NIEHS REPORT on

Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields

Prepared in Response to the 1992 Energy Policy Act (PL 102-486, Section 2118)

NIEHS

National Institute of Environmental Health Sciences
National Institutes of Health

Supported by the NIEHS/DOE

EMF RAPID

NIH Publication No. 99-4493

NIEHS REPORT on

Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields

Prepared in Response to the 1992 Energy Policy Act
(PL 102-486, Section 2118)

National Institute of Environmental Health Sciences
National Institutes of Health

Dr. Kenneth Olden, Director

Prepared by the
NIEHS EMF-RAPID Program Staff

NIH Publication No. 99-4493

Supported by the NIEHS/DOE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

May 4, 1999

Dear Reader:

In 1992, the U.S. Congress authorized the Electric and Magnetic Fields Research and Public Information Dissemination Program (EMF-RAPID Program) in the Energy Policy Act. The Congress instructed the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health and the U.S. Department of Energy (DOE) to direct and manage a program of research and analysis aimed at providing scientific evidence to clarify the potential for health risks from exposure to extremely low frequency electric and magnetic fields (ELF-EMF). The EMF-RAPID Program had three basic components: 1) a research program focusing on health effects research, 2) information compilation and public outreach and 3) a health assessment for evaluation of any potential hazards arising from exposure to ELF-EMF. The NIEHS was directed to oversee the health effects research and evaluation, and the DOE was given the responsibility for overall administration of funding and engineering research aimed at characterizing and mitigating these fields. The Director of the NIEHS was mandated upon completion of the Program to provide this report outlining the possible human health risks associated with exposure to ELF-EMF. The scientific evidence used in preparation of this report has undergone extensive scientific and public review. The entire process was open and transparent. Anyone who wanted “to have a say” was provided the opportunity.

The scientific evidence suggesting that ELF-EMF exposures pose any health risk is weak. The strongest evidence for health effects comes from associations observed in human populations with two forms of cancer: childhood leukemia and chronic lymphocytic leukemia in occupationally exposed adults. While the support from individual studies is weak, the epidemiological studies demonstrate, for some methods of measuring exposure, a fairly consistent pattern of a small, increased risk with increasing exposure that is somewhat weaker for chronic lymphocytic leukemia than for childhood leukemia. In contrast, the mechanistic studies and the animal toxicology literature fail to demonstrate any consistent pattern across studies although sporadic findings of biological effects have been reported. No indication of increased leukemias in experimental animals has been observed.

The lack of connection between the human data and the experimental data (animal and mechanistic) severely complicates the interpretation of these results. The human data are in the "right" species, are tied to "real life" exposures and show some consistency that is difficult to ignore. This assessment is tempered by the observation that given the weak magnitude of these increased risks, some other factor or common source of error could explain these findings. However, no consistent explanation other than exposure to ELF-EMF has been identified.

Epidemiological studies have serious limitations in their ability to demonstrate a cause and effect relationship whereas laboratory studies, by design, can clearly show that cause and effect are possible. Virtually all of the laboratory evidence in animals and humans and most of the mechanistic work done in cells fail to support a causal relationship between exposure to ELF-EMF at environmental levels and changes in biological function or disease status. The lack of consistent, positive findings in animal or mechanistic studies weakens the belief that this association is actually due to ELF-EMF, but it cannot completely discount the epidemiological findings.

The NIEHS concludes that ELF-EMF exposure cannot be recognized at this time as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard. In my opinion, the conclusion of this report is insufficient to warrant aggressive regulatory concern. However, because virtually everyone in the United States uses electricity and therefore is routinely exposed to ELF-EMF, passive regulatory action is warranted such as a continued emphasis on educating both the public and the regulated community on means aimed at reducing exposures. The NIEHS does not believe that other cancers or non-cancer health outcomes provide sufficient evidence of a risk to currently warrant concern.

