 1987; Ottani *et al.* 1984; Philips *et al.* 1986). A one-hour exposure of human lymphoma cells and mouse melanoma cells to a 60-Hz electric field (1 V/m) results in increased levels of ornithine decarboxylase (ODC), a controlling enzyme in the polyamine biosynthesis pathway associated with cell growth (Byus *et al.* 1987). Similar increases in ODC levels and DNA synthesis (as measured by ^{3}H-thymidine uptake) were seen in the livers of partially hepatectomized male Wistar rats exposed to a sinusoidal pulsed 50-Hz magnetic field of 60 G, followed by a pulse of 400 Hz (6 G) (Ottani *et al.* 1984). A 24-hour exposure of human colon adenocarcinoma cells to a 60-Hz magnetic field of 1 G or a 60-Hz combined magnetic field of 1 G and electric field associated with a current density of 300 mA/m^2 results in an increased ability to form colonies in soft agar, and a slight increase in expression of tumor-associated antigens. However, no consistent changes were seen in this study in cells exposed to the electric field alone (Phillips *et al.* 1986).

EMF do not appear to have a direct genotoxic effect (Murphy *et al.* 1993). These observations have led to the concept that EMF may enhance carcinogenesis through tumor-promoting or co-promoting effects. There have been very few and limited animal studies examining this hypothesis.

Classical tumor promotional studies using a wide range of magnetic fields including unusual exposures in mice and rats have been negative. No effects on tumor promotion were seen in female SENCAR mice initiated with the chemical 7,12-dimethylbenzathracene (DMBA) and then exposed to 20 G, 60-Hz magnetic fields for 20 weeks (6 hours per day, 5 days per week) (Stuchly *et al.* 1991; McLean *et al.* 1991). No effects on tumor weights were observed in female Wistar-Furth rats implanted with mammary adenocarcinoma tissue and exposed 25 days later to a 2,000-Hz magnetic field at 1, 10, or 20 G for 1 hour each day for 9 days (Baumann *et al.* 1989). Similarly, no effects were seen on the incidence or progression of P388 leukemic cells implanted into female DBA/2 mice that were subjected to a lifetime exposure to a 60-Hz 0.014, 2, or 5 G magnetic field for 6 hours per days, 5 days per week, starting 2-3 hours after the implant (Thomson *et al.* 1988). Although exposure to a pulsed magnetic field of 12 Hz, 100 Hz, or 460 Hz for either 10 minutes per day, for 3 days per week, or 30 minutes per week, both increased and decreased the weight of virally induced mammary carcinomas in female C3H/Bi mice, lifespans were not altered by the magnetic field exposure (Bellossi *et al.* 1988).

Studies examining the ability of magnetic field exposure to act as a co-promoter for mouse skin cancer showed both negative (McLean *et al.* 1992) and positive (Stuchly *et al.* 1992) results. In the earlier study (McLean *et al.* 1991), skin tumors were initiated in mice by dermal application of DMBA and were promoted by weekly dermal applications of 1 μg of the phorbol ester TPA (tetradecanoyl phorbol acetate). A subset of these mice was exposed to either a 20-G, 60-Hz magnetic field, 6 hours per day, 5 days per week, for 21 weeks, or a sham exposure. No statistically significant differences were observed in either the number of tumors or the time to tumors in the magnetic-field- versus the sham-exposed animals. In contrast, when skin tumors were initiated by dermal application of DMBA and promoted by weekly dermal applications of 0.3 μg of TPA and either 20-G, 60-Hz magnetic field or sham exposure for 6 hours per day, 5 days per week, an increase in the percentage of mice with tumors and the mean number of tumors per mouse was observed at 12 weeks in the magnetic-field-exposed group (Stuchly *et al.* 1992). These differences were not significant after 23 weeks. The significance and reproducibility of the findings remain to be determined. It is therefore important that attempts be made to clarify these results using appropriate animal models and relevant, carefully selected, exposure parameters, and to elucidate the biological mechanisms that may be involved.

<u>Examples of appropriate research areas</u>

1) **Development of relevant animal models.** Because epidemiologic studies have implicated only some types of cancer, it is important to examine the possible relationship of EMF and cancer in experimental models that are relevant to the suggestions from the epidemiology studies. Possible model systems deserving emphasis include those involving types of cancer implicated in EMF epidemiology studies (*e.g.*, childhood leukemia, brain cancer, breast cancer), although other systems are not necessarily excluded. Investigators should explain why these particular models are relevant to the types of cancer observed in the epidemiology studies. Animal models with high spontaneous cancer incidence should be avoided, unless sufficient rationale for their inclusion is provided. In order to effectively evaluate promoting or co-promoting activities, animal models should provide extensive dose-response data on both the carcinogen and promoter under study.

2) **Studies with relevant animal models that address the association, if any, of EMF and the promotion or co-promotion of cancer.** Using the relevant animal models, investigators should apply EMF to these models as a promoter or co-promoter. To evaluate effectively the effects of EMF, animal models should provide extensive dose-response data on the known carcinogen, tumor promoters (if applicable), and EMF. Applications should be well grounded in animal cancer research and in EMF quantification. Characterization of dose-response relationships and elucidation of relevant mechanisms of activity are desired.

3) **Studies examining the role of melatonin or other hormones in possible EMF-associated carcinogenesis.** Investigators should explore links between EMF and changes in levels of melatonin or other hormones. If found, investigators should explore the role of changing levels of such hormones in relevant animal models.

Please see Chapter 6 for discussion of exposure resources and HEI's strategy for defining exposure conditions in studies. The initial application process will emphasize the biological approach and methods. However, involvement of a physical scientist with knowledge about EMF is expected. HEI's EMF Research Committee will work with investigators to define exposure parameters in a coherent way across studies.

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DRAFT RFA 5: HEALTH EFFECTS OF CHRONIC EXPOSURE TO MAGNETIC FIELDS: COLLABORATIVE NTP/HEI STUDIES

Please note: Applications are not being sought at this time for the RFAs.

There are two time periods when HEI may have an opportunity to use the EMF exposure facility constructed by the IIT Research Institute (IITRI) for the National Toxicology Program (NTP) EMF studies. First, there is a very specific "window of opportunity" for collaborating with the NTP in their study of whether exposure to 60-Hz magnetic fields causes developmental, reproductive, or cancer effects. Depending on when studies funded under this RFA are initiated, it may or may not be possible to use the NTP exposure facilities during their studies. However, HEI and IITRI are exploring the possibility of using these facilities after the NTP studies. The first option can only be implemented if HEI has sufficient funds and commitment to proceed quickly with issuing this RFA. The second option can be utilized either as a substitute to the first option or as an adjunct.

OPTION 1

Goal

The purpose of this RFA is to solicit research to determine whether exposure to 60-Hz magnetic fields causes physiological or biochemical changes of oncogenic or preneoplastic significance. These studies will be carried out in a facility developed for animal studies supported by the National Toxicology Program (NTP).

Background

Interest in the health effects of electric and magnetic fields (EMF) associated with power distribution and use has been spurred by epidemiologic studies reporting an association between cancer and EMF exposure (reviewed by Ahlbom 1988; Savitz *et al.* 1989; Theriault 1991; National Radiation Protection Board 1992; Health Effects Institute 1993). Prompted by this evidence, the NTP will be conducting sub-chronic and chronic bioassays in rats and mice. The purpose of these studies is to determine whether exposure to magnetic fields causes adverse developmental, reproductive, or carcinogenic effects.

In order to perform these studies, the NTP, through its contractor IIT Research Institute (IITRI), is constructing an animal exposure facility equipped to expose up to 2060 animals to magnetic fields. This facility will generate continuous 60-Hz sinusoidal wave magnetic fields with less than 3% harmonic distortion. Five different exposure conditions will be used in this facility: 60-Hz linearly polarized fields with intensities of 10 Gauss (G) continuous, 10 G intermittent (one hour on, one hour off), 2 G continuous, 20 mG continuous, and unexposed controls. This facility is scheduled to be completed in 1993.

The NTP bioassay has 4 components: a 2-year chronic study and 3 subchronic studies, including an 8-week subchronic study, a developmental toxicity study, and a continuous breeding reproductive toxicity study. Through arrangements with the NTP, HEI may be able to provide blood or tissue samples from these bioassay animals to HEI investigators for special studies. These samples can only by obtained if investigations do not interfere with the routine histopathological evaluations that are central to NTP protocols.

In addition to the animals required for these NTP bioassays, HEI will arrange to expose supplementary groups of animals to these magnetic fields for ancillary studies by HEI investigators. The facility itself is being built to accommodate a maximum of 2060 animals, the number of animals required in the NTP two-year chronic study. However, space for additional animals for HEI investigators will be available during the shorter-duration studies that will precede the chronic study.

EMF do not appear to have a direct genotoxic effect (Murphy *et al.* 1993). These observations have led to the concept that EMF may enhance carcinogenesis through processes other than initiation. There have been very few and limited animal studies examining this hypothesis. Some investigations of the ability of EMF to act as a tumor promoter, using the classical skin painting protocols, have been negative (Stuchly *et al.* 1991; McLean *et al.* 1991). Studies of the ability of EMF to act as a promoter following injection of nitrosomethylurea (NMU) into the caudal vein of rats showed a significant increase in the incidence of mammary gland tumors in animals exposed daily for 3 hours to static or alternating (50-Hz) magnetic fields at an intensity of 0.2 G (Beniashvili *et al.* 1991). No differences were observed with 0.5 hour daily exposure (Beniashvili *et al.* 1991). Studies examining the ability of EMF to act as a co-promoter for mouse skin cancer or rat mammary gland cancer show both negative (McLean *et al.* 1992) and positive (Stuchly *et al.* 1992; Beniashvili *et al.* 1991) results. A higher incidence of tumors or a decreased latency period was observed in mice exposed to 0.2 G magnetic fields, as compared to sham exposure, and 0.3 μg weekly applications of the tumor promoter tetradecanoyl phorbol acetate (TPA) following dermal application of the carcinogen 7,12-dimethylbenzanthracene (DMBA) (Stuchly *et al.* 1992). No differences attributed to magnetic field exposure were observed when 1 μg weekly applications of TPA were used (McLean *et al.* 1991).

EMF exposure may many affect processes that may either be directly or indirectly involved in carcinogenesis. Transcription of the *c-myc* oncogene was increased in human HL-60 cells exposed over 15 to 150 Hz at 2 to 23 G. Although some increase was seen at each frequency examined, the most pronounced increase occurred after exposure at 45 Hz, with levels greater than four times that of unexposed controls (Wei *et al.* 1990). Although increased levels of *c-myc* transcription were observed in human Daudi cells, normal, or possibly decreased levels of *c-myc* were observed in HL-60 cells exposed to 60 Hz at 1 G (Czerska *et al.* 1992). Changes in cell proliferation were seen in rabbit ligament fibroblast cells exposed to alternating magnetic fields. Markedly different effects, ranging from inhibition to stimulation of proliferation were obtained, depending on the signal parameters of amplitude, frequency, and DC magnetic field (Ross 1990).

EMF exposure may also affect growth and tumor characteristics of neoplastic cells. A 24-hour *in vitro* exposure of human colon adenocarcinoma cells to a 60-Hz magnetic field of 1 G or a 60-Hz combined magnetic field of 1 G and an electric field associated with a current density of 300 mA/m^2 resulted in an increased ability to form colonies in soft agar, and a slight increase in expression of tumor-associated antigens. No consistent changes were seen in cells exposed to the electric field alone (Phillips *et al.* 1986). No effects on tumor weights, incidence, or progression were observed in rodents implanted with mammary adenocarcinoma tissue or leukemic cells and then exposed to magnetic fields of 2,000 Hz (1, 10, or 20 G) or 60 Hz (0.014, 2, or 5 G) (Baumann *et al.* 1989; Thomas *et al.* 1988). Although exposure to a pulsed magnetic field of 12 Hz, 100 Hz, or 460 Hz both increased and decreased the weight of virally induced mammary carcinomas in female mice, lifespans were not altered by the magnetic field exposure (Bellossi *et al.* 1988).

EMF may affect the immune system, and thus could affect tumor surveillance. Exposure of cytotoxic T-lymphocyte effector cells to a 60-Hz sinusoidal electric field of 1 or 1 V/m caused a decrease in the inhibitory effect of allogenic cytotoxicity (Lyle *et al.* 1988). Natural killer (NK) cell-induced cytolysis was also decreased after exposure to a 60-Hz electric field associated with a current density of 300 mA/m^2, a magnetic field of 1 G, or combined electric and magnetic fields of the same intensity (Phillips, 1986). The relevance of these effects to tumor formation *in vivo* remains to be determined.

EMF may depress melatonin levels, an effect that may be related to alterations in pineal gland function. Melatonin provides important time-of-day and time-of-year information to various organs in the body. Changes in blood levels of melatonin occur on a circadian basis with low levels prevailing during the day and high levels at night (Vaughan 1984; Arendt 1988). This variation has been found to be a response to light falling on the retinas, with exposure to light causing a depression in melatonin production (Reiter 1985). Changes in a static magnetic field depress the firing rate of units of the pineal gland in the guinea pig (Semm *et al.* 1980). Exposure of rats at night to an inverted geomagnetic field (i.e., north and south poles reversed) also reduced melatonin levels in the pineal gland (Welker *et al.* 1983). These geomagnetic inversions were found to depress pineal melatonin in other strains of rats and in gerbils as well (Olcese and Reuss 1986; Stehle *et al.* 1988). Lower melatonin output could lead to increased prolactin release by the pituitary and increased estrogen and testosterone release by the gonads (Reiter 1981), and may stimulate growth of breast tissue (Cohen *et al.* 1978). Low levels of melatonin may be associated with the occurrence of several types of cancers, including breast cancer, prostate cancer, ovarian cancer, and melanoma (Gupta *et al.* 1988). Taken with the epidemiologic evidence for a weak association of EMF and breast cancer (Wertheimer and Leeper 1987; Matanoski *et al.* 1991; Demers *et al.* 1991; Tynes and Anderson 1990), these observations have led to the hypothesis that exposure to EMF may be related to breast cancer (Stevens *et al.* 1992), or possibly other hormone-responsive cancers such as prostate cancer.

This RFA requests applications for studies related to carcinogenesis to be performed in animals exposed to magnetic fields in the NTP facility. Applications for studies addressing specific aspects of carcinogenesis are encouraged. The NTP chronic bioassay protocol will be examining the ability of magnetic fields to act as a complete carcinogen (including initiation, promotion, and progression). HEI is interested in supporting studies that will look at events related to carcinogenesis other than initiation. Since there will not be space in the NTP exposure facility for additional animals for HEI investigators during the 2-year chronic exposure, HEI encourages investigators to focus on early measures of promotion, progression, or other factors that can affect the emergence of preneoplastic cells. These studies can be aimed at examining the effects of magnetic fields on any preneoplastic cells, including those that arise spontaneously during the animals' lifetime.

The NTP facility provides a unique opportunity for investigators without experience or resources for EMF exposures to perform studies on animals exposed to several levels of magnetic fields.

Examples of appropriate research areas

1) **Investigations of the emergence of quasi-transformed or preneoplastic cells.** For example, these studies may examine pre-leukemia cells in the blood, bone marrow, or other organs.

2) **Investigations into depression of homeostatic, cancer surveillance, and immune mechanisms.**

3) **Studies investigating alterations in the expression of oncogenes and/or tumor-suppressor genes and expression of other tumor-related characteristics.**

4) **Studies investigating perturbations of pineal and endocrine status.** Both glands and circulating levels of hormones could be studied.

5) **Investigations of cell kinetics.** Effects on cell kinetics can be explored in the bone marrow, central nervous system, endocrine tissues, or other organs.

We also invite investigators to suggest additional parameters for investigation. All investigations should relate any results to the length and intensity of EMF exposure.

Specific consideration of this RFA

This RFA differs in many respects from most other RFAs issued by HEI. The exposure protocol, magnetic field levels, and animal handling procedures for these studies will have to comply with those determined by the NTP. The exposure parameters, such as field strengths, frequency, orientations, and exposure times, will not be subject to change. Although this imposes some limitations, there are many advantages as well. The exposure component of the study will be managed by the NTP and its contractor IITRI, allowing investigators without the resources or expertise for conducting EMF exposure studies to participate. Indeed, we encourage investigators with no prior expertise in EMF research to submit applications for this RFA. **Any questions related to this RFA should be referred to HEI staff. Inquiries should not be made to either the NTP or IITRI.** Details of the exposure protocol, timing of exposure, and number of animals available will be determined at a later date. Special considerations imposed by this common exposure component are outlined below.

An important aspect of this collaborative study is the eventual integration of its individual parts. The studies that will be funded through this RFA provide a unique opportunity to integrate the results from different investigators, and to develop a more comprehensive understanding of any health effects resulting from chronic exposure to magnetic fields.

The availability of the exposed animals through this RFA represents a unique opportunity for investigators interested in the health effects of EMF. Such studies are very demanding in terms of time, financial resources, facilities, and technical personnel. The NTP has unique experience in conducting and managing chronic studies in animals. Investigators interested in the effects of long-term exposure to magnetic fields will have access to sample material and animals from a study with a comprehensive quality assurance program and thoroughly characterized exposures.

Access to live animals. Most studies requiring access to live animals will need to be performed in laboratory space at IITRI in Chicago. Equipment not available at IITRI will have to be transported there. Applicants who require access to live animals should discuss in their application their space, equipment, and other special requirements, and their capability to transport necessary equipment to Illinois.

Choice of animal groups. There will be two possibilities for animals in this study. The first possible group of animals may be supplementary groups of animals exposed to these magnetic fields expressly for ancillary studies sponsored by HEI. Due to timing and space limitations, these exposures will be shorter in duration than the exposures used for the NTP bioassay animals, ranging from 2 to 20 weeks of EMF exposure. Investigators who prefer, for technical reasons, not to be bound by restrictions placed on the NTP bioassay animals should indicate their intention to use the additional HEI animals.

The second possible group of animals is the NTP bioassay group. This group will be subject to exposure to magnetic fields for a period of 2 years. This exposure is not scheduled to begin until sometime after 1994-1995. Investigators proposing studies in the NTP bioassay animals must demonstrate that their studies will not interfere with subsequent histological evaluation. For example, blood samples may be made available to the investigator. It is possible that some measurements can be made immediately prior to necropsy, provided that the investigator can clearly establish that the proposed measurements will in no way interfere with the subsequent gross pathology examination and histopathological analysis.

Statistical considerations. Investigators must address statistical issues in their applications. Questions that must be addressed in the application include the following: What are the principal quantitative end points to be measured? What is the most appropriate way to test differences in response among exposure groups? What is the anticipated amount of variability among animals within an exposure group? How large would effects have to be to have a substantial specified probability of detection if the anticipated variability is realized? Why is this sensitivity appropriate?

Potential for use of material in multiple investigations. Due to the limited number of animals and HEI's desire to support a variety of toxicity end points, individual animals may be utilized in several different studies. Investigators should therefore discuss any research requirements that may effect whether animals can be re-used or shared with other investigators. This discussion should consider both prior treatments that would interfere with their own studies, and the potential for use of animals by others after their own studies are complete.

OPTION 2 (note, much of the text of this RFA is the same as the previous option).

Goal

The purpose of this RFA is to solicit research to determine whether exposure to 60 Hz magnetic fields causes physiological or biochemical changes of oncogenic or preneoplastic significance. These studies will be carried out in a facility built and operated by IIT Research Institute (IITRI).

Background

Interest in the health effects of electric and magnetic fields (EMF) associated with power distribution and use has been spurred by epidemiologic studies reporting an association between cancer and EMF exposure (reviewed by Ahlbom 1988; Savitz *et al.* 1989; Theriault 1991; National Radiation Protection Board 1992; Health Effects Institute 1993). Prompted by this evidence, the NTP will be conducting sub-chronic and chronic bioassays in rats and mice. The purpose of these studies is to determine whether exposure to magnetic fields causes adverse developmental, reproductive, or carcinogenic effects.

In order to perform these studies, the NTP, through its contractor IIT Research Institute (IITRI), is constructing an animal exposure facility equipped to expose up to 2060 animals to magnetic fields. This facility will generate continuous 60-Hz sinusoidal wave magnetic fields with less than 3% harmonic distortion. Five different exposure conditions will be used in this facility: 60-Hz linearly polarized fields with intensities of 10 Gauss (G) continuous, 10 G intermittent (one hour on, one hour off), 2 G continuous, 20 mG continuous, and unexposed controls. This facility is scheduled to be completed in 1993, and the NTP studies are scheduled to be complete in 1996. HEI and IITRI are exploring the possibility of HEI's using these exposure facilities at the end of the NTP studies.

EMF do not appear to have a direct genotoxic effect (Murphy *et al.* 1993). These observations have led to the concept that EMF may enhance carcinogenesis through processes other than initiation. There have been very few and limited animal studies examining this hypothesis. Some investigations of the ability of EMF to act as a tumor promoter, using the classical skin painting protocols, have been negative (Stuchly *et al.* 1991; McLean *et al.* 1991). Other investigations of the ability of EMF to act as a tumor promoter, using other exposure protocols or a co-promotional approach, have shown a higher incidence of tumors or a decreased latency period in animals exposed to magnetic fields (0.2 G) as compared to the animals exposed to either an initiator or an initiator and the tumor promoter tetradecanoyl phorbol acetate (TPA) alone (Beniashvili *et al.* 1991; Stuchly *et al.* 1992).

EMF exposure may many affect processes that may either be directly or indirectly involved in carcinogenesis. Transcription of the *c-myc* oncogene was increased in human HL-60 cells exposed over 15 to 150 Hz at 2 to 23 G. Although some increase was seen at each frequency examined, the most pronounced increase occurred after exposure at 45 Hz, with levels greater than four times that of unexposed controls (Wei *et al.* 1990). Although increased levels of *c-myc* transcription were observed in human Daudi cells, normal, or possibly decreased levels of *c-myc* were observed in HL-60 cells exposed to 60 Hz at 1 G (Czerska *et al.* 1992). Changes in cell proliferation were seen in rabbit ligament fibroblast cells exposed to alternating magnetic fields. Markedly different effects, ranging from inhibition to stimulation of proliferation were obtained, depending on the signal parameters of amplitude, frequency, and DC magnetic field (Ross 1990).

EMF exposure may also affect growth and tumor characteristics of neoplastic cells. A 24-hour *in vitro* exposure of human colon adenocarcinoma cells to a 60-Hz magnetic field of 1 G or a 60-Hz combined magnetic field of 1 G and an electric field associated with a current density of 300 mA/m^2 resulted in an increased ability to form colonies in soft agar, and a slight increase in expression of tumor-associated antigens. No consistent changes were seen in cells exposed to the electric field alone (Phillips *et al.* 1986). No effects on tumor weights, incidence, or progression were observed in rodents implanted with mammary adenocarcinoma tissue or leukemic cells and then exposed to magnetic fields of 2,000 Hz (1, 10, or 20 G) or 60 Hz (0.014, 2, or 5 G) (Baumann *et al.* 1989; Thomas *et al.* 1988). Although exposure to a pulsed magnetic field of 12 Hz, 100 Hz, or 460 Hz both increased and decreased the weight of virally induced mammary carcinomas in female mice, lifespans were not altered by the magnetic field exposure (Bellossi *et al.* 1988).

EMF may affect the immune system, and thus could affect tumor surveillance. Exposure of cytotoxic T-lymphocyte effector cells to a 60-Hz sinusoidal electric field of 1 or 1 V/m caused a decrease in the inhibitory effect of allogenic cytotoxicity (Lyle *et al.* 1988). Natural killer (NK) cell-induced cytolysis was also decreased after exposure to a 60-Hz electric field associated with a current density of 300 mA/m^2, a magnetic field of 1 G, or combined electric and magnetic fields of the same intensity (Phillips, 1986). The relevance of these effects to tumor formation *in vivo* remains to be determined.

EMF may depress melatonin levels, an effect that may be related to alterations in pineal gland function. Melatonin provides important time-of-day and time-of-year information to various organs in the body. Changes in blood levels of melatonin occur on a circadian basis with low levels prevailing during the day and high levels at night (Vaughan 1984; Arendt 1988). This variation has been found to be a response to light falling on the retinas, with exposure to light causing a depression in melatonin production (Reiter 1985). Changes in a static magnetic field depress the firing rate of units of the pineal gland in the guinea pig (Semm *et al.* 1980). Exposure of rats at night to an inverted geomagnetic field (i.e., north and south poles reversed) also reduced melatonin levels in the pineal gland (Welker *et al.* 1983). These geomagnetic inversions were found to depress pineal melatonin in other strains of rats and in gerbils as well (Olcese and Reuss 1986; Stehle *et al.* 1988). Lower melatonin output could lead to increased prolactin release by the pituitary and increased estrogen and testosterone release by the gonads (Reiter 1981), and may stimulate growth of breast tissue (Cohen *et al.* 1978). Low levels of melatonin may be associated with the occurrence of several types of cancers, including breast cancer, prostate cancer, ovarian cancer, and melanoma (Gupta *et al.* 1988). Taken with the epidemiologic evidence for a weak association of EMF and breast cancer (Wertheimer and Leeper 1987; Matanoski *et al.* 1991; Demers *et al.* 1991; Tynes and Anderson 1990), these observations have led to the hypothesis that exposure to EMF may be related to breast cancer (Stevens *et al.* 1992), or possibly other hormone-responsive cancers such as prostate cancer.

This RFA requests applications for studies related to carcinogenesis to be performed in animals exposed to magnetic fields in the IITRI facility. Applications for studies addressing specific aspects of carcinogenesis are encouraged. The NTP chronic bioassay protocol will be examining the ability of magnetic fields to act as a complete carcinogen (including initiation, promotion, and progression). HEI is interested in supporting studies that will look at events related to carcinogenesis other than initiation. Since there will not be space in the exposure facility for additional animals for HEI investigators during the NTP two-year chronic exposure, HEI studies will be limited to the time period following the NTP bioassay, likely to be in 1996.

This exposure facility provides a unique opportunity for investigators without experience or resources for EMF exposures to perform studies on animals exposed to several levels of magnetic fields.

Examples of appropriate research areas

1) **Investigations of the emergence of quasi-transformed or preneoplastic cells.** For example, these studies may examine pre-leukemia cells in the blood, bone marrow, or other organs.

2) **Investigations into depression of homeostatic, cancer surveillance, and immune mechanisms.**

3) **Studies investigating alterations in the expression of oncogenes and/or tumor-suppressor genes and expression of other tumor-related characteristics.**

4) **Studies investigating perturbations of pineal and endocrine status.** Both glands and circulating levels of hormones could be studied.

5) **Investigations of cell kinetics.** Effects on cell kinetics can be explored in the bone marrow, central nervous system, endocrine tissues, or other organs.

We also invite investigators to suggest additional parameters for investigation. All investigations should relate any results to the length and intensity of EMF exposure.

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DRAFT RFA 6: EFFECTS OF EMF ON CELL TRANSFORMATION *IN VITRO*

Please note: Applications are not being sought at this time for the RFAs.

Goal

The purpose of this RFA is to determine whether *in vitro* cell transformation systems are responsive to electric and/or magnetic fields* (EMF). Such a system may either be directly affected by EMF, or be promoted or co-promoted by EMF when transformed by exogenous agents such as chemicals or radiation. If such a system is developed, it could then be used to better define the important parameters of EMF exposure involved in transformation and potentially in human health effects.

Background

Although some epidemiologic studies have suggested a relationship between EMF and carcinogenic effects (reviewed by Ahlbom 1988; Savitz *et al.* 1989; Theriault, 1991; National Radiation Protection Board 1992; Health Effects Institute 1993), neither the carcinogenicity (or its mechanism) nor the specific EMF parameters involved (average field strength, peak field duration, orientation, etc.) have been established. Theoretical analysis of background "noise" in biological systems suggests that multicellular systems offer the best opportunity to explore EMF-cancer relationships.

Cell systems used in studies of neoplastic transformation *in vitro* are multicellular systems which still respond to contact-inhibition and thus still maintain some cell-cell communication. EMF do not appear to have a direct genetic effect (Murphy *et al.* 1993). Recent studies suggest that EMF exposure to various cell culture systems causes membrane changes and Ca^{++} fluxes (Lyle *et al.* 1991; Yost and Liburdy 1992). Ca^{++} is an important second messenger involved in many regulatory aspects of cell growth, including cell proliferation and differentiation (Hennings *et al.* 1980; Nishizuka 1989). Such differences have been seen in cells exposed to various static and alternating magnetic fields (Ross 1990). This has led to the hypothesis that EMF may be acting as a tumor promoter or co-promoter (Adey 1988). Some investigations of the ability of EMF to act as a tumor promoter, using the classical skin painting protocols, have been negative (Stuchly *et al.* 1991; McLean *et al.* 1991). Studies of the ability of EMF to act as a promoter following injection of nitrosomethylurea (NMU) into the caudal vein of rats showed a significant increase in the incidence of mammary gland tumors in animals exposed daily for 3 hours to static or alternating (50-Hz) magnetic fields at an intensity of 0.2 G (Beniashvili *et al.* 1991). No differences were observed with 0.5 hour daily exposure (Beniashvili *et al.* 1991). Studies examining the ability of EMF to act as a co-promoter for mouse skin cancer or rat mammary gland cancer show both negative (McLean *et al.* 1992) and positive (Stuchly *et al.* 1992; Beniashvili *et al.* 1991) results. A higher incidence of tumors or a decreased latency

* Please see Chapter 6 for a description of the range of EMF exposures of potential interest.

period was observed in mice exposed to 0.2 G magnetic fields, as compared to sham exposure, and 0.3 μg weekly applications of the tumor promoter tetradecanoyl phorbol acetate (TPA) following dermal application of the carcinogen 7,12-dimethylbenzanthracene (DMBA) (Stuchly *et al.* 1992). No differences attributed to magnetic field exposure were observed when 1 μg weekly applications of TPA were used (McLean *et al.* 1991).

In certain cell culture systems (for example, Chinese hamster embryo cells, mouse C3H10T½ cells, and mouse keratinocyte cells), treatment with exogenous agents results in a small, but reproducible, fraction of the cells escaping contact inhibition and proliferating to form "neoplastic foci" (Berwald and Sachs 1963; Reznikoff *et al.* 1973). The mouse and human keratinocyte cultures are responsive to changes in intracellular Ca^{++}, an interesting characteristic since EMF exposures have been reported to have effects on Ca^{++} levels (Lyle *et al.* 1991; Yost and Liburdy 1992), and since the response of human cells exposed to EMF may be closer to humans than that of rodent cells. However, neither Ca^{++} responsiveness nor human origins should be considered a prerequisite for these studies.

These cell culture systems show good dose-response relationships between carcinogen, co-carcinogen plus promoter, and focus formation. Therefore, these cell systems may have the potential to detect a promotional or co-promotional effect of EMF on cells that have already been initiated or initiated and promoted. Cell cultures are ideal for measuring exposure-response relations. The cultures are in relatively small volumes and may be easily exposed to ranges of the many parameters thought to be involved in the interaction between EMF and cells.

<u>Examples of appropriate research areas</u>

1) **Studies of *in vitro* cell transformation using EMF.** Cultures of both initiated and uninitiated cells could be exposed to EMF (either with or without other perturbations) over a range of different field strengths and frequencies to investigate cell transformation. The applicants should choose and justify an appropriate biological system and outline suitable end points for detecting promotional or co-promotional changes.

2) **Investigations into the relevant EMF exposure parameters.** Experiments should be designed so that if a response is documented, the relevant exposure parameters and dose-response relations for them can be obtained.

3) **Investigations into mechanism.** If positive results are obtained, the biological system should be amenable to analysis of the underlying perturbation at the cellular and molecular levels.

Please see Chapter 6 for discussion of exposure resources and HEI's strategy for defining exposure conditions in studies. The initial application process will emphasize the biological approach and methods. However, involvement of a physical scientist with knowledge of EMF is expected. In a second phase, HEI's EMF Research Committee will work with investigators to define exposure parameters in a coherent way across all studies.

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DRAFT RFA 7: EFFECTS OF EMF ON SIMPLE, MULTICELLULAR BIOLOGICAL SYSTEMS

Please note: Applications are not being sought at this time for the RFAs.

Goal

The goal of this RFA is to determine if electric and/or magnetic fields* (EMF) affect simple, multicellular systems. Investigators are encouraged to select systems that are biologically well defined and end points that will be useful in determining whether EMF exposure has effects on biological processes requiring cell interaction. Investigators should propose studies that will elucidate mechanisms for any such effects observed.

Background

The energy absorbed by single cells from EMF is often much less than the thermal fluctuation noise estimated to be involved in activating the transmembrane voltage phenomenon in such systems (Adair 1991a,b; Weaver and Astumlan 1990; Pilla *et al.* 1992; Weaver and Astumlan 1992). However, for aggregates of cells or for small organisms in which there is extensive cell-to-cell communication, the signal to noise ratio can be significantly larger for signals resulting from EMF (Weaver and Astumlan 1990). Therefore, this RFA seeks applications for investigation of the effects of exposure to EMF on interactive, cooperative systems of contiguous cells with defined biological properties. If investigations in such systems were shown to give reproducible responses to exogenous EMF, it would then be possible to investigate the mechanisms for such effects, and determine the important exposure parameters, including field strengths, frequency, orientations, and exposure times, in a model system where the study of a large number of organisms is feasible. Studies designed to identify which of the many parameters of EMF that are biologically significant would be encouraged.

Small invertebrates, such as the nematode *C. elegans* and the fruit fly *D. melanogaster*, or small lower vertebrates, such as zebrafish, represent ideal organisms for experiments investigating EMF. In addition to small invertebrates or lower vertebrates, other simple developmental systems, such as *Dictyostelium*, can be utilized to explore EMF effects. The reproduction and development of these organisms have been extensively studied for many years, and the genetic control of these processes has been mapped and is well understood (Wood 1988; Slack 1991; Hill and Sternberg 1992; Krauss *et al.* 1992). In the case of *C. elegans*, the origins of the cells making up the adult nematode have been mapped and many cooperative cell interactions analyzed at both the cellular and molecular levels (Wood 1988).

Although development is under genetic control in these organisms, abnormal development can also result from exogenous perturbations, such as temperature changes,

* Please see Chapter 6 for a description of the range of EMF exposures of potential interest.

chemical exposures, or radiation exposures. Small invertebrates develop rapidly and abnormal development can be observed readily. Since these organisms may be handled in large numbers in reasonably small volumes at low expense, they represent an ideal, organized multicellular system to investigate. These qualities suggest that such organisms constitute a sensitive, reproducible system. However, investigators are encouraged to consider other *in vitro* and *in vivo* tissue systems that may address this research question.

An additional, important goal of this RFA is an understanding of the mechanisms by which any observed effects are produced by EMF because an understanding of the mechanisms of biological effects on such simple systems may allow extrapolation to humans at relevant field levels. Investigators should also consider the possibility that EMF has only a negligible effect on development, but that the combination of EMF and other common environmental perturbations (such as temperature or stress), may have a significant effect.

Examples of appropriate research areas

1) **Use of small invertebrates, lower vertebrates, or other simple systems, to investigate the effects of EMF on development or reproduction.** The applicants should choose an appropriate biological system and outline suitable end points for detecting reproductive or developmental changes. Cultures of small invertebrates, lower vertebrates, or other simple organisms in large numbers, should be exposed to EMF (either with or without other perturbations) over a range of different field strengths to investigate potential developmental or reproductive effects.

2) **Use of simple multicellular systems to investigate the effects of EMF on genetically well defined end points that may be sensitive to external perturbations caused by EMF.** The applicants should choose an appropriate biological system and end points for detecting changes, and provide sufficient justification for their use. Biological systems should be exposed to EMF (either with or without other perturbations) over a range of different field strengths.

3) **Investigations into the relevant EMF exposure parameters.** If effects are seen following exposure to EMF, experiments should be performed to determine the relevant exposure parameters and explore dose response relationships.

4) **Investigations into mechanism.** If effects are seen following exposure to EMF, the biological system should, to the degree possible, be amenable to analysis of the underlying perturbation at the cellular and molecular levels.

The Health Effects Institute can assist investigators in obtaining the necessary EMF field apparatus, and can help arrange for consultations with experts in this field. However, some ongoing collaboration with a nearby physicist or engineer familiar with EMF will be necessary (see Chapter 6).

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DRAFT RFA 8: CELLULAR RESPONSES TO EMF

Please note: Applications are not being sought at this time for the RFAs.

Goal

The goal of this RFA is to investigate the effects of exposure to electric and/or magnetic fields* (EMF) on a variety of cell physiological parameters in vertebrate cells and in tissue slices. A continuum of cellular complexity, ranging from isolated single cells, to confluent cell populations, to living tissue slices are all possible models. Such models will permit the analysis of a large number of exposure conditions that must be explored in order to approach the elucidation of mechanism.

Background

There is a need for quantitative *in vitro* experiments to form a reproducible system for detection of effects of EMF and to help define the mechanisms for any EMF effects. Any mechanism of EMF effects probably involves processes that can best be investigated initially at the cellular or sub-cellular level of organization. *In vitro* studies will also permit a wide range of exposure conditions to be investigated rapidly, which is important because of the large number of possible EMF exposure conditions (field magnitude, waveform, duration, frequency, etc.). The *in vitro* results can then serve as a base for exploring effects on small multi-cellular organisms and whole animals.

A great deal of phenomenological biological data have been produced that are intriguing. However, effects have not been observed consistently in different laboratories, and those studies showing an effect do not effectively address potential mechanisms of action of EMF. Effects of EMF on intracellular calcium levels, levels of RNA transcripts, protein synthesis, cell proliferation, and neuron outgrowth, have stimulated interest in the effects of EMF. However, mixed results have made this data difficult to interpret.

Various effects on intracellular calcium levels, including increases, decreases, and lack of an effect, have been observed in human lymphocytes exposed to EMF. Approximately twice the control levels of intracellular $^{45}Ca^{++}$ were observed in several lines of normal and cancerous mouse T-lymphocytes exposed to a 13.6-Hz magnetic field at 200 mG. The parallel ambient static magnetic field was measured at 165 mG. Increased, although smaller, effects were also observed in activated lymphocytes exposed to 60-Hz magnetic fields at the same intensity (Lyle *et al.* 1991). Conversely, an inhibition of $^{45}Ca^{++}$ influx was observed in Concanavalin A-stimulated rat T-lymphocytes exposed to a horizontal and parallel combined 234-mG static and alternating 421-mG magnetic field at 16 Hz (Yost and Liburdy 1992). No such effect was observed when cells were exposed to either DC or AC field alone, or when resting cells were used. Similarly, no effects of AC magnetic fields combined with

* Please see Chapter 6 for a description of the range of EMF exposures of potential interest.

static geomagnetic fields were seen on intracellular Ca^{++} levels in resting lymphocytes (Parkinson and Hanks 1990).

Electric fields have been shown to affect calcium ion exchange in growing nerve cells. Changes in nerve cell function include alterations in Ca^{++} ion exchange (Blackman *et al.* 1982). Functional alterations in nerve cells have also been seen. Neurites from *Xenopus laevis* tend to grow in the direction of an externally supplied electric field (McCaig 1986). Electric current pulses focally applied to the growth cone of *Xenopus* embryonic neurons in culture stimulated or inhibited the rate of growth cone extension, dependent on the current polarity and the direction of the focal current relative to that of neurite growth (Patel *et al.* 1985). As little as a few V/m elicited this response. Chick dorsal root ganglia explants exposed to static electric fields of 7 to 14 kV/m grew predominantly in the direction of the cathode (Jaffe and Poo 1979).

EMF exposure affect levels of RNA transcription in some cellular and cell-free systems. Exposure to either pulsed magnetic fields or 72-Hz AC magnetic fields increases RNA transcription levels in the X-chromosome of the salivary gland of *Sciara coprophila*. These effects appear to be both frequency and waveform specific (Goodman *et al.* 1987). Transcription of the *c-myc* oncogene and histone were increased in human HL-60 cells exposed over 15 to 150 Hz at 2 to 23 G. Some increase was seen at each frequency examined, with the most pronounced increase in each transcript occurred after exposure at 45-Hz showing levels greater than 4 times that of unexposed controls (Wei *et al.* 1990). Although increased levels of *c-myc* transcription were observed in human Daudi cells, normal, or possibly decreased levels of *c-myc* were observed in HL-60 cells exposed to 60 Hz at 1 G (Czerska *et al.* 1992).

EMF exposure appears to also affect levels of protein synthesis. Two-dimensional gel patterns of specific polypeptides in human HL60 cells are altered after exposure to either pulsed magnetic fields or sine waves of 60 or 72 Hz from 11 G to 35 G (Goodman and Henderson 1988). Overall protein synthesis, as measured by ^{3}H-proline incorporation, was reduced by an average of 30% when cells are exposed to currents of approximately 10^{-2} V/m. This exposure was a frequency-specific threshold current, with most effective frequency in the 1-10-Hz range (McLeod *et al.* 1987). Cell-free preparations derived from *E. coli* also show an effect of pulsed magnetic field effect on protein synthesis, suggesting membrane interaction is not necessary (Goodman *et al.* 1993).