The interaction of humans with ELF-EMF is complicated and will undoubtedly continue to be an area of public concern. The EMF-RAPID Program successfully contributed to the scientific knowledge on ELF-EMF through its support of high quality, hypothesis-based research. While some questions were answered, others remain. Building upon the knowledge base developed under the EMF-RAPID Program, meritorious research on ELF-EMF through carefully designed, hypothesis-driven studies should continue for areas warranting fundamental study including leukemia. Recent research in two areas, neurodegenerative diseases and cardiac diseases associated with heart rate variability, have identified some interesting and novel findings for which further study is ongoing.

Advocacy groups have opposing views concerning the health effects of ELF-EMF. Some advocacy groups want complete exoneration and others want a more serious indictment. Our conclusions are prudent and consistent with the scientific data. I am satisfied with the report and believe it provides a pragmatic, scientifically-driven basis for any further regulatory review.

I am pleased to transmit this report to the U.S. Congress.

Sincerely,

Kenneth Olden, Ph.D.
Director

NIEHS EMF-RAPID PROGRAM STAFF

Gary A. Boorman, D.V.M., Ph.D., Associate Director for Special Programs, Environmental Toxicology Program and Director, EMF-RAPID Program

Naomi J. Bernheim, M.S., Biologist, Office of Special Programs, Environmental Toxicology Program and Program Assistant, EMF-RAPID Program

Michael J. Galvin, Ph.D., Health Scientist Administrator, Division of Extramural Research and Training and Extramural Program Administrator, EMF-RAPID Program

Sheila A. Newton, Ph.D., Director, Office of Policy, Planning and Evaluation

Fred M. Parham, Ph.D., Staff Scientist, Laboratory of Computational Biology and Risk Analysis

Christopher J. Portier, Ph.D., Associate Director for Risk Assessment, Environmental Toxicology Program; Chief, Laboratory of Computational Biology and Risk Analysis; and Coordinator, EMF Hazard Evaluation

Mary S. Wolfe, Ph.D., Associate Coordinator, EMF Hazard Evaluation, Environmental Toxicology Program

ACKNOWLEDGEMENTS

This report would not have been possible without the concerted and generous help of literally hundreds of research scientists. Many of the scientists who wrote the articles, which are cited in this report, attended our science review symposia where their research was carefully evaluated and critiqued. Their patience with our questions and their professional attitude in evaluating their own work was extraordinary and is greatly appreciated. We are also indebted to the many scientists from outside of the electric and magnetic fields (EMF) research community who participated in our symposia and spent time and effort evaluating these data on our behalf; this provides a clear example of the dedication of scientists concerned about health issues.

Special thanks are extended to the 30 scientists who attended the Working Group Meeting in June 1998. Their hard work and conscientious effort led to one of the most concise and clear reviews of the extremely low frequency (ELF) EMF literature ever developed. The thousands of man-hours extended by this group in such a short period of time provided us with a background document on ELF-EMF health risks that made this report a much simpler task. We wish especially to thank Dr. Arnold Brown for attending our public meetings on the Working Group Report; his extensive experience and insightful comments helped to make these meetings a great success. We would also like to thank Dr. Brown and Dr. Paul Gailey for reviewing this report prior to its release and Mr. Fred Dietrich for advising us on exposure issues during the preparation of this document. Finally we would like to acknowledge the U.S. Department of Energy as our partner in the EMF-RAPID Program and its EMF program officer, Dr. Imre Gyuk.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Introduction

Electrical energy has been used to great advantage for over 100 years. Associated with the generation, transmission, and use of electrical energy is the production of weak electric and magnetic fields (EMF). In the United States, electricity is usually delivered as alternating current that oscillates at 60 cycles per second (Hertz, Hz) putting fields generated by this electrical energy in the extremely low frequency (ELF) range.

Prior to 1979 there was limited awareness of any potential adverse effects from the use of electricity aside from possible electrocution associated with direct contact or fire from faulty wiring. Interest in this area was catalyzed with the report of a possible association between childhood cancer mortality and proximity of homes to power distribution lines. Over the next dozen years, the U.S. Department of Energy (DOE) and others conducted numerous studies on the effects of ELF-EMF on biological systems that helped to clarify the risks and provide increased understanding. Despite much study in this area, considerable debate remained over what, if any, health effects could be attributed to ELF-EMF exposure.

In 1992, the U.S. Congress authorized the Electric and Magnetic Fields Research and Public Information Dissemination Program (EMF-RAPID Program) in the Energy Policy Act (PL 102-486, Section 2118). The Congress instructed the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health and the DOE to direct and manage a program of research and analysis aimed at providing scientific evidence to clarify the potential for health risks from exposure to ELF-EMF. The EMF-RAPID Program had three basic components: 1) a research program focusing on health effects research, 2) information compilation and public outreach and 3) a health assessment for evaluation of any potential hazards arising from exposure to ELF-EMF. The NIEHS was directed to oversee the health effects research and evaluation and the DOE was given the responsibility for overall administration of funding and engineering research aimed at characterizing and mitigating these fields. The Director of the NIEHS was mandated upon completion of the Program to provide a report outlining the

possible human health risks associated with exposure to ELF-EMF. This document responds to this requirement of the law.

This five-year effort was signed into law in October 1992 and provisions of this Act were extended for one year in 1997. The Program ended December 31, 1998. The EMF-RAPID Program was funded jointly by Federal and matching private funds and has been an extremely successful Federal/private partnership with substantial financial support from the utility industry. The NIEHS received $30.1 million from this program for research, public outreach, administration and the health assessment evaluation of ELF-EMF. In addition to EMF-RAPID Program funds from the DOE, the NIEHS contributed $14.5 million for support of extramural and intramural research including long-term toxicity studies conducted by the National Toxicology Program.

NIEHS Conclusion

The scientific evidence suggesting that ELF-EMF exposures pose any health risk is weak. The strongest evidence for health effects comes from associations observed in human populations with two forms of cancer: childhood leukemia and chronic lymphocytic leukemia in occupationally exposed adults. While the support from individual studies is weak, the epidemiological studies demonstrate, for some methods of measuring exposure, a fairly consistent pattern of a small, increased risk with increasing exposure that is somewhat weaker for chronic lymphocytic leukemia than for childhood leukemia. In contrast, the mechanistic studies and the animal toxicology literature fail to demonstrate any consistent pattern across studies although sporadic findings of biological effects (including increased cancers in animals) have been reported. No indication of increased leukemias in experimental animals has been observed.

The lack of connection between the human data and the experimental data (animal and mechanistic) severely complicates the interpretation of these results. The human data are in the “right” species, are tied to “real-life” exposures and show some consistency that is difficult to ignore. This assessment is tempered by the observation that given the weak magnitude of these increased risks, some other factor or common source of error could explain these findings. However, no consistent explanation other than exposure to ELF-EMF has been identified.

Epidemiological studies have serious limitations in their ability to demonstrate a cause and effect relationship whereas laboratory studies, by design, can clearly show that cause and effect are possible. Virtually all of the laboratory evidence in animals and humans and most of the mechanistic work done in cells fail to support a causal relationship between exposure to ELF-EMF at environmental levels and changes in biological function or disease status. The lack of consistent, positive findings in animal or mechanistic studies weakens the belief that this

association is actually due to ELF-EMF, but it cannot completely discount the epidemiological findings.

The NIEHS concludes that ELF-EMF exposure cannot be recognized as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard. In our opinion, this finding is insufficient to warrant aggressive regulatory concern. However, because virtually everyone in the United States uses electricity and therefore is routinely exposed to ELF-EMF, passive regulatory action is warranted such as a continued emphasis on educating both the public and the regulated community on means aimed at reducing exposures. The NIEHS does not believe that other cancers or non-cancer health outcomes provide sufficient evidence of a risk to currently warrant concern.

The interaction of humans with ELF-EMF is complicated and will undoubtedly continue to be an area of public concern. The EMF-RAPID Program successfully contributed to the scientific knowledge on ELF-EMF through its support of high quality, hypothesis-based research. While some questions were answered, others remain. Building upon the knowledge base developed under the EMF-RAPID Program, meritorious research on ELF-EMF through carefully designed, hypothesis-driven studies should continue for areas warranting fundamental study including leukemia. Recent research in two areas, neurodegenerative diseases and cardiac diseases associated with heart rate variability, have identified some interesting and novel findings for which further study is ongoing.