Changes in cell proliferation were seen in rabbit ligament fibroblast cells exposed to 16-, 75-, and 100-Hz alternating magnetic fields of 0.42, 1.96, and 2.61 G. Markedly different effects, ranging from inhibition to stimulation of proliferation were obtained, depending on the signal parameters of amplitude, frequency, and DC magnetic field, which ranged from 0.21-1.31 G (Ross 1990). This is in contrast with earlier studies showing no effect on growth of hamster cells (Livingston et al. 1991) or human cells (Cohen et al. 1986; Adolphe et al. 1987) in culture following in vitro exposure to 50-Hz magnetic fields at 5 G or to combined electric and magnetic fields at 60 Hz (1 to 22 G; 3 to 3000 $\mu A/cm^2$).

Clearly, many of the observations in the literature have been made on vastly different cellular systems, using considerably different exposure conditions. However, a careful, systematic study of these observations, keeping environmental exposures in mind, can reveal important information about the mechanism of these effects.

Many of these observations can now be extended and clarified by using modern instrumentation and techniques. Patch recording techniques, for example, provide the opportunity to study the effects of EMF on membrane depolarization and localized calcium ion influx through individual membrane channels. The wide availability of fluorescent probes allows testing of hypotheses *in vitro* and *in situ*. For example, the fluorescent probe fura2 is particularly sensitive for measuring intracellular Ca^{++} concentrations, and thus investigating calcium flux changes (Parkinson and Hanks 1989; Walleczek and Liburdy 1990).

<u>Examples of appropriate research areas include</u>

1) **Investigations of EMF effects on the cell under controlled conditions.** Techniques are now available that permit the quantification of a wide variety of physiological parameters in living cells and tissues. Fluorescence-based reagents are available that can measure parameters such as membrane potential, free calcium, pH, enzyme activities, and mobility of membranes and cytoplasmic constituents. Light microscope imaging systems such as confocal microscopy can quantify the "real-time" changes in physiological parameters, and flow cytometry can produce cell statistics on large populations of individual cells in suspension. For example, the plasma membrane is believed to be a possible site of EMF effects on cells. Therefore, membrane-associated processes such as receptor organization, ion metabolism, phosphatidyl inositol metabolism, and cytoskeletal assembly could be analyzed over a range of exposure parameters.

2) **Transduction mechanism elucidation.** If a reproducible effect of EMF on physiological parameters is found, investigators should investigate the mechanism of these changes. The chain of events from the initial interaction of EMF with cells through the observed effect should be explored, and hypotheses linking these effects to biological effects should be tested.

Please see Chapter 6 for discussion of exposure resources and HEI's strategy for defining exposure conditions in studies. The initial application process will emphasize the biological approach and methods. However, involvement of a physical scientist with knowledge of EMF is expected. In a second phase, HEI's EMF Research Committee will work with investigators to define exposure parameters in a coherent way across all studies. HEI recognizes that new exposure chambers designed specifically for light microscopes and flow cytometers might need to be designed for some studies funded under this RFA. HEI will support investigators in development of such plans.

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DRAFT RFA 9: EFFECTS OF ELECTRIC AND MAGNETIC FIELDS ON THE RETINA AND VISUAL SYSTEM

Please note: Applications are not being sought at this time for the RFAs.

Goal

This RFA seeks research to investigate effects of exposure to electric and/or magnetic fields (EMF)* on the visual system at a variety of levels in several species. If effects are observed at one level in one or several species, they can be looked for and evaluated at different levels and in different species. The goal is not only to identify reliable changes that occur in the retina/visual system in response to EMF, but also to uncover the physiological and/or biochemical mechanisms underlying these changes. If changes are found, then it will be important to explore the significance of the changes for neural and endocrine function.

Background

Effects of EMF exposure on melatonin synthesis have suggested the possibility that EMF may be detected by the retina, which in mammals is neuronally connected to the pineal gland. The pineal gland is an endocrine organ located near the center of the brain, which produces the hormone melatonin. Changes in blood levels of melatonin occur on a circadian basis with higher levels at night than during the day (Vaughan 1984; Arendt 1988). This variation is due to suppression of the production and secretion of melatonin by light, detected by the retina (Reiter 1985). There is a nocturnal rise in pineal activity of N-acetyl-transferase (NAT), the immediate precursor of melatonin, which is initiated by stimulation of adenylate cyclase activity via an adrenergic receptor mechanism. Melatonin provides important time-of-day and time-of-year information to various organs of the body.

Both electric and magnetic fields have been reported to have effects on melatonin synthesis in rodents. For example, adult rats exposed to 60-Hz electric fields in the range of 2 to 60 kV/m for three weeks, showed an attenuation of the circadian peaks and valleys in pineal melatonin content (Wilson *et al.* 1981, 1983). They also had reduced changes in the activity of pineal NAT whose activity determines the quantity of melatonin produced. In a later study, these deficits were found not to be permanent since normal pineal circadian rhythm returned three days after the end of electric-field exposure (Wilson *et al.* 1986). The authors suggested that the effect is neuronally mediated.

Magnetic field exposure has also been reported to affect pineal gland function. This was first reported by Semm *et al.* (1980), who found that changes in a static magnetic field depressed the firing rates of individual pinealocytes in guinea pigs. Welker *et al.* (1983)

* Please see Chapter 6 for a description of the range of EMF exposures of potential interest.

reported that exposure of rats at night to an inverted geomagnetic field reduced nocturnal NAT activity and decreased melatonin content in the pineal gland.

To determine whether the effects of magnetic fields on pineal gland function in mammals are direct or mediated by the visual system, particularly the retinae, Olcese *et al.* (1985) investigated whether inhibition of pineal melatonin synthesis requires an intact visual system. Rats blinded by transection of the optic nerves did not respond to a 50° rotation of the horizontal component of the magnetic field whereas intact rats did.

To investigate the role of retinal pigmentation on sensitivity to magnetic fields, experiments with albino as well as normally pigmented strains of rodents have been conducted. In one study, Long-Evans hooded rats and albino rats showed decreased nocturnal melatonin synthesis following a 30 minute exposure to a 50° rotation of the earth's magnetic field whereas golden hamsters did not (Olcese and Reuss 1986). In another study, albino gerbils and Sprague-Dawley (SD) rats exhibited decreases in pineal NAT activity and melatonin content following exposure to a 60° rotation of the horizontal component of the ambient magnetic field, while pigmented gerbils did not (Stehle *et al.* 1988). Stehle and coworkers pointed out that SD rats are unpigmented and Long-Evans rats are hypopigmented. They proposed that these results may indicate differences in sensitivity of the retinal system related to degree of pigmentation. For support, they cite studies showing that higher stimulus intensities are needed in pigmented than albino animals to produce an equivalent electroretinogram response. These results suggest that there could be considerable variation among people in their response to such exposures.

It has been demonstrated that altered magnetic fields at night reduce catecholamine levels in retinae of SD rats with intact photoreceptors (Olcese *et al.* 1987). This finding was followed up by experiments to investigate whether the dopamine response to a 30-minute exposure to altered magnetic fields (72° rotation) varies among species and with exposure at other times of the day (Olcese and Hurlbut 1989). After daytime exposure, retinal levels of dopamine declined in the rat and ground squirrel, but increased in the golden hamster. The investigators comment that the differential dopamine responses to the altered magnetic field do not appear to relate in any obvious manner to ocular pigmentation or to the type of photoreceptor cell (rod or cone) that dominates in the retina.

Lerchl *et al.* (1991) suggested that the rate at which the magnetic field is changing may be the critical factor. In their study, in which the field was inverted at two different rates, only animals exposed to a rapidly changing field had depressed melatonin production. The authors proposed that this effect is mediated by induced electrical currents produced by the changing magnetic fields. An alternating magnetic field sets up an induced electric field within an animal that would cause the current to flow in phase with the rate of change of the magnetic field. This hypothesis is consistent with effects seen with electrical fields also since an alternating electric field would lead to an alternating current flowing within the animal in phase with the applied field. Some papers did not report the rate at which the magnetic field changed, which is critical information in comparing studies. Normal movement of the experimental animals would also constantly change the field, but not as rapidly as it could be changed experimentally.

If there are effects of either electric or magnetic fields on melatonin synthesis in humans, then it seems likely that the pathway is through the visual system. The purpose of this RFA is to encourage studies to investigate EMF effects on the visual system, and in particular, on the retina. If significant effects are found, then their mechanisms and EMF parameters will be investigated. Later research could follow any findings through to effects on melatonin levels and perhaps effects on other hormones, such as reproductive hormones. Other RFAs provide opportunities to investigate effects on melatonin synthesis or on possible effects related to effects on melatonin synthesis.

Examples of appropriate research areas

In this section we outline types of studies of interest. Some may be sensitive assays of EMF effects on visual performance, which offer limited information about mechanisms. Others can provide information on the mechanism for the visual effects. It is important that investigators working at these different levels interact with each other and design their experiments to follow up on findings in the other studies. One approach to these studies would be to fund research in three areas - human, animal, and cellular studies. HEI will facilitate interactions among the investigators in developing final plans for their studies and interactions during the course of their studies.

Previous studies of effects on pineal gland function have indicated responsiveness to both electric and time-varying magnetic field exposure. It has been proposed that the common mechanism is induced electrical field. The kinds of exposures used in these studies should be considered in conducting direct studies of the visual system. If these studies find effects of EMF exposure on the retina and visual system, then they can be used to investigate EMF exposure parameters and mechanisms of interaction with the visual system.

Studies of interest include, but are not limited to, the following:

1) **Human studies**: Relatively routine measurements that can detect small changes in visual performance may detect effects of EMF on the retina or visual system in people. Possible types of studies are suggested below:

   Psychophysics - Studies of visual performance could investigate the effect of EMF exposure on absolute, color, and contrast sensitivity. If EMF exposure affects visual performance, then the types of sensitivity changes can offer some information about the possible mechanisms of effects.

   Electroretinographic (ERG) and other non-invasive electrophysiological measures - These methods can be used to study the effects of EMF on such parameters as rod and cone responses and synaptic transmission in the outer retina.

2) **Animal studies:** Animal studies can be used to investigate some of the same end points as in human studies, with the possibility of exploration of a wider range of exposure parameters. Other animal studies can focus on mechanisms of effects.

ERG studies in rats or mice - ERG studies in animals can be used to examine in detail the effects of exposure to EMF on voltage-intensity relations, waveforms of responses, and light and dark adaptation properties of the responses.

Single unit studies in frogs or fish - These studies can investigate the effects of EMF exposure on ganglion cell discharge properties, receptive field organization, absolute sensitivity of ganglion cells and color responses.

3) **Isolated cell studies** (fish horizontal and ganglion cells, mouse ganglion cells) This objective overlaps with RFA 8.

Biophysical studies - Possible studies include investigation of the effects of EMF exposure on membrane potential, voltage and ligand-gated channel conductances.

Biochemical and structural studies - Topics might include investigation of the effects of EMF exposure on growth, structure and longevity of cultured cells and measurement of the effects of EMF on pertinent biochemical components, such as second-messenger pathways and kinases.

Exposure resources

Please see Chapter 6 for discussion of exposure resources and HEI's strategy for defining exposure conditions in studies. The initial application process will emphasize the biological approach and methods. However, involvement of a physical scientist with knowledge of EMF is expected at this stage. In a second phase, HEI's EMF Research Committee will work with investigators to define exposure parameters in a coherent way across all studies.

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DRAFT RFA 10: DETERMINATION OF ENDOGENOUS ELECTRIC AND MAGNETIC FIELDS

Please note: Applications are not being sought at this time for the RFAs.

General goal

Quantitative determination of naturally occurring fields within the body of the living body is sought, in order to establish the bounds for significant interactions with external electromagnetic fields. Electric fields and/or magnetic fields are to be determined in terms of their power spectrum at different sites within the body. That is, what are the field magnitudes at each frequency component of each localized field? A basic question is: are there relatively electrically or magnetically "quiet" sites at which environmental EMF fields can successfully compete with the endogenous fields? Also, are there electrically or magnetically "quiet" times when environmental EMF can successfully compete with endogenous fields?

Motivation

Critics of EMF effects question whether (1) any weak field EMF effects have been credibly observed, and (2) the reported effects are possible at all in the context of biologically generated fields and fundamental physical noise. Regarding the latter, some physical calculations predict that EMF could not influence biological systems (Adair 1991). With this in mind, any comprehensive research program should include quantitative determination of naturally occurring fields within the body. These should then be quantitatively compared to fields induced within the body by external EMF fields.

Background

Some calculations of the environmental fields associated with EMF predict that they would exert no effect on biological systems. However, at least one clear example that biological systems can respond to very small fields is that of sharks and rays that can detect near DC electric fields of order 10^{-6} V/m (Kalmijn 1982). The detection mechanism has yet to be elucidated.

In order for an external field to be considered as causing an effect on a system which has its own, internal fields, it must satisfy criteria involving the relative size of the signal and the size of confounding background and noise. In this sense the "signal" is the external (environmental field), and the background and noise are the confounding fluctuations.

Two sources that obscure the signal of interest can be distinguished: (1) "background" electromagnetic fields of physical and biological origin, and (2) fundamental "noise" due to inescapable fluctuations associated with chemical and physical processes. In addition, laboratory sources of background (e.g. capacitive coupling, mechanical vibration, temperature variations) must usually be reduced to low levels in order to measure endogenous fields at the cell or tissue level.

If the power of the background and noise are known through a combination of measurement and calculation, a sufficient energy for a detectable signal can be estimated. Background and noise will generally have different power at different frequencies, so determination of each as a function of frequency is necessary. If characteristics of the system under study restrict the response to a specific band of frequencies, then only the frequencies in that band would be included. Typically, the power of a signal is compared to that of the background and noise as a ratio (S/B+N). Although it is unknown what an adequate S/(B+N) must be to yield a detectable EMF signal, a ratio of one is a valuable and widely used estimate. This may or may not be too conservative depending on what mechanisms are involved. An example of how this criterion can be used to generate a threshold estimate for "thermal noise" is given in Weaver and Astumian (1990).

Endogenous fields can be distinguished: (1) fields at the level of tissues or the whole animal, and (2) fields at the cellular level (the latter including fundamental membrane noise). Both are of interest.

Fields at the tissue or whole animal level

Fields at the tissue/animal level are generated by the heart, nervous system, muscular activity and electrokinetic phenomena associated with moving tissue. The largest source of endogenous electrical activity in the body is the heart. The peak to peak value of the highest amplitude of the surface potential measured by an electrocardiogram is approximately 1 mV (i.e., from the QRS complex, associated with contraction of the ventricles). The magnitude of brain waves on the surface of the scalp range from 0 to 300 μV. Their frequencies are usually less than 25 Hz but do reach 50 Hz (Guyton 1987). By looking at differences in potential between two body surfaces an absolute lower limit of electric field intensity can be derived.

The 60-Hz component of endogenous fields generated by the human heart reveals that 0.2% of the electric field energy density is expected to be between 40 and 80 Hz. Given about 1 mV at the fundamental frequency, about 3 μV can be expected within a 60+/- 2.5 Hz band (Bergeron 1992). Again, to convert measured electric potentials to fields, one can divide the distance between the measuring electrodes.

Measurements on different animal species have shown that endogenous transcellular or transembryonic current densities on the order of 1 μA/cm2 have been found to traverse single cells; currents on the order of 100 $\mu A/cm^2$ traverse epithelia and tissues (Nuccitelli 1988). Studies of galvanotaxis of neural crest cells in chick development (Hotary and Robinson 1990) and wound healing (Barker *et al.* 1982; Chiang *et al.* 1989; McGinnis and Vanable 1986) suggest that the range of endogenous, "physiological" electric fields naturally occurring in animal is 1-200 V/m. These fields are primarily steady, dc electric fields.

With the exception of strongly magnetic material such as magnetite (Kirschvink 1992), biologically generated magnetic fields have a distinct waveform with peak values expected to be very small (brain fields are about 4 x 10^{-13} T (4 nanogauss), heart fields about 10^{-10} T (1 μgauss), and skeletal fields about 8 x 10^{-12} T (0.08 μgauss), (Cohen 1975). Magnetic fields associated with magnetite are microscopically localized, falling off rapidly on a scale of 10 μm (essentially DC).

Fields at the cellular level

Fields at the cellular levels are caused by metabolic activity such as ion concentration gradients generated by ion pumps in the plasma membranes which result in current flow, and other metabolic activity such as excitable membrane processes. Fields at the cellular level also include equivalent noise fields (e.g. excess channel noise, thermal noise, 1/f noise and shot noise). Definitions of these types of noise are in Chapter 8.

Examples of appropriate research areas

Both experimental and theoretical approaches are appropriate, as a purely experimental approach is likely to encounter very challenging measurement problems.

Theoretical methods

Theoretical methods can utilize state-of-the-art computational methods that allow electric current and field distributions to be determined within the body for given internal (or external) field sources (Gao 1992).

Experimental methods

Experimental methods can investigate the use of microelectrode systems to measure electric fields within living tissue, with emphasis on the local power spectrum. Corrections for motion artifacts and other experimental errors can be expected to be very challenging.

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DRAFT RFPA 11: REQUEST FOR PRELIMINARY APPLICATIONS: DOES EXPOSURE TO ELECTRIC AND/OR MAGNETIC FIELDS CAUSE ADVERSE HEALTH EFFECTS?

Please note: Applications are not being sought at this time for the RFAs.

HEI's EMF Research Planning Committee has developed a set of ten Requests for Applications defining specific objectives for research to clarify whether or not exposure to power frequency electric or magnetic fields affects health. These requests are aimed at general goals described in the research strategy in Chapter 3: 1) Does exposure to EMF increase risk for development of leukemia, brain cancer or other types of cancer? 2) Can relatively simple measurements, using cells in culture or simple multicellular organisms, be used to define the biologically active component of EMF and provide mechanistic support for health effects? The purpose of this Request for Preliminary Applications is to give investigators an opportunity to submit applications for research outside of the specific areas described by the RFAs, but still addressing the goal of HEI's EMF research program to clarify whether there are adverse health effects of exposure to electric or magnetic fields associated with electric power distribution and use.

Preliminary applications will be much shorter than applications to RFAs. They will provide a brief description of the proposed research and of the rationale for it. The personnel involved and an estimate of total direct costs should also be included. The preliminary application should be no more than three pages long. If the HEI EMF Research Committee finds a preliminary application particularly promising, then a full application would be requested.

CHAPTER 6: EXPOSURE RESOURCES AND STRATEGY

This chapter explains HEI's planned RFA application process for experimental studies, which is designed to encourage and assist investigators without experience with EMF research in developing exposure plans for their studies. This chapter also provides practical information, pertinent to both epidemiologic and experimental investigations, on HEI's perspective on the range of EMF exposures of interest in studies. It provides information that may be useful in designing and executing exposure protocols for experimental studies.

Because of the lack of understanding of which parameters of the EMF exposure may be related to biological effects, selecting appropriate exposure conditions from the multitude of possibilities in experimental studies is difficult. Nevertheless, there must be specific definition of exposure parameters to be used as well as careful design and execution of experiments. This will ensure comparability of conditions among laboratories so that results of experiments can be compared. HEI will take an active role in working with investigators to define exposure parameters in studies and in assuring that exposure methods and measurements are satisfactory.

Application process and definition of exposure parameters

For experimental studies, HEI would like to attract investigators who are at the forefront in developing biological approaches relevant to goals of the RFAs. Many of these investigators may not be experts in EMF exposure. To facilitate their participation, there will be a two-step process for application and definition of experimental studies. To avoid placing an unreasonable burden on applicants who cannot know whether their proposed studies will be of interest to HEI, applicants will not be asked to specify all details of their exposure protocols in their applications. The first stage will emphasize the biological approach and methods. At this stage, investigators will be asked to submit only a brief discussion of their thoughts about exposure conditions to be investigated in their studies. At this time, applicants will also be asked to identify a physical scientist knowledgeable about electric and magnetic fields. This collaborator should contribute to the initial application and would be involved later in the design and conduct of experiments for the proposed study.