Background

Program Oversight and Management

The 1992 Energy Policy Act created two committees to provide guidance and direction to this program. The first, the Interagency Committee (IAC), was established by the President of the United States and composed of representatives from the NIEHS, the DOE and seven other Federal agencies with responsibilities related to ELF-EMF. This group receives the report from the NIEHS Director and must prepare its own report for Congress. The IAC had responsibility for developing a strategic research agenda for the EMF-RAPID Program, facilitating interagency coordination of Federal research activities and communication to the public and monitoring and evaluating the Program.

The second committee, the National EMF Advisory Committee (NEMFAC), consisted of representatives from public interest groups, organized labor, state governments and industry. This group was involved in all aspects of the EMF-RAPID Program providing advice and critical review to the DOE and the NIEHS on the design and implementation of the EMF-RAPID Program's activities.

ELF-EMF Health Effects Research

The EMF-RAPID Program's health effects research initiative relied upon accepted principles of hazard identification and risk assessment to establish priorities. All studies supported by the NIEHS and the DOE under this program were selected for their potential to provide solid, scientific data on whether ELF-EMF exposure represents a human health hazard, and if so, whether risks are increased under exposure conditions in the general population. Research efforts did not focus on epidemiological studies (i.e. those in the human population) because of time constraints and the number of ongoing, well-conducted studies. The NIEHS health effects research program focused on mechanistic, cellular and laboratory studies in the areas of neurophysiology, behavior, reproduction, development, cellular research, genetic research, cancer and melatonin. Mechanistic, cellular and laboratory studies are part of the overall criteria used to determine causality in interpreting epidemiological studies. In this situation, the most cost-effective and efficient use of the EMF-RAPID Program's research funds was clearly for trying to clarify existing associations identified from population studies. The DOE research initiatives focused on assessment of exposure and techniques of mitigation.

The EMF-RAPID Program through the combined efforts of the NIEHS and the DOE radically changed and markedly improved the quality of ELF-EMF research. This was accomplished by providing biological and engineering expertise to investigators and emphasizing hypothesis-driven, peer-reviewed research. Four regional facilities were also set-up where state-of-the-art magnetic field exposure systems were available for in-house and outside investigators to conduct mechanistic research. The EMF-RAPID Program through rigorous review and use of multi-disciplinary research teams greatly enhanced the understanding of the interaction of biological systems with ELF-EMF.

Information Dissemination and Public Outreach

The EMF-RAPID Program provided the public, regulated industry and scientists with useful, targeted information that addressed the issue of uncertainty regarding ELF-EMF health effects. Two booklets, a question and answer booklet on ELF-EMF and a layman's booklet addressing ELF-EMF in the workplace, were published. A telephone information line for ELF-EMF was available where callers could request copies of ELF-EMF documents and receive answers to standard questions from operators. The NIEHS also developed a web-site for the EMF-RAPID Program where all of the Program's documents are on-line and links are available to other useful sites on ELF-EMF. Efforts were made to include the public in EMF-RAPID Program activities through sponsorship of scholarships to meetings; holding open, scientific workshops; and setting aside a two-month period for public comment and review on ELF-EMF and the workshop reports. In addition, the NIEHS sponsored attendance of NEMFAC

members at relevant scientific meetings and at each of the public comment meetings.

Health Risk Assessment of ELF-EMF Exposure

In preparation of the NIEHS Director's Report, the NIEHS developed a process to evaluate the potential health hazards of ELF-EMF exposure that was designed to be open, transparent, objective, scholarly and timely under the mandate of the 1992 Energy Policy Act. The NIEHS used a three-tiered strategy for collection and evaluation of the scientific information on ELF-EMF that included: 1) three science review symposia for targeted ELF-EMF research areas, 2) a working group meeting and 3) a period of public review and comment. Each of the three symposia focused on a different, broad area of ELF-EMF research: mechanistic and cellular research (24-27 March 1997, Durham, NC), human population studies (12-14 January 1998, San Antonio, TX) and laboratory human and clinical work (6-9 April 1998, Phoenix, AZ). These meetings were aimed at including a broad spectrum of the research community and the public in the evaluation of ELF-EMF health hazards, identifying key research findings and providing opinion on the quality of this research. Discussion reports from small discussion groups held for specific topics were prepared for each meeting.