The second stage in the process of application will involve specification of the exposure protocol. Investigators with promising applications from the first stage (highly ranked by reviewers and fitting well into a coordinated set of studies) would then work with the HEI EMF Research Committee to develop detailed plans for the study, particularly in defining exposure conditions and measurements. The exposure plan for each study to be funded will be developed as part of a coherent overall plan for all of the studies. Part of this process will involve a workshop of investigators with EMF Research Committee members. The discussion of exposure parameters provided by investigators in their original applications will ensure that HEI considers an appropriate range of possibilities in preparation for the workshop.

Following the workshop and further discussion with EMF Research Committee members and staff, investigators will be asked to develop detailed written project plans specifying exposure equipment and protocols. These will be reviewed by appropriate experts, and final plans will be negotiated with investigators before studies are initiated.

The EMF Research Committee will monitor the state of knowledge with respect to EMF from ongoing HEI studies and others. If some studies demonstrate effects of EMF, then investigators will be encouraged to consider whether exposure conditions or responses to be monitored should be altered in their studies. Flexibility to modify study plans based on current results will be essential in developing an efficient program of investigations of both exposure and biological components. Oversight of EMF studies will also include a quality assurance program to ensure that exposure conditions are carried out as planned.

The application process for epidemiologic studies (RFAs 1-3) will be different from that for experimental studies because definition of the exposure will be an integral part of the initial application. For these studies the initial application should contain a complete description of project plans.

Range of exposure conditions of interest

Despite a great deal of research, the answer to the question of whether there are any biological or health effects of EMF from electrical power transmission has remained elusive. EMF exposure can be thought of as a "complex mixture" in which the biologically important parameters are not known. Besides 60 Hz electric and magnetic fields of different intensities, there may be higher frequency harmonics, transients with high frequency components (from load switching or short circuits), slow changes in magnetic fields due to changes in demand for electricity, and combinations of these components resulting in complex waveforms.

Most HEI-funded studies should be centered on 60 Hz exposures since this is the predominant component of environmental exposure. But, if investigators present strong rationales for other frequencies, based, for example, on projection of physical differences between humans and animals or because of hypothesized effects of harmonics, they will be welcomed, especially in simple systems where a variety of exposure parameters can be investigated readily.

Magnetic fields have been hypothesized to be responsible for the increased relative risk for some types of cancer seen in some epidemiologic studies because electric field exposure is attenuated by most objects, such as houses and even the human body. The planned studies by the National Toxicology Program (see RFA 5) is using 60 Hz magnetic fields of several intensities (10 G, 2 G, and 20 mG) for its animal studies. Emphasis on magnetic fields is probably appropriate, but this need not restrict studies to magnetic fields, especially in studies where a variety of exposure parameters can be explored easily. In animal studies, where a limited number of exposure conditions will be possible, they should generally represent high ambient - indoor or outdoor - exposure conditions. However, we do not preclude exploring higher exposure levels and all studies may want to consider including also harmonics or daily variations in field intensities that may be important. If reproducible end points can be found using a representative "whole exposure," then it may be possible to vary components of the EMF mixture and consequently elucidate the important exposure parameters.

Factors to be considered in designing exposure facilities

Fabrication of laboratory equipment for study of the biological effects of electric and magnetic fields presents unique problems. The exposure facility and nearby ancillary equipment, unless carefully designed, may produce significant electric and/or magnetic field exposures in addition to the one intended for the investigation. The following brief discussion is presented only to acquaint the applicant with the major issues that must be considered. Resolution of problems specific to a given research plan should be managed by an electrical engineer or physicist conversant with the nature of electric and magnetic fields.

Magnetic fields - exposure generation

Uniformity

For *in vivo* and *in vitro* laboratory exposures, the simplest method of generating of a uniform magnetic field is by using two coils with opposite poles facing one another and operating at equal field intensity, with one on either side of the exposure volume. Such pairing produces a relatively small volume over which the field is uniform. Several other designs have been developed to produce larger usable volumes and greater field uniformity. These designs, reviewed by Kirschvink (1992), employ three, four, or five coils, arranged and wound in specific configurations. Computer programs are available that can predict with some accuracy the distribution and intensity of a magnetic field generated by coils, and certainly should be used in the design phase. However, once coils are fabricated and energized, magnetometric measurements must be taken throughout the exposure volume to establish empirically the degree of uniformity and distribution of the field.

Harmonics and spurious frequencies

Any exposure system producing a time-varying field can generate harmonics in addition to the fundamental frequency component of the field. In addition, very rapid initiation or cessation of the flow of current in coils, such as that caused by using a switch, contains high frequency components. These high frequencies may in turn induce time-varying voltages in the coils that, in turn, produce currents and magnetic fields of short duration in the coil different from the frequency of interest. Measurements must be made to establish the presence or absence of these phenomena; if they are found, appropriate circuitry can be added to the coils to substantially reduce them if they are an unintended part of the exposure.

Unintended electric field exposures

Since electric fields are associated with voltage, coils should be operated at as low a voltage as possible during an intended magnetic field exposure . This implies that the coils should be designed to have a low electrical resistance, and, in cases where time-varying fields are being generated, low electrical impedance. (Impedance to time-varying currents is a function of the inductance of a coil, which, in turn, depends on the number of turns of wire used, among other factors. Hence, minimizing the number of turns of wire to achieve the desired exposure is advisable for generation of any type of magnetic field, since this would minimize both resistance and impedance.) If unwanted electric fields are found to be a problem after the optimal coil configuration is determined, then the coils can be shielded with conductive metal, such as copper. If such shields are used, several small gaps should be left in the material to prevent the flow of currents induced by changes in the magnetic field. Such changes include turning the field on and off, and the continuing changes associated with a time-varying field exposure.

Heating

In order to produce strong magnetic fields or fields in large exposure volumes, relatively large amounts of current may have to be used to drive the coils. This may result in very noticeable heating of the coils with concomitant heating of the exposure chamber. Cooling systems generally must be incorporated into the design of the coils, or a temperature control and measurement system must be used in the exposure chamber.

Control groups

It is essential that coils and associated circuitry identical to those used for exposures be placed in the chamber(s) used for control subjects. These control coils should have windings that are arranged such that the net magnetic field from them, when energized, is zero. Such coils are referred to as "double-wrapped," or as having "bifilar windings," in which the coil is wound with two parallel wires. Each wire, when the coil is energized carries current in the opposite direction, resulting in a net zero magnetic field. Energization of these coils in the control chamber is critical for producing a true non-exposed control group, because everything about the EMF exposure will be reproduced (heat, noise, odors, etc.) except the field itself. (Note that a double-wrapped coil can also be easily converted to a field-generating coil by causing the currents in the two parallel windings to go in same direction. This would allow a chamber to be used for either an exposure or control condition, which would permit randomization of conditions between two or more chambers.) Measurements should be taken in the control group chamber to ensure that magnetic field exposure is not coming from other sources (e.g., motorized laboratory apparatus, computers, or equipment such as nearby elevators).

Magnetic fields - chamber characteristics

Size

The volumes within the chamber that will be used for exposures must be shown, by measurement to be volumes over which the magnetic field is approximately uniform. Outside a specific volume, field intensity may vary greatly over very short distances; hence, any change in the arrangement of subjects must be accompanied by measurements that confirm the intended field exposure.

Materials

Although magnetic fields are essentially unaffected by biological tissue and non-conductors, the distribution of a field may be affected by conductors and ferromagnetic (usually iron-containing) materials. Time-varying magnetic fields can induce currents in conductors that, in turn, produce small, local magnetic fields opposite in direction to the field of interest. This effect is usually small enough to be ignored, but at high frequencies or field intensities, it may become important. Ferromagnetic materials may alter the distribution of a magnetic field by providing a pathway for the field of far greater permeability than the surrounding air. For these reasons, fabrication of chambers for magnetic field exposures should avoid these materials if at all possible. For example, plastic can be used. If certain conductive or ferromagnetic materials must be used, then alterations (or lack thereof) to the intended magnetic field should be confirmed by measurements. Of course, these restrictions on materials also apply to the apparatus and containment used for maintenance of *in vitro* preparations. Since, the cells or tissues being used for the investigation would be in close proximity to these items, establishing their effects on exposure is critical.

Electric fields - generation

Corona (heat, light, noise, ozone)

For exposures of animals or humans, electric field exposures are typically generated by parallel, plate-like electrodes, with one electrode energized to a specific voltages, and the other at ground potential, thereby establishing an electric field between the plates. The space between the electrodes is the exposure volume, and several pairs of plates may be used within a chamber to establish several exposure spaces. When the electric field at any point on the surface of an electrode exceeds a certain threshold (about 1800 kV/m rms for 60 Hz), this causes local discharge into the air somewhat like a continuous spark. This is called "corona." Corona produces heat, light, a hissing noise, and sometimes ozone, all of which must be avoided during the exposure. Established methods for corona avoidance involve proper design, machining, and operation of the field-producing electrodes at the lowest possible voltage to achieve the desired field.

Uniformity

Unlike magnetic fields, electric fields are perturbed by most materials, including biological tissue. The difference in electric field intensity between field generation electrodes with and without interposing subjects and equipment can be substantial. For this reason, exposures in the electric field literature are usually described as "nominal," meaning the measured field without subjects and other materials in place, or "effective," which refers to the field under actual exposure conditions. To determine actual exposure levels in a chamber, field-strength measurements within a chamber are advisable with the subjects in place. (Such measurements would typically be made between subjects, rather than directly at a subject's surfaces, which introduces other perturbations.) Since such measurements may be difficult, a possible alternative is to model the effective exposure based on published data on electric field perturbations and induced body currents measured in experimental exposures and/or derived from calculations (e.g., Kaune and Phillips, 1980; Kaune, 1981; Tenforde and Kaune, 1987; Kaune and Forsythe, 1988).

Harmonics and spurious frequencies

As in the case with magnetic fields, the possibility of generating harmonics and other frequencies must always be considered. Measurements must be conducted to confirm their presence or absence, and appropriate circuity added to minimize their occurrence when desired.

In vitro exposures

In vitro studies with electric fields are normally performed with plate electrodes placed in the culture vessel, oriented at right angle to the gap between them. The electrodes are imbedded in agar bridges that rest in the culture medium, since the possibility of electrolysis of the metallic surface of the electrodes exists, which may confound an experiment. The electric field and current densities within the medium are typically uniform at points between the electrodes; the conductivity of the medium will influence the current density in the medium. At high current densities, some heating of the medium may occur, and should be monitored. *In vitro* experiments with electric fields can also be performed by placing a culture dish in an external electric field. However, because of the poor coupling between the electric field and the culture medium, very large external electric fields are required to obtain induced fields comparable to those obtained with electrodes immersed in the culture vessel.

Control groups

Control groups need to be kept in an environment that mimics the electric field exposure environment as closely as possible, but which contains an essentially zero electric field. For *in vivo* studies, this can be achieved by using an chamber identical to that used for the exposed group, but which contains a grounded conductive enclosure into which the subjects will be placed (a Faraday cage). When the electrodes are energized, the electric field is intercepted by the enclosure and the subjects within are left in a zero electric field. Optimally, this enclosure should be removable so that a chamber can be used for either exposure or control conditions, thus permitting randomization of conditions among two or more chambers. For *in vitro* studies using electrodes in agar bridges, control preparations typically use unenergized electrodes. In this case, any heating effects of the exposed preparation should be closely simulated in the control culture vessel.

Electric fields - exposure chamber

Materials and grounding

The presence of an electric field in a chamber will charge both the experimental subjects and the internal components of the chamber. The possibility of microshocks between experimental subjects and the exposure chamber and associated paraphernalia must therefore be minimized. This involves the use of nonconductive materials wherever possible, and, if conducting materials must be used, attempting to make sure they are roughly at the same potential as the subjects. In some animal studies, for example, the bottoms of cages are conductive and in direct electrical contact with the grounded electrode. In such setups, conductive sipper tubes or food containers are also connected to the grounded electrode through an impedance designed to match the approximate impedance of the animal, in order to minimize the possibility of microshocks and consequent unwanted effects on eating and drinking.

Field measurements

Measurements should be taken in the exposure chamber with all apparatus and subjects in place, or appropriately modeled, as discussed above under "Uniformity" in this section. Note also that an electric field may change somewhat in local strength and distribution during animal exposures due to soiling of the cages. The degree of such changes should be monitored, at least initially, to determine whether or not this is an important effect that should be dealt with on a regular basis during exposure.

Factors to be considered in designing experiments

When specifying the exposure metric for EMF experiments, a number of choices and specifications need to be made. The list of possibilities includes the following:

General field type

- Electric or magnetic fields or a combination
- Fields as a "playback" of specific environmental/occupational exposures

Frequency, waveform, and amplitude characteristics

- AC or DC
- Pulsed or continuous wave or modulated field(s)
- Field frequency
- Harmonic, subharmonic content
- Characteristics of on-transients/ramps and off-transients/ramps
- Field amplitude

Temporal exposure characteristics

- Duration of exposure
- Continuous or intermittent
- If intermittent, duty cycle of application

Spatial exposure characteristics

- Field spatial homogeneity or inhomogeneity
- Percentage of circular or linear polarization
- Orientation of the field relative to ambient or relative orientation of two applied fields

Once the exposure metric has been specified, additional considerations apply that may influence the outcome and interpretation of the experimental exposures. Among these are:

- Characteristics of the geometry of the exposed system (human/animal/cell) within the field. The size, orientation, conductivity, and ferromagnetic content of the subject determines the magnitude of induced currents and forces, and thus the validity of extrapolation from the experimental situation to human exposure.

- Control of ferromagnetic materials in the diet, culture solution, or general environment. Unless one is specifically examining the role of ferromagnetic material in EMF interactions, it is important to ascertain that such materials are not inadvertently present in the system of interest, particularly if fields in the gauss range or above are being used. (Ferromagnetic particles can respond to applied fields by changing their orientation, thereby applying mechanical forces at the cellular or subcellular level.)

- Elimination of ambient and unwanted fields for both the control and exposed biological systems. EMF are ubiquitous in the environment, and the exposure system merely adds (or subtracts) from what's already present. It must be kept in mind that EMF, unlike chemicals, can both constructively and destructively interfere (i.e., add or subtract). Thus, the EMF exposure is not determined solely by the field from a single experimental source. This is another compelling reason why measurements are preferable to relying solely on the calculation of the applied fields from known currents and voltages.

- For contemporaneous controls, assure that all aspects of the exposed-population environment are duplicated *except* the EMF. This issue, with regard to exposure, is discussed in the previous section on design of exposure facilities. Of course, other aspects of the exposed and controlled subjects' environment should be matched as closely as possible, such as climatic conditions, nutrition, noise levels, and cage cleaning (if applicable). When subjects are not being exposed or sham-exposed, the ambient EMF environment in the area where they are housed should be monitored to ascertain that the non-experimental exposures are comparable.

- The exposure studies, insofar as possible, should be conducted with the investigators and their associates blinded to the specific exposure (or lack thereof) received by any given subject when gathering results. If human subjects are involved, a double-blind study is recommended.

- If possible, two or more systems should be constructed so that each can be operated as either exposure or control chambers. This would permit randomized use of the chambers for either condition, thereby reducing any systematic bias that might be introduced by one chamber or the other.

- For any effect that is identified, determine a dose-response function. The dose-response function of EMF does not necessarily have to be "more is worse." Many of the experiments currently in the literature fail to show how the measured response varies with field intensity, frequency, or other relevant features of the EMF exposure.

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CHAPTER 7: FUNDAMENTALS OF EMF EXPOSURE

The following section provides basic information on electricity and magnetism and on EMF exposure considerations. It is intended to introduce the electrical and exposure quantities mentioned in the draft Requests for Applications.

Basic tutorial on electricity and magnetism

Electric current and voltage

The use of electrical energy for a variety of purposes pervades every aspect of modern society. In order for such energy to be useful, however, it often must be converted into other forms. We see the results of this conversion as light, heat, or mechanical motion, or sometimes as a different form of electrical energy, such as radio waves. These conversions are possible because of the properties of electrical energy that cause charged particles to flow through electrical devices. This flow or electric current occurs at the atomic level, where electrons move from atom to atom within a conductor such as a copper wire. Currents are measured in units of amperes (A). The rate at which current flows in a particular device depends on the magnitude of the voltage at which the device is operating. Voltage is the driving force for the current flow; it can be thought of as electrical pressure, and it is analogous to the water pressure in a hose that determines the rate of water flow. It is expressed in units of volts (V).

If the same voltage is applied to two different electrical devices, the current through them will not necessarily be the same. This is because they may differ in resistance, which is the tendency to oppose the flow of electrons. When electric current flows through an electrical device, a type of friction develops to the flow of electrons, which is a consequence of the resistance. This generates heat.

Electric and magnetic fields

Electric fields

An electric field surrounds an electric charge, whether the charge is fixed in space or part of an electric current. The intensity of an electric field depends directly on the amount of charge producing it, and this intensity decreases with the square of the distance from the charge (assuming a point source of charge). When two objects with like charges are brought near to one another they repel, while those with opposite charges attract. Electric fields are measured in units of volts per meter (V/m).

Electric fields also exist between two nearby objects at different electrical "potentials." A person who walks across a carpet on a cold dry day alters his/her charge content, and is therefore at an electric potential that differs from an uncharged object, such as a "grounded" water faucet or appliance. (Grounding refers to direct or indirect contact with the earth, and can be thought of as zero potential.) When the person comes near the measurable electric field is established between them; the field is reduced when the person touches the object and the resulting "spark," which is an electric current of short duration, partially equalizes the distribution of charge between them. The larger the potential difference between two charged objects, the stronger is the electric field between them.

The strength of an electric field from a wire or electrical device depends on the voltage at which it is operating. The higher the voltage, the stronger is the electric field that surrounds the wire or device. Just as in the example mentioned above, which involved the common phenomenon of "static" electricity, electric fields exist between electrical devices and objects at a different electrical potential, including uncharged or "grounded" people and objects. Electric fields from a long straight wire decrease in direct proportion to distance.

Magnetic fields

A magnetic field is produced as a result of charges in motion, the most common example being an electric current.* The strength of a magnetic field is proportional to the amount of current flowing, if other factors remain the same. In a straight wire, the magnetic field strength decreases in proportion to distance from the wire. Magnetic fields in EMF exposures are most often measured in units of gauss (G) or tesla (T) (10,000 G = 1 T). This quantity is formally called "flux density." Another unit sometimes used is amperes per meter (A/m), which is the measure of field intensity. The two quantities are related by the "permeability" of the medium through which the magnetic field passes; it is a measure of the degree to which the field is concentrated by the medium. Using the traditional symbols for these quantities, if B represents flux density, H represents field intensity, and μ represents permeability, then flux density and field intensity are related according to $B = \mu H$. Most biological materials have roughly the same permeability as free space (air), so for practical purposes in EMF health research, flux density and field intensity can be considered to be related by a constant permeability. This leads to the equivalence 1 A/m = .01257 G. As mentioned, gauss and tesla are the more commonly used units; for convenience, they both may be preceded by the prefixes milli- (one-thousandth) or micro- (one-millionth).

Magnetic fields of high intensities can be created by driving current through wire that has been wound into a coil. When a magnetic material with a high permeability, such as iron, is inserted into the core of the coil, the magnetic field can be enhanced as much as a thousand times. A coil that has been wound around a magnetic core to produce a magnetic field is called an electromagnet. Like bar magnets, coils of wire produce magnetic fields

*Although not a source of concern for the purposes of this chapter, most readers are familiar with the phenomenon of permanent magnetization. This phenomenon is due to the fact that individual atoms and molecules produce magnetic fields. In magnetized materials, the fields of the individual atoms and molecules add to produce large-scale macroscopic fields. The magnetic fields of atoms and molecules can be thought of as being produced by the motion of electrons, and thus are identical to the macroscopic fields which are produced by the motion of charges in wires (i.e., current flow). We do not consider permanent magnets in the remainder of this Appendix.

with a north and south pole. As with electric charges, magnetic poles that are the same repel, while unlike poles attract.

Like the magnetic field from a long straight wire, the intensity of the field from a coil depends directly on the amount of current flowing through it, but the direction of the field is primarily concentrated along the length of the coil more than anywhere else. The degree to which the field decreases as distance increases from the coil largely depends on its geometry (i.e., length and diameter). At distances greater that three lengths of a coil away from either end of it, the coil may be considered for practical purposes a point source of magnetism. In that case, the magnetic field decreases in proportion to the cube of the distance from the coil.

Field lines

Electric and magnetic fields, produced by voltage and current respectively, are simultaneously present around an electric wire or device. Figure 7-1 shows the electric and magnetic fields from a cross-section of wire carrying current into the page. Each of the fields is represented by "field lines," which are conventions developed by physical scientists to represent schematically the directions and distributions of electric and magnetic fields in space. Note that electric fields are arranged radially around the wire, while magnetic fields are depicted as circles with the wire at the center, and that the directions of the magnetic and electric fields are perpendicular to one another.

Time-varying fields

Up to this point, voltage, current, and electric and magnetic fields have been discussed as if they were constant in direction and magnitude. This is true only for applications using direct current (DC), which flows only in one direction and is the type of current that comes from a battery. The electricity supplied to all homes from utilities is "AC," which stands for alternating current. This means that the voltages and currents alternate, or change polarity continuously from positive to negative to positive, etc. In the United States and Canada this oscillation occurs at a frequency of 60 cycles per second, which is more commonly referred to as 60 hertz (Hz) (1 Hz = 1 cycle per second). In European countries, the electrical system operates at 50 Hz. Although the voltage at a wall socket in the home may differ by a factor of several thousand from that on a large overhead transmission line, they are identical in frequency of oscillation and in waveform, which is the pattern of change within each cycle. (The waveform is a sinusoid and will be described further in a later section.) The electric and magnetic fields produced by power lines change in synchrony with the currents and voltages from which they originate. Referring again to Figure 7-1, the configuration of the field lines shown may be considered as coming from a DC source, in which case they would be unvarying, or as a snapshot of the fields from a low frequency AC source, such as one operating at 60 Hz.

Although electricity is provided at the wall socket at 60 Hz, electrical devices and appliances may transform the electrical energy into other frequencies or waveforms for specialized uses. For example, a microwave oven transforms 60-Hz electrical energy at the outlet to microwaves, which are electric and magnetic fields that oscillate at several billion

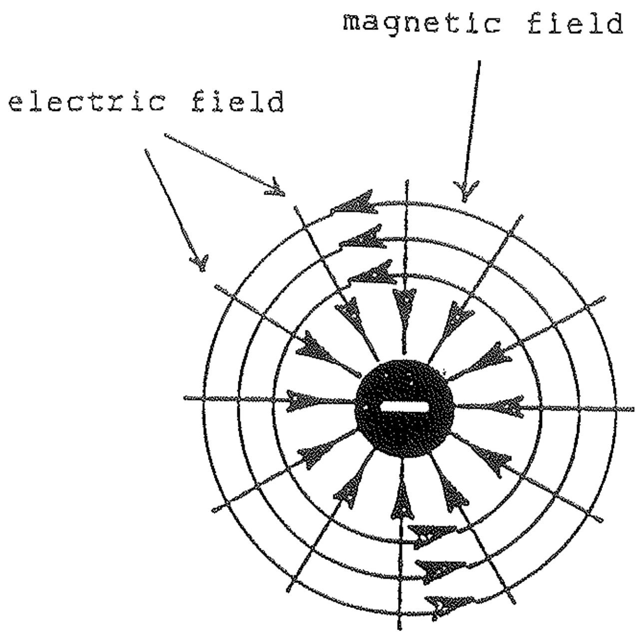


Figure 7-1: Electric and magnetic fields from a cross-section of long wire carrying current into the page. The fields shown may be steady, as in the case of a DC current and voltage, or varying, as in the case of AC current and voltage. In the latter case, the fields shown above would be a "snapshot" of the AC fields.

Hz. Most foods can absorb the energy of microwaves and change it into heat. Television sets and VDTs convert 60-Hz electrical energy into electrical energy at 17,000 to 31,000 Hz (and some higher frequencies) that help to produce video images. In addition, TVs and VDTs change the waveform of the electrical energy to a "sawtooth" form, which has much sharper peaks and valleys than a sinusoid. Another example, which is essentially ubiquitous, is the immense variety of time-varying fields produced by radio and television transmission, which range in frequency from tens of kilohertz (kHz) to hundreds of megahertz (MHz).

All time-varying fields are part of the "electromagnetic spectrum," which is the term given to the infinite continuum of frequencies at which electric and magnetic fields may oscillate. Table 7-1 lists the frequencies that comprise this spectrum, divided according to their usual classifications. Fields at different frequencies have very different properties and thus are used for different purposes. For example, 50 and 60 Hz are used for electric power transmission. Frequencies in the kHz and MHz range can be made to propagate through space and are thus appropriate for radio transmission. Note that visible light and X-rays are electromagnetic waves of very much higher frequency.

Table 7-1: The Electromagnetic Spectrum

Definitions: kHz = kilohertz (thousands of hertz)
MHz = megahertz (millions of hertz)
GHz = gigahertz (billions of hertz)

Classification	Frequency Range	Examples of Uses
Extremely Low Frequencies	30 - 300 Hz	Power transmission vertical TV and VDT scan
Very Low Frequencies	3 kHz - 30 kHz	Marine navigation, horizontal TV and VDT scan
Low, Medium, High, and Very High Frequencies	30 kHz - 300 MHz	AM and FM broadcast, commercial radio
Microwave Frequencies	300 MHz - 300 GHz	Radar, satellite communications
Infrared Light	3000 GHz - 400,000 GHz	Heating, night-vision devices
Visible Light	400,000 GHz - 800,000 GHz	Range of human vision
Ultraviolet Light	800,000 GHz - 30,000,000 GHz	Killing bacteria and fungi; ozone production
X-rays	30,000,000 GHz - 30,000,000,000 GHz	Medical diagnostics; killing tumor cells

This spectrum can be roughly divided into two groups in terms of the effects that waves may have on the structure of atoms. Above the middle of the ultraviolet region, the energy of propagating electromagnetic waves is able to ionize atoms. This means that an electron can actually be broken away from an atom, leaving a positive ion and a free electron; this free electron may then join with a neutral atom and form a negative ion. Electromagnetic waves in this range are thus referred to as "ionizing radiation." The radiation produced by radioactive materials is an electromagnetic wave and falls into this category at the high end of the X-ray range. Propagating electromagnetic waves with frequencies below the ultraviolet range are sometimes called "non-ionizing radiation." The fields associated with the use of VDTs, and even those of much higher frequencies used for radio/TV and microwave communication are all nonionizing.

Induction and coupling of electric and magnetic fields

Electric and magnetic fields can be produced by other time-varying fields, not just voltage and current. This is referred to as induction. A time-varying electric field can induce a magnetic field; similarly, a time-varying magnetic field can induce an electric field.

In many cases, the time-varying sources and the fields they produce are "coupled." Coupling occurs in situations where the magnetic fields are produced primarily by the time variations of the electric fields, and the electric fields are produced primarily by the time variations of the magnetic fields. The degree of coupling between the electric and magnetic fields depends on the rate of variation of the fields: the more rapid the changes, the more the fields are coupled. In cases where the fields are tightly coupled, it is not possible to consider them individually. It is the coupling of the electric and magnetic fields that enables radio signals, for example, to propagate over long distances.

As a general rule, determination of the degree of coupling between electric and magnetic fields also depends upon the size of the region of space over which the distribution of fields is to be examined. If a characteristic length of the region of interest is much less than a wavelength, then field coupling is unimportant. (For this calculation, the wavelength is given by the speed of light (300,000 kilometers/second) divided by the frequency of interest expressed in hertz. Engineers use the term quasi-static to describe situations which fall in this category. For example, the wavelength at the power-line frequency of 60 Hz is 5,000 kilometers (a bit over 3000 miles). Thus, for the dimensions of people and buildings, coupling between 60-Hz electric and magnetic fields is not an important consideration. In such cases, electric fields can be determined simply from a knowledge of the electric charge distribution in a given region (in practice, voltage) and magnetic fields can be determined from a knowledge of currents.

As a result, for power-line-frequency and other "low-frequency-" electrical phenomena, the important sources of electrical and magnetic fields can be summarized as:

> Electric fields: Electric fields are produced by the net effect of electric charges. Typically these charges can be found at the surfaces of electrical conductors and appear there when the conductor is connected to a source of electrical potential difference (voltage) such as an electric generator or a battery. For a specified arrangement of conductors, the magnitude of the electric fields is directly proportional to the applied voltage, e.g., doubling the voltage will double the electric fields.
>
> Interestingly, materials that are poor conductors can pick up an electric charge from low-frequency or non-time-varying field sources, and hence become the source of an electric field themselves. For example, electric charges can easily be induced on such things as the surface of the earth, on living organisms, and on water droplets (clouds) in the presence of another source of electric field (e.g., a storm cloud).

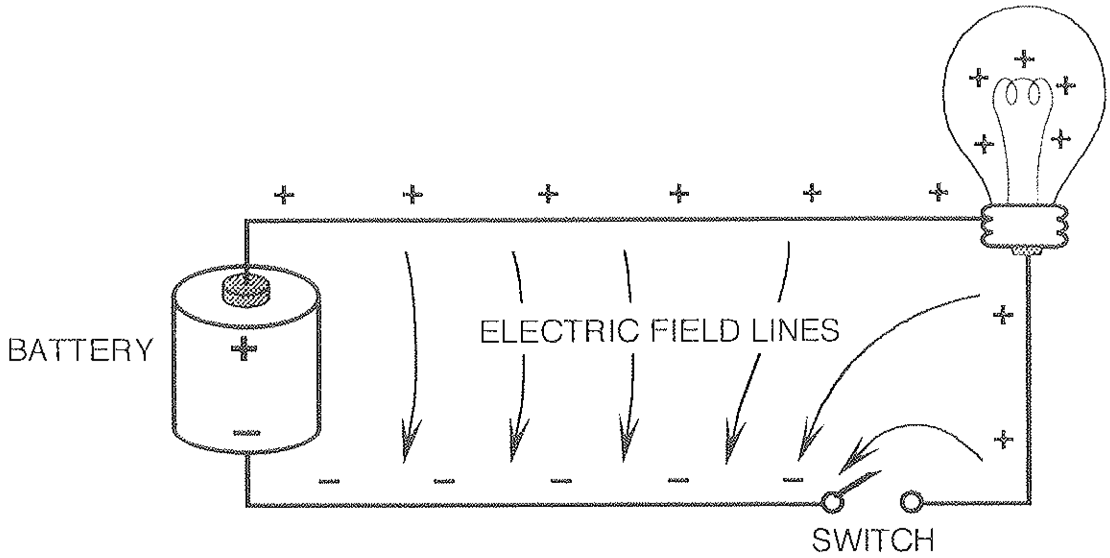
Magnetic fields: Magnetic fields are produced by the net effect of current flow. Typically, currents flow through electrical conductors when those conductors form part of a complete conducting path between the terminals of a source of electrical potential; for example, current flows when a switch is closed to turn on an electric light. For a specified distribution of currents, the magnitude of the magnetic fields is directly proportional to the current magnitude, e.g., doubling the current will double the magnetic fields.

Electrical circuits and associated fields

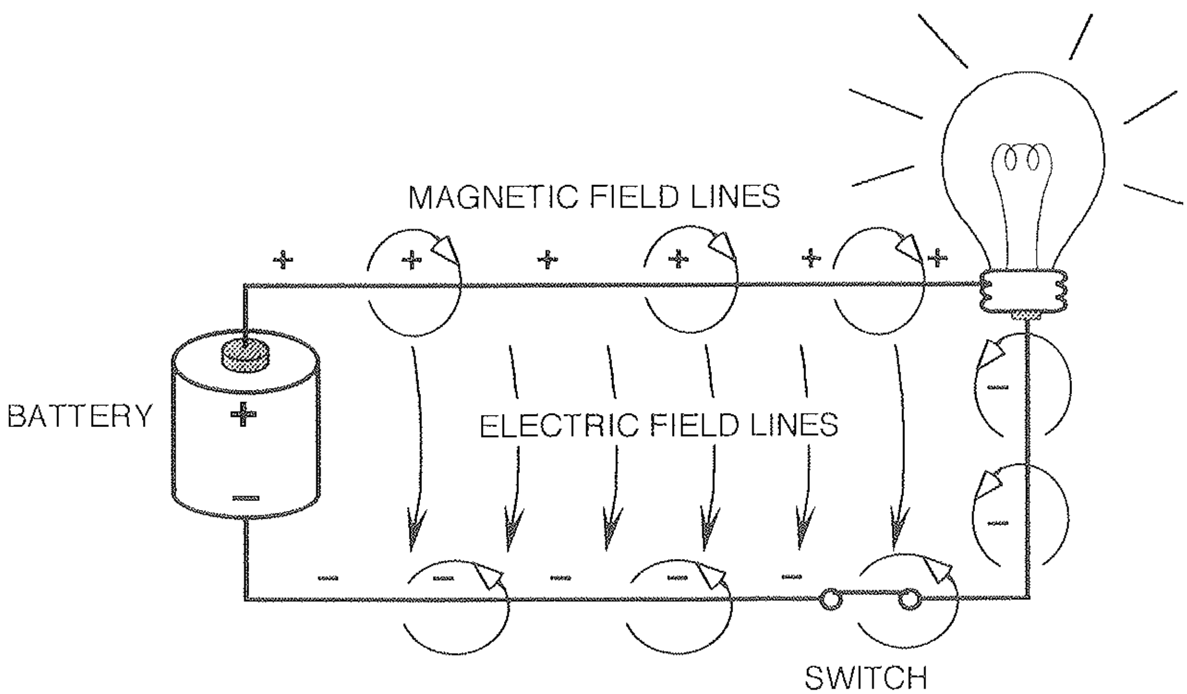
Consider the situation shown in Figure 7-2, in which we see a light bulb connected to a battery through a switch. The battery is a source of electrical "potential." In Figure 7-2(a) the switch is opened and the circuit is incomplete. Here we see that the wire connected to the positive terminal of the battery is energized with a net positive charge (indicated by the '+' signs) and the wire connected to the negative terminal is energized with a net negative charge (indicated by the '-' signs). These charges, in turn, produce an electric field, which is indicated schematically in the figure by the set of arrows which point from the positive to the negative charge. Note, however, that because the switch is opened, there is not a complete conducting path between the positive and negative terminals of the battery. Hence there is no current flow, there are no magnetic fields, and the light is not energized. In Figure 7-2(b), the switch is closed, completing the conducting path between the battery terminals. This results in the flow of current through the electrical system and the production of DC magnetic fields, which are indicated by the circular arrows that surround the wires. Note that in this case the distribution of electric fields is changed somewhat from Figure 7-2(a); the electric field that had appeared across the switch is now gone, and an electric field now appears across the bulb. The field distribution between the conductors, however, is unchanged. This is often the case in 60-Hz power systems: electric field distributions remain relatively constant in both time and spatial distribution, except for localized changes at the points of use and at certain switching points. Magnetic field distributions, however, change significantly depending upon the configuration and current requirements of the loads (electricity-requiring devices) that are being supplied by the system; these loads determine how much current is flowing through the system.

If we replace the DC voltage from the battery with an AC (60-Hz) voltage source (e.g., a power line) the same sort of picture as shown in Figure 7-2(a) applies at any instant, though the field direction changes 120 times/second (i.e., twice per cycle). Closing the switch changes the distribution of alternating fields in the same way it changes the steady fields.

Figure 7-2 illustrates a number of important characteristics of electric and magnetic fields. Both of these fields are vector quantities, which means that they must be described by both their magnitude (intensity) and their direction at any given point in space. As a result, the fields from multiple sources can reinforce each other if they point in the same direction, but they can also cancel each other if they point in opposite directions. Note also that electric fields originate on positive charges and terminate on negative charges. Magnetic fields, on the other hand, form closed loops around current carrying conductors.



(a) Switch opened - electric fields only



(b) Switch closed - electric and magnetic fields

Figure 7-2: The two simple electrical circuits above illustrate the generation and distribution of electric and magnetic fields. The arrows with solid points schematically represent electric fields; those with unfilled points represent magnetic fields.

The direction of these magnetic fields follows the "right-hand rule": when the thumb points in the direction of current flow, the curved fingers indicate the orientation of the resulting magnetic field.

Simple systems using a battery (such as a flashlight) produce voltages and currents that are constant in time, as are the corresponding electric and magnetic fields. Systems of this type are known as direct-current or DC systems. We often preface the electrical quantities associated with such systems with the term "DC," e.g., DC current and DC voltage.

Power in most large-scale power systems, however, is produced by large electrical generators. Such generators produce time-varying voltages and currents (and hence time-varying electric and magnetic fields). Each quantity varies in a sinusoidal fashion, which means that for half a cycle it is positive and for the other half of the cycle it is negative; thus it goes to zero twice each cycle. Figure 7-3 shows a plot of a sinusoidally varying voltage. These variations occur periodically at 60 times per second in 60-Hz power systems and at 50 times per second in 50-Hz systems (by far the two most prevalent systems in use in the world today). Because the electrical quantities in these systems alternate in time, they are known as alternating-current or AC systems, and the preface "AC" is used (e.g., AC current and AC voltage).

When dealing with a DC current or voltage, expressing the magnitude of associated electric and magnetic fields is straightforward; it is unvarying. With alternating current, however, assigning a specific number to the fields is more complicated. One way of characterizing the size of an alternating field is to measure its "amplitude"; this is the peak magnitude of the current in either the positive or negative direction (V_{peak} in Figure 7-3). However, amplitude is an incomplete expression of the energy available from a time-varying field because this value is reached for extremely short times only twice per cycle. A much more useful value is the "effective" value of the field, which is an expression of its average energy content. For fields with a sinusoidal waveform, the effective value, commonly called the "root-mean-square" (rms) value, can be calculated according to the following formula:

$$V_{rms} = 0.707\ V_{peak}$$

One important point to emphasize about low-frequency electric and magnetic fields, such as those produced by power transmission, is that they behave very differently in the presence of slightly conducting materials such as water, soil, and biological tissues. Specifically, these materials are sufficiently conducting that low-frequency electric fields are largely excluded from penetrating these materials. For example, when a person stands under a high-voltage transmission line, the electric fields from the line will be almost completely shielded from penetrating that person. This is because electric charges of the opposite sign are induced on the skin surface by the field from the transmission line. The electric field from these induced opposite charges produces an electric field that is opposite in direction and roughly equal in magnitude to the field produced by the transmission line at the skin's surface, thus reducing the net field within the body to essentially zero. As the rate of time-variation of a field increases, this shielding effect decreases.

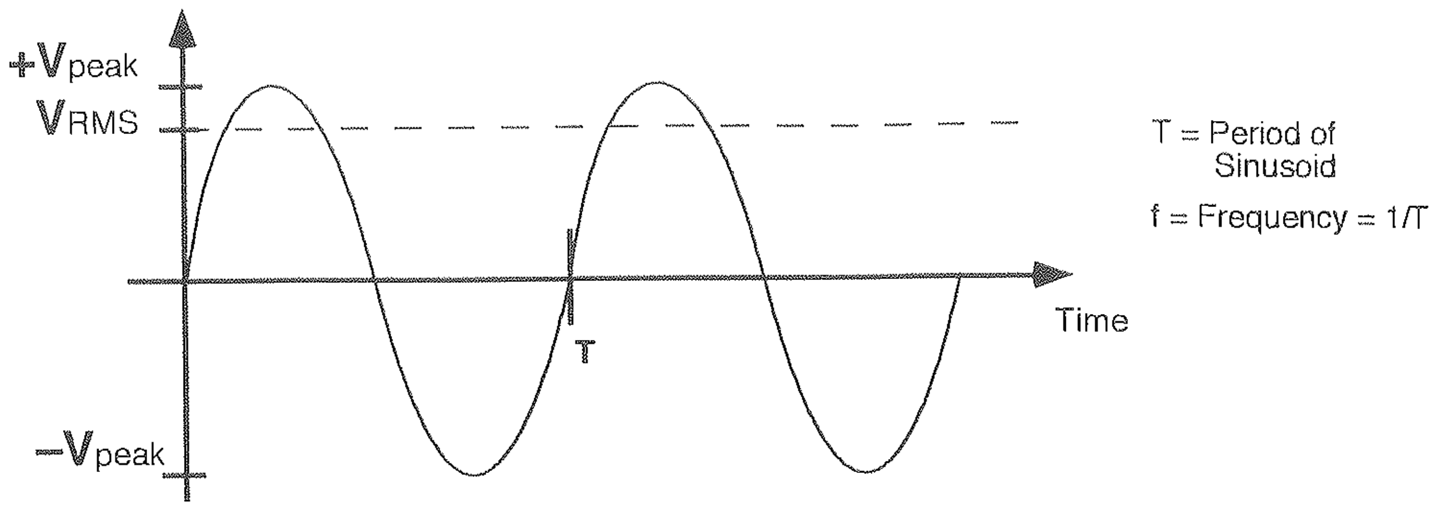


Figure 7-3: Graph of a sinusoidally varying voltage over time, illustrating peak and root-mean-square.