Following the symposia, a working group meeting (16-24 June 1998, Brooklyn Park, MN) was held where a scientific panel reviewed historical and novel evidence on ELF-EMF and determined the strength of the evidence for human health and biological effects. Stakeholders and the public attended this meeting and were given the opportunity to comment during the process. The Working Group conducted a formal, comprehensive review of the literature for research areas identified from the symposia as being important to the assessment of ELF-EMF-related biological or health effects. Separate draft documents covering areas of animal carcinogenicity, animal non-cancer findings, physiological effects, cellular effects, theories and human population studies (epidemiology studies) in children and adults for both occupational and residential ELF-EMF exposures were rewritten into a single book. The Working Group characterized the strength of the evidence for a causative link between ELF-EMF exposure and disease in each category of research using the criteria developed by the International Agency for Research on Cancer (IARC).

The IARC criteria fall into four basic categories: sufficient, limited, inadequate and evidence suggesting the lack of an effect. After critical review and discussion, members of the Working Group were asked to determine the categorization for each research area; the range of responses reflected the scientific uncertainty in each area. A majority of the Working Group members concluded that childhood leukemia and adult chronic lymphocytic leukemia from occupational exposure were areas of concern. For other cancers and for non-cancer health endpoints, the Working Group categorized the experimental data as

providing much weaker evidence or no support for effects from exposure to ELF-EMF.

Following the Working Group Meeting, the NIEHS established a formal review period for solicitation of comments on the symposia and Working Group reports. The NIEHS hosted four public meetings (14-15 September 1998, Tucson, AZ; 28 September, Washington, DC; 1 October 1998, San Francisco, CA; and 5 October 1998, Chicago, IL) where individuals and groups could voice their opinions; the meetings were recorded and transcripts prepared. In addition, the NIEHS received 178 written comments that were also reviewed in preparation of this report. The remarks that NIEHS received covered many areas related to ELF-EMF and provided insight about areas of concern on behalf of the public, researchers, regulatory agencies and industry.

INTRODUCTION

Electricity is used to the benefit of people all over the world. Wherever electricity is generated, transmitted or used, electric fields and magnetic fields are created. These fields are a direct consequence of the presence and/or motion of electric charges. It is impossible to generate and use electrical energy without creating these fields; hence they are an inevitable consequence of our reliance on this form of energy. Electrical energy is generally supplied as alternating current where the electricity flows in one direction and then in the other to complete a cycle. The number of cycles completed in a fixed period of time (such as a second) is known as the frequency and is generally measured in units of Hertz (Hz), which are cycles per second. In the United States, electricity is usually delivered as 60 Hz alternating current; 50 to 60 Hz cycles are generally referred to as the power-line frequency of alternating current electricity. Just as alternating current electricity has a frequency, so do the associated electric and magnetic fields (EMF). Thus, 60 Hz alternating current electricity will generate a 60 Hz electric field and a 60 Hz magnetic field. EMF with cycle frequencies of greater than 3 Hz and less that 3000 Hz is generally referred to as extremely low frequency (ELF) EMF. In addition to magnetic fields associated with electricity, the earth also has a static magnetic field (frequency of 0 Hz) that varies by location from approximately 30 to 50 μT.

Electricity has been used, to great advantage, for 100 years and with this widespread use, there has been limited awareness of any potential adverse health effects other than effects caused by direct contact such as electrocution or by faulty wiring such as fire. Research into potential health effects caused by the ELF-EMF resulting from indirect exposure to electrical energy has been underway for several decades. The catalyst that sparked increased study in this area of research was the 1979 report by Wertheimer and Leeper (*1*) that children living near power lines had an increased risk for developing cancer. Since that initial finding, there have been numerous studies of human populations, animals and isolated cells aimed at clarification of the observations of Wertheimer and Leeper and others. Despite this multitude of research, considerable debate remains over what, if any, health effects can be attributed to ELF-EMF exposure.