A different mechanism is responsible for shielding of magnetic fields. A time-varying magnetic field at a conductive surface of will induce a current in that surface; that current, in turn, will induce a magnetic field that is opposite in sign to the original field, thus negating it to some degree. The faster the time variation of the original field, the larger the shielding effect. This is the opposite of the electric field case, in which shielding decreases as the rate of time variation increases. At 60 Hz, the currents induced in most biological systems are so small that the resultant magnetic shielding is negligible. Thus, the magnetic fields produced by a transmission line will not be significantly modified by the presence of a person standing under the line, and will totally penetrate that individual. The earth's magnetic field, which is much larger in magnitude than a typical transmission-line field, is non-time-varying and hence, completely penetrates through all of us.

Power-system electric and magnetic fields

Although it is difficult to generalize, it is possible to think of electric power systems as consisting of various major components. Each of these components is sufficiently distinct that it is possible to discuss their technical nature and consequences relatively independently. For the purposes of this chapter, we will discuss three such components; the transmission system, the distribution system, and residential and commercial loads.

Transmission systems

Transmission of electric energy to the point of use typically occurs over a system of overhead transmission lines, although over relatively short distances within cities underground cables may be used. In general, it is most economical (i.e., lowest energy loss over distance) to transmit power at high voltages. This is a consequence of the fact that the magnitude of power that can be transmitted over a given transmission line is the product of the rated voltage and rated current of that line. For a given amount of power to be transferred, raising the voltage at which a given line operates (which requires larger towers and right-of-ways) reduces the current which must flow through the line. Since current flow through conductors results in resistive heating, a lower current tends to reduce the power that is dissipated in the transmission lines over distance, and hence increases the efficiency of the transmission system.

Figure 7-4 shows the configuration of a typical high-voltage transmission tower. In this case, the tower supports a single line, consisting of three phase-conductors. It is not uncommon to see towers supporting two lines (a total of six phase-conductors) on moderately high-voltage transmission lines. However, only a single line per tower is found on the highest voltage lines.

Three-phase transmission systems are designed to be operated under what is known as "balanced, three-phase conditions." This means that both the currents and voltages associated with the three phase-conductors are intended to be sinusoidal in time, equal in magnitude, but displaced ("phase-shifted") from each other in time by 120 degrees. Figure 7-5 shows a set of balanced, three-phase sinusoidal quantities.

As can be seen from Figure 7-5, at any given instant of time, the currents and voltages in a balanced, three-phase set of conductors will sum to zero. This has important implications with respect to the fields produced by a transmission line, which is operating under balanced, three-phase conditions. Specifically, because the voltages sum to zero, there will be no net electric charge on the conductors, although there will be a sinusoidally time-varying charge distribution among the conductors. As a result, the electric fields produced by these charges will tend to decrease in magnitude relatively rapidly with distance from the center of the transmission line because of cancellation of the three electric field contributions. To the extent that the line is unbalanced, meaning that the voltage on one of the conductors differs from the other two, there is a net charge at some positions along the line. The component, usually small, of the total electric field produced by this net charge will decrease in magnitude much more slowly as a function of the distance.

The distribution of electric fields from a transmission is influenced by the presence of the earth under the line. As was mentioned earlier, at power-line frequencies, the earth is sufficiently conducting that electric fields are terminated by charges induced on the surface of the earth and do not penetrate into the earth. Similar effects are produced by many natural and man-made structures, such as trees and buildings.

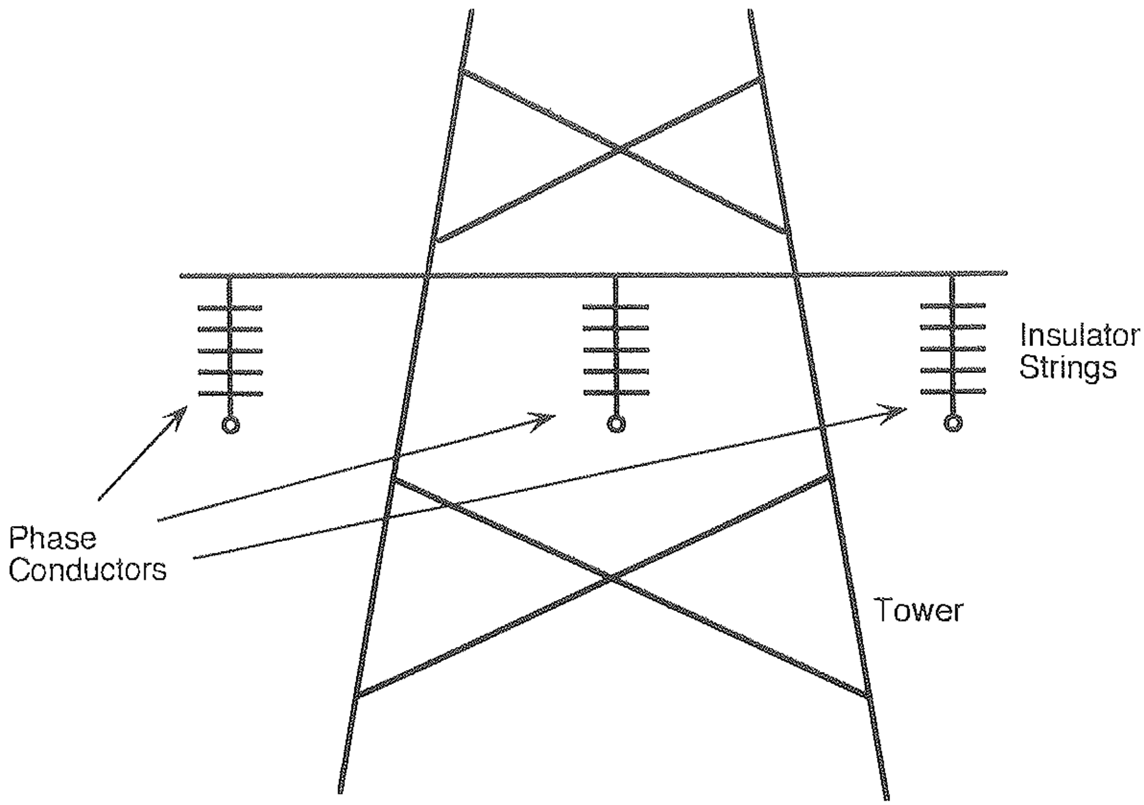


Figure 7-4: Configuration of a typical high-voltage transmission tower.

The magnetic field picture is similar, in the sense that under balanced, three-phase conditions, the phase currents sum to zero at any given instant of time and the magnitude of the magnetic fields decays rapidly with distance from the lines due to cancellation effects. As with electric fields, if the phases are slightly unbalanced, there will be a small amount of net current flowing on the line. The small magnetic field produced by this component of current will decay much more slowly with distance from the line than will the magnetic field produced by the balanced components of the current.

A major distinction between the behavior of 60-Hz electric and magnetic fields is that the magnetic fields penetrate quite a long distance into the earth, for the same reason they penetrate into individuals; the conductivity of the earth is much too small for significant shielding currents to be induced. Similarly, these magnetic fields are, in general, not significantly affected by the presence of structures, with the exception of structures which

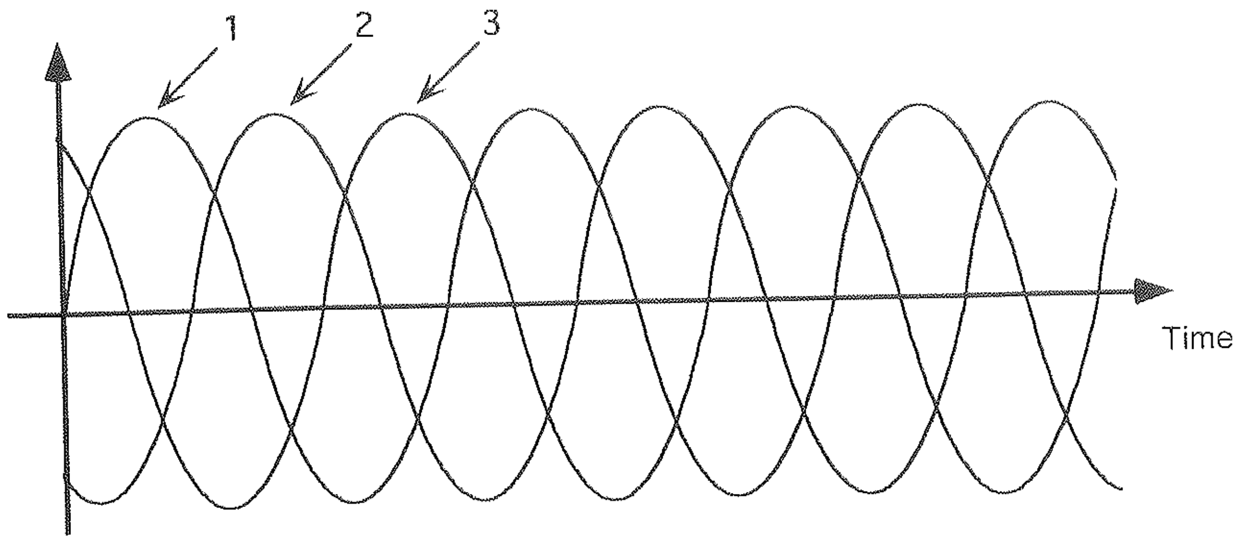


Figure 7-5: Graph of three sinusoidal quantities in balanced, three-phase condition. The quantities are 120 degrees out of phase with one another, and could represent either current or voltage in a typical, three-phase transmission system.

are built with steel beams and other types of ferromagnetic materials.

It should be emphasized that the assumption of balanced three-phase operation on large transmission lines is quite good. Unbalances at the transmission level can have significant adverse impacts on power systems performance and considerable care is taken, both in design and operation, to insure that imbalances are kept small.

Distribution lines and equipment

Bulk transmission of large amounts of electrical energy from generation sources is accomplished by high voltage transmission lines that may run for hundreds of miles without any changes in configuration. At points where power is to used, a much more complex system is required to distribute the electric energy from the transmission system to the thousands of locations where it will be used. On one end of the distribution system are electric substations in which power is stepped down in voltage (using devices called transformers) from the high voltages used on the transmission system to the intermediate voltages used for distribution. Each substation supplies many feeders that distribute the power to local areas within the power system. These feeders, in turn, connect to typically additional transformers, which further reduce the voltage and are connected to yet more localized parts of the system; these may be buildings, industrial complexes or neighborhoods.

It is more difficult to generalize about the distribution system than about the transmission of bulk power from the point of generation. Power distribution may occur over overhead lines or through under-ground cables. Although much of the distribution system is three-phase like transmission lines, balanced conditions are difficult to maintain and are rarely found in practice. In addition, at the low-voltage end of the distribution system (i.e., the end where the loads are), power is ultimately supplied to various loads from a single phase (i.e., a single sinusoidally varying voltage and current). For example, in a given neighborhood, one block may be supplied from one phase and another block from a second.

As a result, the magnetic and electric fields associated with the distribution system are much more difficult to estimate with any degree of accuracy based simply upon the knowledge of how the system is wired. This is especially true of the magnetic fields, since the currents depend upon the loads on the system, which can vary significantly with time. In addition, because the system is not balanced, there may be significant current components which flow through various "grounding" systems, including ground wires which are included in the distribution system, grounded pipes in gas and water systems, and the earth itself.

Residential and commercial loads

The issue of magnetic and electrical field production becomes almost impossibly complex at the loads themselves, that is, inside residential and commercial buildings. In these structures, wires tend to run in fairly random and undocumented patterns, loads are continually being turned on and off, and there are typically many paths over which ground currents can flow. In fact, these systems are so complex that it is almost impossible to predict with any degree of certainty the fields that will be observed by measurement at an arbitrary location within the building.

Perhaps one fortunate point that tends to limit the fields in such structures is that to a great extent, each of the lines that supplies individual loads tends to be somewhat balanced. For example, most light bulbs are supplied by two wires and the sum of the currents in those two wires is zero; at any given instant of time, one can think of the current being supplied to the light bulb by one wire and returned to the source by the other. This tends to greatly reduce the magnetic (and also the electric) fields produced by this wiring, because the two wires are quite close together and charges and currents on these wires tend to cancel.

Unfortunately, there is often also a small but significant amount of current imbalance. This imbalance is due to the presence of multiple ground paths for current return to the distribution system; water pipes are a typical example. These "stray" ground currents are typically not balanced by an equal but opposite current component in close proximity; hence, they can tend to produce somewhat larger magnetic fields. Although these fields are relatively small, they are typically the dominant component of 60-Hz magnetic fields that can be found in any location within a building. It is interesting to note that unbalanced currents found in one location (e.g., a residence) can often be shown to be produced by current imbalances which are caused by loads in other nearby structures.

Figure 7-6 shows schematically the types of ground-current paths that can exist in a residence and the surrounding low-voltage distribution system. Here we see that the return current divides between paths including the house wiring and the house water pipes. Such relatively large current loops can easily produce the low levels of magnetic fields that have been implicated in epidemiological studies of EMF.

Other field sources

Although power transmission and distribution lines have received the majority of public attention with regard to EMF exposures, there are many other sources of such fields commonly encountered in everyday life. Household electric appliances can produce large fields in their immediate vicinity, but these fields decrease very rapidly in intensity with increasing distance. This localization results from the relatively small size of appliances and from the characteristic rates of decay of electric and magnetic fields with increasing distance from their sources. When the distance (R) from such a source is large in comparison to the dimensions of the source, magnetic fields decrease in proportion to the cube of the distance ($1/R^3$), while electric fields decrease in proportion to the square of the distance ($1/R^2$). Measurement of field strengths at different distances from appliances, but still in their general vicinity, will only roughly conform to these formulae, since the sources of EMF are not perfectly localized (i.e., not point sources) and have varying geometries.

Table 7-2 shows electric fields measured at 30 cm from several different appliances (adapted from WHO, 1984). Table 7-3 shows magnetic field strengths at varying distances from different appliances (Gauger 1985).

Exposure to EMF from electric blankets has been a specific source of concern since Wertheimer and Leeper (1986) published a study in which they reported that the use of such blankets and heated waterbeds were associated with fetal losses and an increased gestation eriod. They speculated that these changes were associated with magnetic field exposure. Since electric blankets produce whole-body exposure for sustained periods of time, and are positioned directly against the body, resulting in minimal field diminution from distance, their use can cause greater EMF exposure than other home appliances. Florig and Hoburg (1990) estimated the power-frequency magnetic fields produced by electric blankets from a three-dimensional computer model. They found that the average magnetic flux density over the whole body ranged from 15 - 33 mG, using a variety of estimates to characterize the blanket-using population. New electric blanket designs are being developed that greatly reduce magnetic field exposure by using heating elements that contain two parallel, side-by-side conductors that carry equal but opposite currents.

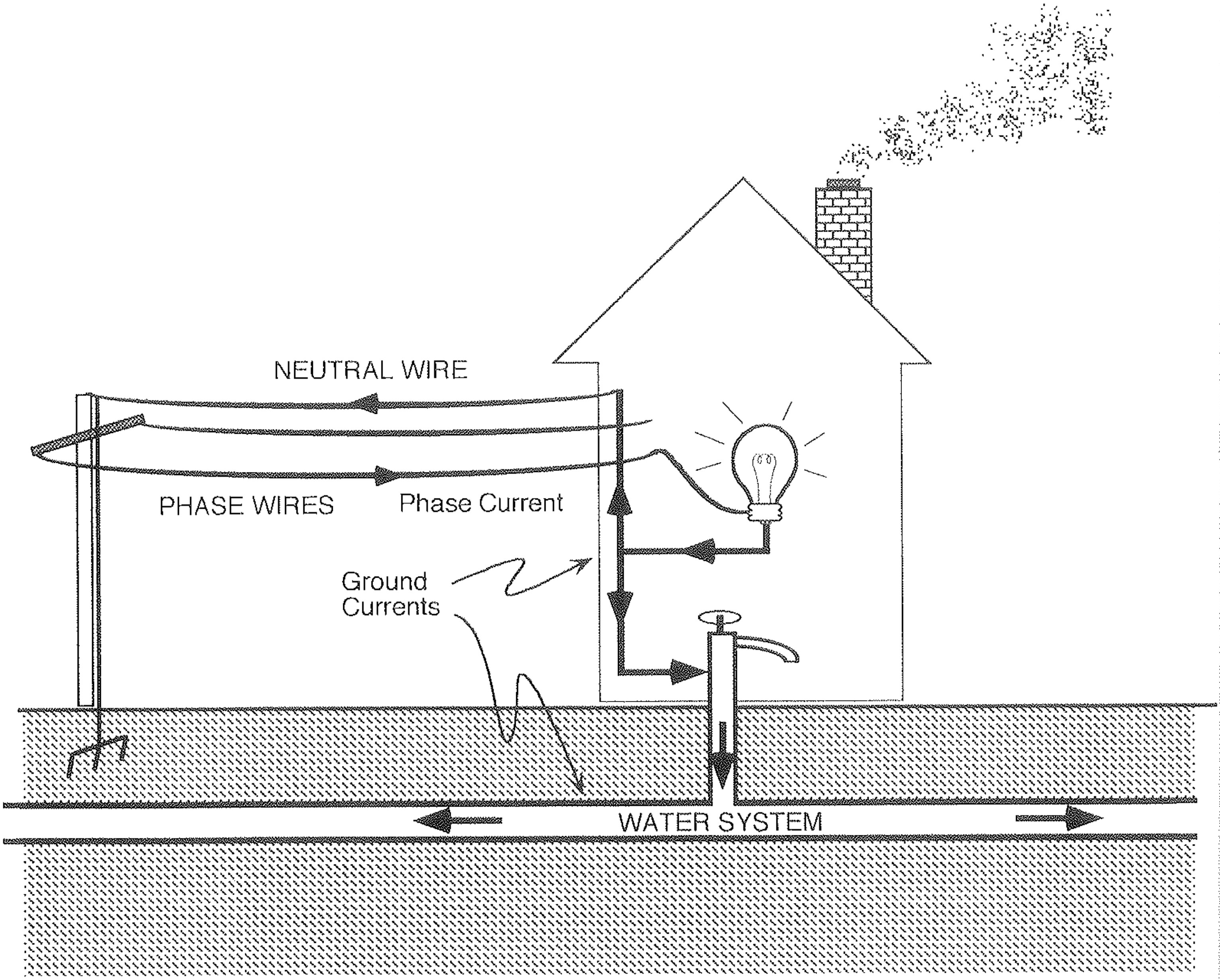


Figure 7-6: Diagram of simplified current paths in a residence, from the distribution line to ground. Note that the return current divides between the house wiring and the grounded water pipes.

Table 7-2: 60-Hz Electric Fields from Household Appliances 30 cm from Source

Appliance	Field (V/m)
Broiler	130
Stereo	90
Refrigerator	60
Toaster	40
Vacuum Cleaner	16

Table 7-3: 60-Hz Magnetic Fields from Household Appliances at Varying Distances from Source

Appliance	Field (mG)		
	3 cm	30 cm	100 cm
Microwave Oven*	750-2000	40-80	3-8
Clothes Washer	8-400	2-30	0.1-2
Electric Range	60-2000	4-40	0.1-1
Fluorescent Lamp	400-4000	5-20	0.1-3
Television*	25-500	0.4-20	0.1-2

* These data on microwave ovens and television include only the 60-Hz component and not the field strengths of the other frequencies generated by these devices.

The electric and magnetic fields associated with the home appliances discussed thus far are similar to those produced by power transmission and distribution lines -- they have a sinusoidal waveform that oscillates at 60 Hz. Video display terminals, (VDTs), on the other hand, which have been the subject of several recent occupational exposure studies, produce a much more complex electrical environment. The display of information by a VDT is accomplished using a cathode-ray tube (CRT). A beam of electrons originating at the rear of the CRT is directed onto the interior of surface of the display screen, which causes a chemical coating, called a phosphor, to glow. This beam is accelerated toward the screen by a DC electric field on the screen's surface. Controlled horizontal and vertical movements of the electron beam produce images on the screen, and the forces to move the beam are produced by two magnetic fields inside the CRT which exert Lorentz forces on the electron beam.