In 1992, under the Energy Policy Act (PL 102-486, Section 2118), the U.S. Congress instructed the National Institute of Environmental Health Sciences

(NIEHS), National Institutes of Health and the U.S. Department of Energy (DOE) to direct and manage a program of research and analysis aimed at providing scientific evidence to clarify the potential for health risks from exposure to ELF-EMF. This resulted in formation of the EMF Research and Public Information Dissemination Program (EMF-RAPID Program). The EMF-RAPID Program had three basic components: 1) a research program focusing on health effects research primarily through mechanistic studies of ELF-EMF and engineering research targeting measurement, characterization and management of ELF-EMF; 2) information compilation and dissemination through brochures, public outreach and an ELF-EMF information line for communicating with the public; and 3) a health assessment including an analysis of the research data aimed at summarizing the strength of the evidence for evaluation of any hazard possibly arising from exposure to ELF-EMF. The NIEHS was directed to oversee the health effects research and evaluation and the DOE was given responsibility for engineering research aimed at characterizing and mitigating these fields. Under the Energy Policy Act, the Director of the NIEHS is mandated upon completion of the EMF-RAPID Program to provide a report outlining the possible human health risks associated with exposure to ELF-EMF. This document responds to this requirement of the law.

Funding

The EMF-RAPID Program was funded jointly by Federal and matching private funds; through fiscal year 1998, authorized funding for this program was approximately $46 million. Administration of funding for the EMF-RAPID Program was the responsibility of the DOE with funds for NIEHS-sponsored program activities transferred from the DOE to the NIEHS. The EMF-RAPID Program has been an extremely successful Federal/private partnership with substantial financial support from the utility industry. The NIEHS received $30.1 million from this program for research, public outreach, administration and the health assessment evaluation of ELF-EMF. Of the funds received, the NIEHS spent the majority (89%) for research through grants and contracts. The remainder was used for public outreach/administration (2%) and the health risk evaluation (9%). In addition to EMF-RAPID Program funds from the DOE, the NIEHS contributed $14.5 million for support of extramural grants and contracts and intramural research as well as long-term toxicity studies conducted by the National Toxicology Program.

Oversight and Program Management

The 1992 Energy Policy Act created two committees that have provided guidance and direction to the EMF-RAPID Program. One committee is the Interagency Committee (IAC) and is composed of representatives from NIEHS, DOE and the seven Federal agencies (listed below) with responsibilities related to ELF-EMF:

- Department of Defense
- Department of Transportation
- Environmental Protection Agency
- Federal Energy Regulatory Commission
- National Institute of Standards and Technology
- Occupational Safety and Health Administration
- Rural Electrification Administration

The IAC, which was established by the President of the United States, will receive the report from the NIEHS Director, and must prepare its own report for Congress. The IAC had responsibility for developing a strategic research agenda for the Program, making recommendations for coordination of Federal research activities and communication to the public and monitoring and evaluating the EMF-RAPID Program.

The second committee is the National Electric and Magnetic Fields Advisory Committee (NEMFAC) that consists of representatives from public interest groups, organized labor, state governments and industry. This group advised DOE and NIEHS on design and implementation of the EMF-RAPID Program and provided input and recommendations to the IAC. The NEMFAC was involved in all aspects of the EMF-RAPID Program, providing critical public review throughout the process of evaluating evidence for potential health effects.

ELF-EMF Health Effects Research

The research initiative sponsored under the EMF-RAPID Program's health effects research program relied on the accepted principles of hazard identification and risk assessment to establish priorities. All studies supported by the NIEHS and the DOE under this program were selected for their potential to provide solid, scientific data on whether ELF-EMF exposure represents a human health hazard, and if so, whether risks are increased under exposure conditions in the general population.