These magnetic fields do not have a sinusoidal waveform, but rather, have a sawtooth shape, whereby they change direction almost instantaneously at the peaks of their cycles. One of the sawtooth magnetic fields produces a horizontal sweep of the electron beam, from left to right across the entire screen and then rapidly back to the left side. This repeating horizontal sweep, often called horizontal deflection or scanning, starts at the top of the screen and works it way down, line by line, toward the bottom. The frequency of the magnetic field producing this horizontal movement is from 17 to 31 KHz in most VDTs. Another sawtooth magnetic field is responsible for moving the beam vertically down the screen; this field also returns the beam to the top of the screen after it reaches the bottom (often called "vertical deflection" or "refreshing"). The frequency of field responsible for these vertical movements is 60-75 Hz.

The external electrical environment of the VDT can be characterized primarily by the electric and magnetic fields that originate inside the CRT. At the operator position in front of a VDT there are measurable sawtooth magnetic fields at the frequencies specified above, and a DC electric field originating from the screen. Electric fields of the same frequency and similar waveform are produced by modulation of the DC (i.e., static) field on the screen and from internal circuitry within the CRT. Table 7-4 summarizes some measurements taken in front of VDTs.

Table 7-4: Electric and Magnetic Fields in Front of a VDT
Measurements Taken at 30 cm from Screen

Field Source	Elec. Field* (V/m)	Mag. Field* (mG)	Frequency (Hz)
Vertical Defl.	≤ 10**	≤ 13**	60-75
Horizontal Defl.	≤ 15**	≤ 2.1**	17,000-31,000
Screen Charge	8-75 kV/m***	--	0 (DC)

* Root-mean-square values, except for screen charge, which is a DC field.

** Range of maximum values, from review by Marriot and Stuchly, 1986.

*** Range of mean values, from WHO, 1987.

Characteristics of ELF (extremely low frequency) electromagnetic fields

"Real-world" fields

Natural fields

Electric and magnetic fields have existed in our environment throughout history. The earth's atmosphere produces a ground-level electric field with a mean value of about 130 V/m. During thunderstorms, the field levels can go up to 100,000 V/m. The earth's core also produces a static magnetic field that ranges from 300 to 700 mG, generally increasing in magnitude from the equator to the earth's poles. Even though these sources of EMF are predominantly static, thunderstorms and solar activity can modulate these steady fields to produce time-varying EMF with frequencies in the electric-power frequency range.

Power system transmission and distribution fields

Electric power transmission lines generally operate at 100,000 volts or more and many hundreds of amperes. A typical 115-kV line carrying a current of 300 A will produce fields of 2 kV/m and 80 mG directly under the line, and fields greater than 5 V/m and 1 mG up to about 70 m to either side of the line. Distribution lines carry current from substations over the last few miles to the ultimate customer. Voltages are reduced to the 5-50 kV level, although the currents can still be hundreds of amperes. However, due to their lower voltage, the conductors of distribution lines are much closer together than the conductors of transmission lines. This would generally mean that the magnetic fields drop off more rapidly with distance as long as the currents in the lines remain balanced. Often, however, there are "net" currents on distribution lines, as discussed earlier, and the magnetic fields produced by these unbalanced currents drop off slowly with distance.

In the home, EMF arise from electrical wiring and all electrical appliances, including electric stoves, electric washers and dryers, fluorescent lights, hair dryers, televisions, and electric blankets. Because electric fields are shielded by common building materials and are rapidly attenuated by the conducting nature of body surface tissues, the search for health effects has primarily centered on magnetic fields, which are not easily shielded. For appliances, the magnitudes of EMF can be high (100 mG or more in their immediate vicinity), but these fields diminish rapidly with distance from the appliance. Background levels (i.e., ambient levels in the house) are generally reached within a few feet. For the majority of homes, baseline 60-Hz magnetic fields of the order of a milligauss are, to a large extent, produced by outdoor distribution wiring and ground return pathways.

Because electrical conduits in a house consist of two wires located in close proximity and carrying equal and opposite currents, they are generally not a significant source of EMF. However, when three-way switches are used to control a load from multiple points, the possibility exists that the wiring has been installed in such a way that net current in the connecting cables is not zero but is rather the full current required to energize the light. The large loop of current can produce a measurable magnetic field throughout a room.

Fields associated with specific occupations

Many studies have assessed occupational exposure to EMF and have attempted to correlate job titles to level of EMF exposure. Although electrical workers can be shown to be exposed to fields higher than is typical of the residential environment, there is no clear ranking of exposure by job title. Whereas the geometric mean electric and magnetic fields measured for residences are about 2.5 V/m and 0.6 mG, the comparable numbers for electrical workers are of the range 5 V/m and 5 mG (Bowman *et al.* 1988).

A variety of occupations and special circumstances can give rise to large fields. Magnetic Resonance Imaging (MRI) utilizes very strong DC (20,000 G) and pulsed (100 G) magnetic fields. Although these are the fields experienced by patients for a very short duration and not those at the operator positions, MRI operators and nurses are likely to have higher than normal DC and pulsed magnetic field exposures, on the average. Likewise, many science and technology researchers working with magnets of all sorts may be exposed to higher than normal fields. Welders, subway operators, and electric train engineers are additional potentially highly exposed populations. Because aluminum manufacture requires huge DC electric currents, magnetic field exposures in this occupation can be correspondingly large.

EMF measures linked to health effects by epidemiologic studies

Although several epidemiologic studies have incorporated actual measurements in their exposure assessment, correlations with disease outcome have only been found for surrogate measures of EMF. It is not known what characteristics (if any) of residential electric and magnetic fields are best correlated with the measured human health effects.

Wiring configurations coding has been used in a number of epidemiological studies as a surrogate measure of exposure. This approach uses several characteristics of transmission lines, three-phase primary distribution lines, and secondary distribution lines, to arrive at a four-step scale of increasing magnetic field exposure. Primary distribution lines are categorized into "thick" and "thin" according to a visually estimated diameter. Sections of secondary distribution lines are further categorized as being first or second spans according to the distance from the line's distribution transformer. A key consideration is the distance of closest approach to the home. There are four possible codes: very high current configuration (VHCC); ordinary high current configuration (OHCC); ordinary low current configuration (OLCC); and very low current configuration (VLCC). Houses served by underground primary wiring are usually placed in the VLCC category, but some researchers put them in a separate category. The matrix of choices that yields these wiring configuration from the various input considerations was developed by Wertheimer and Leeper. Research has shown that the Wertheimer-Leeper coding scheme yields results moderately correlated with measured magnetic fields (but not electric fields), even though the wire coding leaves unexplained 80% of the total variation among homes (Kaune 1993). Given the fact that the system has no parameter for net (unbalanced) currents and grounding currents, which have been found to be the major sources of home fields, it is surprising that any degree of correlation exists.

In addition to wiring configuration coding, residential EMF exposure is also often estimated by theoretical field calculations and questionnaires. Although various actual measurements have been made for electric and magnetic fields (spot measurements, 24-hour averages, personal exposures, fixed-site magnetic field recordings), all these measures of magnetic fields are only weakly associated with wiring codes. There continues to be an ongoing debate as to what assessment technique is the best predictor of long-term, historical EMF exposure.

Magnetic field measurements in the home are often made under high-power and low-power conditions. Low-power measurements are made after power consumption in a home is reduced to as low a level as practical, and the results are interpreted as indicating the contribution of magnetic fields produced by sources outside the home.
Likewise, high power measurements are made after energizing lights and appliances so as to obtain the maximal contribution from field sources inside the home.

Fields used in biological-effects experiments

The EMF that have been used in biological-effects experiments are surprisingly diverse. Certainly, most attention has been given to sinusoidal waveforms at typical power frequencies (50 or 60 Hz), although sinusoidal exposures have been carried out at frequencies as low as 7 Hz (Gavalas *et al.* 1970), and as high as 600 Hz (Ramon *et al.* 1981). Overall, the categories are: continuous sinusoidal magnetic and/or electric fields of various frequencies, and pulsed magnetic and/or electric fields with different pulse rise times and lengths. For some cell culture experiments, electric currents are applied directly through the culture medium. For experiments with applied fields rather than currents, the actual induced electric currents in the humans/animals/cells depend on the geometry of the situation and the size of the humans/animals/cells (*i.e.*, cell culture dish). The use of a wide diversity of exposure metrics is, in fact, one of the aspects of this area of research that makes it difficult to integrate EMF bioeffects into a coherent picture.

A partial listing of the types of exposure metrics that have been used can be found in review publications (for example, WHO 1984).

Commonly-used exposure metrics

Transmission/distribution system EMF characteristics

Apart from experiments that have utilized colonies of animals living under transmission lines, little effort has been devoted to duplicating, in animal or cell experiments, the fields produced by distribution lines. It has generally been assumed that wiring configuration codes are correlated to time-weighted-averages (TWA) of magnetic field intensity. Of course, the puzzle that the epidemiology studies present is that the correlation of disease outcome is stronger with wiring configuration codes than it is with measured TWA fields.

Recently, there has been more emphasis on obtaining personal exposure measurements. In these studies, subjects are asked to wear personal exposure meters for periods from 1 to 7 days, and the output data consist either of time averaged or moment-by-moment field results. In a study of 29 young children, Kaune *et al.* (1991) found that TWA bedroom, kitchen spot, and family-room spot measurements were well correlated with measured personal exposures assessed by portable meters. Wiring codes, on the other hand, were only weakly associated with the measured personal exposures. Another interesting conclusion that derives from personal exposure monitoring is that the at-home component of personal exposure is more variable than the away-from-home component of personal exposure (Kavet *et al.* 1992).

Intensity and duration of sinusoidal fields

Power-frequency electric and magnetic fields, like other vector quantities, can be described in terms of their components. One can, for example, give the x, y, and z components of the field and the time variation of each. The relative phase angle between the components will determine whether the vector will be linearly polarized, circularly polarized, or some intermediate combination. The time dependence of power-line fields is nearly sinusoidal, but a more accurate description of the waveform includes small or moderate integral multiples of the fundamental frequency, which are called harmonics. The amplitude (strength) of real-world fields can vary substantially over time periods of the order of minutes. In the home environment, fields tend to be the highest in the evening, when many appliances are being used, and lowest in the period between midnight and dawn.

Most research experiments do not attempt to duplicate the nature of residential or occupational fields, but rather opt for an exposure pattern that is either a continuously applied field over a period of hours to weeks, or an intermittently applied field that is on during the normal work week and then off the remainder of the time. The exposures are reported either as the intensities used during the "on" period, or, rarely, as time-weighted averages (TWA).

Instrumentation for measuring fields

Instrumentation for measuring electric and magnetic fields is well-developed and readily available. Since electric and magnetic fields can be produced in a wide variety of waveforms and frequencies, equipment must be chosen that is designed to measure field intensities under the conditions of the exposure in question. Also, since these fields are vector quantities, the operator of any measuring device must understand how to orient it properly to reflect the maximum field strength or the component of field strength in a given direction.

Some meters are designed to respond only to a 60-Hz fundamental sinusoidal frequency by using filters to reject all other frequencies. This type of device is adequate if no harmonics of relevant size are being generated, or if 60 Hz is the only frequency of interest. Most experimental and environmental exposures to power frequency fields, however, contain frequency components above 60 Hz due to generation of harmonics. Also, much experimental work has been performed using other fundamental frequencies and using non-sinusoidal fields; for most measurement purposes, non-sinusoidal fields can be treated as being composed of several different sinusoidal waveforms. Therefore, it is more common to use measuring instruments that cover a range of frequencies, generally extending from about 30-40 Hz to several hundred or several thousand Hz. These are known as "broad-band" instruments; meters of this type can be combined with analytic devices to provide detailed information on the specific waveform(s) of the field being measured. For example, the output from a broad-band magnetometer could be sent directly to a Fourier analyzer, which would provide a real-time assessment of the sinusoidal frequency components of the field being measured.

Electric fields

Reliable instrumentation exists for measurement of electric fields. These are so-called free-body instruments, and are designed to measure electric fields that are relatively removed from ground potential. A free-body instrument essentially consists of two halves of a (usually) spherical metallic shell. The two halves are insulated from one another. When the device is placed in an electric field, a potential difference develops between the two halves; a meter with a high resistance, connected to both halves, measures the current resulting from this potential difference. Free-body devices can be used for both indoor and outdoor measurements.

An important caveat when measuring electric fields is that they are easily perturbed by human beings, animals, vegetation, and structures of almost any kind. Therefore, the most accurate measurements of electric field exposure are made when all elements normally at a site are in place, with the measurement taken at the actual point where the exposure takes place. This is sometimes referred to as the "perturbed" value of the electric field. It is also useful to measure the "unperturbed" value of the electric field, in which no objects are in the electric field, for reference and calibration purposes. When measuring an electric field, it is important that the operator remain at least several feet from the meter, because his/her own body will perturb the local electric field. Free-body meters, therefore, are often attached to a long insulating handle, enabling the operator to maintain an adequate distance from the field.

Magnetic fields

The two most common types of magnetic field sensors are search coils and Hall probes, both of which are commercially available and portable. A search coil placed in an alternating magnetic field will have an alternating voltage induced in its loops. The amount of voltage induced in any given coil is a function of the frequency of the magnetic field and the orientation of the coil relative to that of the field. When the axis of the coil is parallel to the orientation of the magnetic field, voltage induction in the coil is maximized. Some measuring devices based on this principle use a single coil, in which case the coil must be rotated to gain a maximum reading. More sophisticated devices contain three mutually perpendicular coils, which simultaneously measure the x, y, and z components of the magnetic field. These latter instruments are used to measure the "resultant" field, which is the vector sum of the field components in three axes.

A Hall probe is comprised of a flat strip of semi-conducting material, through which a current runs along its long axis. When a magnetic field is oriented perpendicular to the long axis of the probe and also perpendicular to its surface, a potential difference develops across the short axis of the probe. This induced voltage is referred to as the Hall effect. The Hall voltage is amplified and measured by meter circuitry to produce a readout. Since the Hall effect is dependent on the component of the magnetic field that is in the correct orientation, Hall probes, like search coils, must be rotated to determine the maximum magnetic field. The use of Hall effect probes to measure low-level power frequency magnetic fields has been discouraged by the Institute of Electrical and Electronic Engineers (IEEE). Some Hall effect meters, when used to measure such fields, are adversely affected by the much stronger DC geomagnetic field of the earth.

Other devices, which operate on principles other than those described above, are used to measure very weak magnetic fields. For example fluxgate magnetometers can measure fields down to .001 mG , while a superconducting quantum interference device (SQUID) can measure fields down to 0.1 pT. These magnetometers, especially the SQUIDs, are used in research involving measurements of endogenous fields from the body (e.g., from the brain or heart), or other similarly small magnetic fields. They are usually used inside magnetic shielding to screen out surrounding magnetic fields, because the ambient fields typically found in laboratories are much larger than the fields being measured.

The most recent development in magnetic field measurement technology is the MultiWave™ Monitoring system, developed for the Electric Power Research Institute (EPRI). The primary feature of this device is that it captures the actual waveform of the magnetic field, saving the three orthogonal components of each waveform in a digital format. These data can be analyzed to provide intensity, phase, spatial orientation, polarization of the 60-Hz component and all harmonics up to the thirty-second.

Personal dosimeters

For occupational or epidemiologic studies, portable measurement devices exist that can be worn for long periods of time to record magnetic and electric field exposures. One such device is the Electric and Magnetic Field Digital Exposure System (EMDEX), whose development was sponsored by EPRI (Enertech, 1989a). The EMDEX contains three mutually perpendicular coils for taking field measurements. It is a digital device that can record both electric and magnetic field exposures at a selected sample rate and store them in an on-board memory, the contents of which can be downloaded to a personal computer. The EMDEX is small enough to be worn on a belt at the waist, and can operate on battery power for several days. If only magnetic field data is required, no further equipment must be worn; if electric field data is needed, then a conductive sash is worn over the user's shoulder.

Another even smaller device, also developed for EPRI, is the Field-Time Integrator. This device is worn on the wrist and contains either a single coil (AMEX) or three orthogonal coils (AMEX-3D). There are two versions of the device, one for magnetic field exposures and another for electric fields. These integrators can be used to measure cumulative field exposures (i.e., [mG]×[hr] or [kV/m]×[hr]y) over the course of several weeks. They both operate by storing a cumulative field-induced charge in a small electrolytic cell, which is measured at the end of the exposure period. The integrators are calibrated by placing them in known electric or magnetic fields for specified periods of time to determine the rate of charge accumulation. Note that these devices, unlike the EMDEX, cannot provide information on changes in field strength over time.

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CHAPTER 8: MECHANISMS BY WHICH EMF MAY INTERACT WITH BIOLOGICAL SYSTEMS

Energy of 60-Hz EMF fields

The mechanism by which environmental levels of EMF may produce biological effects in humans is, at the present time, an open question. Moreover, "signal-to-noise" considerations pose a serious challenge to suggested mechanisms. At a fundamental level, the interactions of electric charges (on ions, on molecules, on proteins, and on membranes) are integral to many biological phenomena. They control a variety of physiological an pathological processes. They control a variety of physiological and pathological processes. Hence, it is plausible to expect that exposure to environmental electric and magnetic fields, which can exert forces on fixed and moving charges, may have the potential to modulate the function of biological systems. However, the molecular and ionic sites at which EMF interact with biological systems are not well established.

Unlike X-rays, which can ionize biological molecules, or light photons, which can bend biological molecules, or microwave photons, which can vibrate biological molecules, the energy contained in photons of 50- to 60-Hz electromagnetic radiation is less than 1 pico-electron-volt (*i.e.*, 10^{-12} eV *versus* light photons with about 2 eV of energy) and is much too feeble to alter biological molecules directly. EMF oscillating at 50-60 Hz *can* induce weak currents and voltages in the body, but when physical principles are used to analyze the interaction between EMF and single, isolated cells, the results strongly support the conclusion that, unless biological phenomena occur over an inordinately narrow band of frequencies, transmembrane voltages induced by most weak environmental sources of EMF are small compared to thermal noise voltages and are far below the levels of natural electrical activity that occur in living organisms. That is, for single, isolated cells the ability of any transmembrane-voltage-responsive mechanism to distinguish externally-induced weak electric fields from thermal noise in the transmembrane voltage appears to be a violation of physical laws (Weaver and Astumian, 1990), (Adair 1991a), (Adair 1991b). We know that the molecules of life are constructed so as to resist the normal buffeting of thermal energies (1/40 eV), so it is helpful to compare induced EMF energy to thermal energy. Since the maximum voltage inducible across cells in conducting tissues is about 1 V/m, the maximum potential across a 10 μm diameter cell would be 10 μV, and the maximum energy a singly-charged molecule can attain within this potential is 10 μeV. In comparison, the thermal energy of the same molecule is 25,000 μeV.

The single-cell analysis may not preclude detection of these weak fields at a multicellular level. A useful analogy can be made with single-particle *versus* multiple-particle behavior. Individual molecules suspended in fluid do not "settle out" under the influence of gravity because of thermal agitation by other molecules in the fluid. However, if the individual molecules become joined together, i.e. into a small solid particle, this allows them to respond as a larger entity, and the whole assembly can now settle by gravity. In an analogous fashion, cells interconnected electrically (by gap junctions) can respond as a unit to fields that span these cells. In a sense, the assembly of cells behaves like a radio antenna; even though the voltages induced across small segments of the antenna may not exceed thermal noise, the voltage output of the whole antenna does. Likewise, a whole network of electrically-connected cells could concentrate induced fields across limited portions of a few cell membranes, where interaction with membrane proteins could occur.

Biological organization can also integrate single-cell effects. In higher-level organisms, many neural pathways are known to be highly convergent on neurons where presynaptic activity in any one of the incoming neurons is not sufficient to cause activity in the postsynaptic neuron, but activity in a large number of incoming neurons simultaneously will dramatically increase the firing rate of the postsynaptic neuron and produce a response. If the presynaptic neurons are on the verge of firing, thermal effects may push some of them over the edge in a random fashion with little effect in the output neuron. However, the coherent effects of external EMF may simultaneously push a substantial number of the presynaptic neurons into firing and hence give rise to a definitive "EMF signal" in the postsynaptic neuron. This is analogous to signal-to-noise ratio (S/N) enhancement by coincidence detection in radiation-detection instruments.

"Resonant" mechanisms

Among the several mechanisms of EMF interaction proposed, "resonance" has been popular because such responses predict maximal effect for a small energy input; a necessary condition, however, is that the biological system is most sensitive to energy input at a particular frequency. If, for example, the interaction mechanism is finely tuned to exactly the 60-Hz frequency (*i.e.*, "resonant"), then the induced electric fields within a sufficiently narrow band of frequency (*e.g.*, 59.5 to 60.5 Hz) in the biological system can be greater than thermal noise. A resonance response tuned to the "ion cyclotron frequency" was first proposed by Liboff (1985), who applied to biological systems the same equations that describe circular motions of ions (in a vacuum) under the influence of a magnetic field. Although the cyclotron resonance hypothesis is very attractive for explaining the Ca^{2+} efflux experiments that show a strong dependence on frequency, the extrapolation from ions in a vacuum to ions in a cell has been heavily criticized because molecular collisions (damping) could not possibly allow this phenomenon to occur in biological material (Sandweiss 1990).

Another resonant mechanism for "caged ions" was proposed by Lednev (1991) and also advocated by Male (1992). Lednev's mechanism predicts enhanced bioeffects for certain combinations of DC and AC magnetic field amplitudes and frequencies. Lednev uses as his starting point the "striking resonance character" in the biological effects reported by Liboff and others following the application of weak static and low-frequency alternating magnetic fields (Liboff 1989). Lednev acknowledges that the interaction of weak magnetic fields with biological systems is "anomalous" because of the low energy content of the interacting magnetic fields when compared to ion thermal energies. However, he claims that his theory shows an increase in the probability of transitions between vibrational energy levels *without* any energy pumping into the system. He calls it analogous to "parametric resonance" or the "quantum-beats effects." This mechanism has also been subject to significant criticism (Adair 1992). However, observation of resonance-like behavior in calcium efflux, diatom mobility, and most recently, mitogen activated lymphocytes (Yost and Liburdy 1992) has been reported.

McLauchlan has proposed another resonant mechanism in which the putative health effects of power-line magnetic fields might be due to the effects of 60-Hz magnetic fields on free radicals (McLauchlan 1991, 1992). A free radical is a highly reactive molecule with an unpaired electron; the unpaired electron endows the radical with a significant magnetic moment. The mechanism by which static magnetic fields may modify free radical interactions rests on the fact that bond formation between reacting radicals requires that they be in the singlet state (spins antiparallel, total electron spin 0) rather than the triplet state (spins parallel, total electron spin 1). The Pauli Exclusion Principle does not allow overlap of the electron wave functions in the same quantum state (spins parallel). McLauchlan proposes that a pair of radicals that initially cannot react because they have the wrong relative spin directions (triplet) diffuse apart and may experience different magnetic fields; one spin may reorient, permitting the reaction to occur if the radicals re-encounter in the singlet state. In systems of organic radicals, the rate of triplet-singlet (T-S) interchange occurs as a result of the two radicals responding to different applied magnetic fields. In effect, at magnetic field strengths below the point at which the Zeeman splitting (electronic magnetic moment interaction with an applied magnetic field) exceeds the magnitude of the hyperfine interaction (electron magnetic moment interaction with the nuclear magnetic moment), the number of energy levels available to the electron-spin system increases with applied field, and the reaction probabilities for T-S interconversion increase. At higher field levels the opposite is seen: reaction probabilities decrease with increasing field. The effect does not depend on the specific chemical identity of the radicals. Thus far McLauchlan has not hypothesized which candidate EMF bioeffects are coupled to free-radical interactions.

Direct magnetic field interactions with ferromagnetic material

Another mechanistic hypothesis involves direct interaction of magnetic fields with ferromagnetic material. Most body tissues and proteins are not ferromagnetic, and the usual mechanism by which time-varying magnetic fields may produce an effect in tissue is *via* induced currents. Ferromagnetic crystals, however, have a permanent magnetization, and magnetic fields can exert forces on these particles. They have been described in magnetotactic bacteria and in the brains of some birds and fishes. The physical motion of the particles in response to such forces may be transduced by neurons or by cell membranes into a biological response. Kirschvink has found evidence for the presence of pure, microscopic, magnetite crystals in the human brain (Kirschvink *et al.* 1992). Because these "microscopic bar magnets" can interact with ambient magnetic fields, it is proposed that biogenic magnetite may account for a variety of biological effects of low-frequency magnetic fields. A large number of Kirschvink's single-domain magnetic crystals need to act in concert in order for the interaction energy with ambient magnetic fields to exceed the randomizing effects of thermal agitations. Currently, the amount and significance of magnetite in humans is unknown.

Indirect magnetic field interactions

Induced electric fields due to time varying magnetic fields can be regarded as indirect interactions. The final result of both magnetically and electrically induced electric fields is to drive currents. The key consideration in the biological effects of such currents is how they compare to endogenous currents that already exist due to normal membrane and tissue electrical activity such as muscle contraction and nerve conduction.. Although the exact nature of endogenous electric fields is poorly understood, experimental evidence shows that to induce action potentials in nerves (even in long neurons), the threshold power-frequency current density required is about 10 - 20 A/m^2. Even for long nerve cells oriented parallel to the current-density vector, currents in excess of 1 - 2 A/m^2 are necessary. At 60 Hz, a whole-body magnetic field of about 700 Gauss would be required to achieve this level of induced current density (Kaune 1993).

Magnetic-field transients

Rapid fluctuations in the magnetic field may play a role in causing biological effects. For example, the reported efficacy of periodic magnetic field pulse bursts in enhancing the fusion of fractured bones suggests that the electric fields induced may stimulate bone remodeling. When 60-Hz currents are switched on or off, the time rate of change of magnetic fields (dB/dt) can far exceed the value of dB/dt that exists in the steady 60-Hz case. Time rate of change values can vary from a few gauss per second up to 400 kilogauss/sec when a mechanical switch interrupts a 450-watt light fixture. By Lenz's law, the electric current induced by a time-varying field is directly proportional to dB/dt. An ambient level of steady rms field amplitude of 3 mG at 60 Hz would translate into a maximum rate of change of about 1 G/sec. Adair has shown that for such levels of steady 60-Hz fields, the voltages induced in single cells do not rise above the level of thermal noise (Adair 1991b). The transient with a dB/dt 400,000 times greater than 1 G/sec may be a much larger signal in terms of cellular response, but not necessarily so. First, the range of frequencies over which any given cell will respond in some way to EMF are unknown. Also, the 400 KG/sec transient lasting only 50 nanoseconds persists for a very much shorter time than any half cycle of the 60-Hz 1G/sec steady periodic. Moreover the much higher frequency broad-band transient must compete with thermal noise over a much greater bandwidth, that of several megahertz, compared to the .05-Hz bandwidth for the 60-Hz steady periodic. Hence, a question remains as to whether sporadic transients can give rise to long-term biological effects. Also, a clear understanding of the pulse-stimulated bone healing process at the cell level has not been obtained.

Transmembrane Voltage-Response Interaction Mechanisms

Electric field interactions

Biological systems have significant heterogeneity in the distribution of electrical properties. For example, the phospholipid rich cell membrane is highly resistive, but the extracellular space with many soluble ions has a low resistance. Even so, the conductivity of living tissue is about 100 million times less than that of copper. Moreover, application of a very large external electric field, *e.g.*, 100 kV/m, is reduced by the conductivity of the body by at least a factor of 100,000 to 1,000,000, so that the tissue field in this case would be less than 1 V/m. For the sake of comparison, the cell membrane has a thickness of 7 nanometers and sustains a transmembrane voltage of about 70 millivolts, so that the electric field experienced by membrane proteins is in the order of 10 million volts per meter. An average field of 1 V/m would appear predominantly across the more resistive elements of the tissue, namely epithelial barriers and cell membranes. Adair has calculated that the resting transmembrane field would be approximately 3000 times the field in the surrounding tissue (Adair 1991). But even so, this does not result in fields comparable to the resting membrane potential.

Channel gating

Channel gating is a well known process that controls fluxes of small ions and molecules across cell membranes. Channels are now intensely studied using physiological and molecular biological techniques. Changes in the transmembrane voltage result in conformational changes of channel proteins that greatly alter the conductance of a channel for the specific ion or molecule normally transported by that channel. This could be an amplification mechanism for small effects.

Electroconformational coupling

Electric coupling of membrane enzymes is believed to occur through deformation of the enzyme as the transmembrane voltage is altered. This alters the enzyme's activity. As a result, electric field energy can be converted to chemical energy, with alterations in the product flux of the enzyme catalyzed reaction (Tsong *et al.* 1986).

Protein protrusion changes

Protein protrusion changes due to changes in the transmembrane field are also generally expected, because the electrical forces on a membrane protein shift as the transmembrane voltage changes. Although not well established, there is experimental support (Balazs 1986), and an initial theoretical exposition (Weaver 1992), of this mechanism. Changes in membrane receptor protrusion could, for example, alter the frequency of binding of hormones.

Membrane deformations

Membrane deformations leading to aqueous indentations and even perforations ("pores", therefore "electroporation") are favored with increasing transmembrane voltage (Chang *et al.* 1992). It is not clear how indentations can lead to alteration of a biochemical pathway. Clearly, formation of "pores" could mediate such changes through transport of ions and molecules across the membrane, but the frequency-of-occurrence of pores due to small changes in the transmembrane voltage is not yet understood. This phenomenon has been clearly demonstrated at high voltages but not at levels relevant to environmental EMF.

Direct electric field interaction mechanisms

Cell deformations

Cell deformations due to an external electric field are also possible (Winterhalter and Helfrich 1988), but the consequences for biochemical pathways has not been established. Moreover, normal deformations associated with moving tissue constitute a background against which electric field-caused deformations compete.

Charge shifts for soluble macromolecules

Charge shifts for soluble macromolecules in the form of spatial shifts of the counterion cloud are expected (Oosawa 1971), but the magnitude of such shifts and their effect on the activity of the macromolecule are not understood.

Natural sources of EMF "noise" and "background"

If external electric and magnetic fields are to cause significant changes in biological systems, it is believed that the field effects must compete successfully with confounding fields of biological origin ("background"), and with confounding fluctuations ("noise") that are present at the microscopic level due to the unavoidable thermal motions of charged particles (Adair 1991). Fundamental fluctuations on the microscopic level of molecules and cells constitute noise against which the effects of external fields can be compared (DeFelice 1981; Fishman and Leuchtag 1990).

Background electric fields in living tissues

Biologically generated electric fields are known to exist, but have been quantitatively characterized primarily in the frequency range DC $< f <$ 3 Hz (Nucitelli 1992). Background electric fields are easily measured from cardiac, neural and muscular sources, and also from electrokinetic effects in moving tissue. The magnitude of these fields as a function of frequency and their distribution within the body are generally not established, so that, for example, it is not known whether there exist "electrically quiet" regions in the human body.

Channel noise

Although termed a "noise," the fluctuations in transmembrane voltage due to membrane ion channels depend on the existence of these biological entities. The channels are associated with an "excess noise" which can be significantly larger than "thermal noise." Presently "channel noise" has been characterized mainly in excitable membranes, so that this source of fluctuation in other types of cells is suspected but not well characterized (Fishman 1981).

Magnetic field background

Strong, microscopically localized magnetic fields may also exist if ferromagnetic materials either contaminate tissue or are endogenously synthesized (Kirschvink *et al.* 1992). Orders of magnitude weaker magnetic fields are expected from biologically generated current (e.g. currents associated with the heart and brain) (Cohen 1975).

Thermal noise

Noise proportional to the temperature, or "kT noise", is present in all systems, and is therefore unavoidable. Thermal noise is associated with the random collisions of ions and molecules, and leads to both mechanical and electrical fluctuations. "Johnson noise" is the associated voltage noise that occurs in all electrically dissipative systems, including the cell membrane, and Nyquist's formula for this thermal electric field allows estimation of the minimum electric field that could cause transmembrane voltage-effects (Weaver and Astumian 1990).

1/f noise

Although not yet completely described by a theory, fluctuations with a 1/f spectrum are ubiquitous in nature, and therefore suspected to be universal (Keshner 1982). These fluctuations are expected to occur in parameters such as the transmembrane voltage, and thus to provide competition for changes in the transmembrane voltage caused by an external electric field.

Shot noise

All microscopic phenomena that involve random, discrete events are subject to the well-known fluctuations in the count, $\Delta N = \pm (N)^{1/2}$, for such events and such fluctuations produce "shot noise" (Villars and Benedek 1974). This includes transport rates and chemical reactions of ions and molecules, so that all molecular processes that involve a small number, N, of events are fundamentally characterized by significant fluctuations. Consideration of the fluctuation (ΔN) magnitude in comparison to the changed flux due to applied EMF provides another constraint on the field magnitude which can cause effects.

Summary

No generally accepted mechanism has emerged by which EMF might produce important cancer effects at the cell or cell-membrane level. Unavoidable thermal fluctuations provide a source of natural fields that define a threshold of electrical noise; if externally-induced fields fall below this threshold their importance as a potential threat to health is difficult to accept. Thermal noise increases with bandwidth and decreases with volume, and some proposed mechanisms attempt to overcome noise by postulating that effects occur in narrow "resonance" bands or that effects require integration over many electrically-connected cells. However, none of the mechanisms that can currently be considered viable possibilities have been unambiguously shown to operate in the biological effects thus far reported. A desirable avenue for progress would be to reexamine some of the more provocative bioeffects (*e.g.*, modification of pineal gland secretions, ion-efflux changes, stimulation of RNA transcription) both by experimental verification and careful theoretical analysis. Physical theory can be used to predict how effects should vary as exposure parameters are changed, and experimentation can determine if the predictions are obeyed.

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APPENDIX 1: SUMMARY OF HEI'S EMF RESEARCH PLANNING EFFORT

HEI's EMF Research Planning Effort: Phase I

In the summer of 1990, the U.S. Environmental Protection Agency (EPA) and representatives of companies of the Large Public Power Council requested that the Health Effects Institute (HEI) consider the development and management of a research program on the biological and potential health effects of electric and magnetic fields (EMF). After further discussion with EPA, state government regulators, and the electric power industry, the HEI Board of Directors instructed the then HEI President, Andrew Sivak, to prepare an evaluation of research efforts on the biological and health effects of electric and magnetic fields and to define research issues that might be addressed by HEI. Two complementary efforts were undertaken to develop an understanding of the state of knowledge and of research needs with respect to health effects of power frequency EMF. The Feasibility Study emphasized biological approaches while the EMF epidemiology Planning Project emphasized epidemiologic approaches.

EMF Feasibility Study

An EMF Feasibility Study Committee, chaired by Dr. Richard Setlow of Brookhaven National Laboratory, was appointed, composed of active investigators in EMF research. Members of the committee are listed in Table A-1. Interested parties from Federal executive departments and agencies, state government agencies, and the electric power industry participated as observers. The committee worked through the spring and summer of 1991 to prepare a set of research recommendations focusing on the identification and replication of biological effects of EMF exposure in simple systems. The goal of the proposed set of studies was to find a system in which biologically effective components of the complex EMF signal from electric power transmission could be identified. Funding for this Feasibility Study was provided by the EPA and the two public power companies, Department of Power and Water, City of Los Angeles, and Seattle City Light.

Table A-1: EMF Feasibility Study Committee Members

Charles F. Ehret, General Chronobionics Incorporated	Jeffrey D. Saffer, Jackson Laboratory (now at Battelle Pacific Northwest Laboratories)
Theodore A. Litovitz, the Catholic University of America	David A. Savitz, University of North Carolina
Martin Misakian, National Institute for Standards and Technology	Richard Setlow, *Chair*, Brookhaven National Laboratories
William Moloney, Brigham and Women's Hospital	Asher R. Sheppard, Jerry L. Pettis Veterans Administration Hospital
Richard Nuccitelli, University of California at Davis	Thomas S. Tenforde, Battelle Pacific Northwest Laboratories
Russel J. Reiter, University of Texas Health Science Center	James C. Weaver, Massachusetts Institute of Technology

EMF Epidemiology Planning Project

During the same period, HEI was responding to another request from EPA--to organize an Environmental Epidemiology Planning Project to explore research needs and opportunities in environmental epidemiology. Working groups were organized on ozone, complex mixtures, methodological issues, and EMF.

The EMF working group was chaired by Dr. David Savitz of the University of North Carolina and comprised of six experts in areas of epidemiologic research and exposure measurements relevant to EMF health effects research. Members of the EMF working group are listed in Table A-2. They wrote a series of papers that summarized and critically assessed the scientific evidence on EMF health effects. They also made recommendations for epidemiologic research that would advance the understanding of human health effects of EMF exposure. These papers, along with those of the other working groups, will be published in *Environmental Health Perspectives* in the summer of 1993. Funding for the project was received from several private sources (American Petroleum Institute, Chemical Manufacturers Association, Electric Power Research Institute, Engine Manufacturers Association, Gas Research Institute, Motor Vehicle Manufacturers Association) as well as from the EPA.

Table A-2: Environmental Epidemiology Planning Project EMF Working Group Members

William T. Kaune, EM Factors	Gary Shaw, March of Dimes California Birth Defects Monitoring Program
Nigel Paneth, Michigan State University	Jack Siemiatycki, Institut Armand-Frappier
David, A. Savitz, *Working Group Leader* University of North Carolina	Richard Stevens, Battelle Pacific Northwest Laboratories

Decisions of the HEI Board of Directors

On February 2, 1992, the HEI Board of Directors met to consider the research recommendations of the EMF Feasibility Study Committee and of the Epidemiology Planning Project EMF working group. The Board concluded that there is a need for scientific research of high quality to address the public concern about possible health effects of EMF exposure and that HEI, upon receipt of adequate funding provided jointly from the government and private sectors, has an obligation to pursue EMF research. The Board authorized formation of an EMF Research Planning Committee that would complete HEI's EMF research planning effort by defining a five-year research program derived from recommendations of both the EMF Feasibility Study Committee and the EMF working group of the Environmental Epidemiology Planning Project. This research program is to be directed to the question: "Does EMF exposure cause human health effects?"

HEI's EMF Planning Effort: Phase II

An EMF Research Planning Committee, chaired by Joseph Brain, Chair, Department of Environmental Health, Harvard School of Public Health, and member of HEI's Research Committee, was approved by the HEI Board of Directors in July 1992, with additional members approved in September 1992. In selecting members of the EMF Research Planning Committee several factors were considered: 1) Inclusion of representatives (including both chairmen) of the Feasibility Study Committee and the EMF working group of the Environmental Epidemiology Planning Project, who would help the committee understand the thinking behind the conclusions of these groups; 2) inclusion of a broad range of expertise with respect to both basic biological approaches and epidemiologic studies; 3) inclusion of some scientists with experience in EMF research and others who have not been involved in EMF research. Table A-3 provides more detailed information about members of the EMF Research Planning Committee.

The EMF Research Planning Committee met three times in the late summer and fall of 1992. The committee considered the information developed by both the Feasibility Study Committee and the EMF working group of the Environmental Epidemiology Planning Project, as well as additional information, in developing the research strategy. The research plan, summarized in Chapter 3 and in the form of a set of Requests for Applications in Chapter 5, combines epidemiologic and experimental approaches.

Table A-3: Members of HEI EMF Research Planning Committee

Name	Institution	Expertise
From HEI Research Committee		
Joseph Brain, Chair	Harvard School of Public Health	Physiology
Leon Gordis	Johns Hopkins University	Epidemiology
John Tukey	Princeton University	Statistics
From HEI Review Committee		
Arthur Upton	New York University Institute of Environmental Medicine	Cancer biology, Environmental medicine
From HEI Feasibility Study Committee		
Richard Setlow	Brookhaven National Laboratories	Physics, Radiation biology
James Weaver	Massachusetts Institute of Technology	Biophysics, EMF research
From HEI Epidemiology Planning Project EMF Working Group		
David Savitz (also on Feasibility Study Com)	University of North Carolina	Epidemiology (EMF)
Other		
John Dowling	Harvard University	Neurobiology
David McCall	Retired from Bell Laboratories	Physical chemistry
Thomas Slaga	University of Texas M. D. Anderson Cancer Center	Cancer biology
D. Lansing Taylor	Carnegie Mellon University	Cell biology
Duncan Thomas	University of Southern California	Statistics
Stephen Umans	Massachusetts Institute of Technology	Electrical engineering

APPENDIX 2: REVIEWERS OF THE EMF REPORT

HEI acknowledges with appreciation the thoughtful comments, both technical and philosophical, of the following reviewers of a draft of this report. Their suggestions and criticisms led to many modifications that improved this report. We point out, though, that the reviewers do not necessarily agree with all of the contents of the report and are, of course, not responsible for them.

Gary Boorman, National Institute of Environmental Health Sciences
Glenn Davis, Oak Ridge Associated Universities
Donald Hornig, Harvard School of Public Health
Robert Kavet, Electric Power Research Institute
Martin Misakian, National Institute of Standards and Technology
Charles Poole, Boston University School of Public Health
Russell Reiter, University of Texas Health Science Center
Jeffrey Saffer, Battelle Pacific Northwest Laboratories
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