Research efforts did not focus on epidemiological studies (i.e. those in the human population) because of time constraints and the number of ongoing, well-conducted studies. The NIEHS health effects research program focused on

mechanistic, cellular and laboratory studies in the areas of neurophysiology, behavior, reproduction, development, cellular research, genetic research, cancer and melatonin. Information about the health effects research projects that were supported by the NIEHS is compiled into a booklet (*2*). Mechanistic, cellular and laboratory studies are part of the overall criteria used to determine causality in interpreting epidemiological studies. In this situation, the most cost-effective and efficient use of the EMF-RAPID Program's research funds was clearly for trying to clarify existing associations identified from population studies. The DOE research initiatives focused on assessment of exposure and techniques of mitigation. Presentation of the DOE-sponsored research was presented at an engineering review symposium in April 1998 (*3*).

The EMF-RAPID Program through the combined efforts of the NIEHS and the DOE radically changed and markedly improved the quality of ELF-EMF research. This was accomplished by providing biological and engineering expertise to investigators and emphasizing hypothesis-driven, peer-reviewed research. These efforts resulted in better exposure systems, better documentation of the exposure systems and more complete reporting of the exposures in the literature. The EMF-RAPID Program through rigorous review and use of multi-disciplinary research teams greatly enhanced the understanding of the interaction of biological systems with ELF-EMF.

The EMF-RAPID Program, in a collaborative effort between the DOE and NIEHS, established four regional ELF-EMF exposure facilities where state-of-the-art magnetic field exposures could be conducted. Two facilities were located in DOE laboratories (Pacific Northwest Laboratories, Richland, WA and Oak Ridge National Laboratories, Oak Ridge, TN) while NIEHS oversaw ELF-EMF exposure facilities at the Food and Drug Administration (FDA, Rockville, MD) and at the National Institute for Occupational Safety and Health (NIOSH, Cincinnati, OH). During the course of the EMF-RAPID Program, these facilities focused on in-house mechanistic studies, and advances were made in conducting studies that have minimal bias. These centers also served as sites for investigators who wanted to conduct preliminary investigations without the expense of having to build their own exposure facilities.

Information Dissemination and Public Outreach

One of the three major components of the EMF-RAPID Program is dissemination of information on ELF-EMF. Both NIEHS and DOE share responsibility for the communication aspects of the program and jointly developed an outreach plan and oversaw its implementation. Both the IAC and NEMFAC reviewed information materials developed under this program.

The EMF-RAPID Program provided information to any interested parties about possible human health effects of ELF-EMF, the types and extent of human

exposure, technologies for measuring and characterizing fields, methods for assessing and managing exposure and other topics specified in the legislation. The Program strove to provide the public, regulated industry and scientists with useful, targeted information based upon established risk communication principles (*4, 5*). The communication program candidly addressed the issue of scientific uncertainty regarding ELF-EMF health effects and the overall complexity of the ELF-EMF issue, while providing information in a format appropriate for a variety of audiences.

The EMF-RAPID Program developed a question and answer booklet on ELF-EMF that was published in January 1995. This booklet is easy to read and has become very popular with more than 100,000 copies distributed nationwide. Because of the diversity of the U.S. population and the needs of the Spanish speaking community, a Spanish version of this booklet was also developed and more than 10,000 copies have been distributed. The EMF-RAPID Program, in conjunction with NIOSH, also developed and published a booklet entitled "EMF in the Workplace" in September 1996. This publication provides basic information in lay terms about ELF-EMF exposures in the workplace.

The EMF-RAPID Program made available an ELF-EMF public information line where interested parties could call with questions about ELF-EMF and request information. The U.S. Environmental Protection Agency (EPA) initiated this telephone line with funds from the EMF-RAPID Program in 1995 and transferred its oversight to the NIEHS in August 1997. The information line was open 10 hours a day for five days a week and received approximately 380 calls per month. Callers were provided copies of the ELF-EMF public information documents, and the operators were trained to give accurate responses to standard questions.

The NIEHS took the lead in developing the EMF-RAPID Program web-site (www.niehs.nih.gov/emfrapid/home.htm) that began operation on October 1, 1996. All of the EMF-RAPID Program's documents are available online in their entirety including the public information booklets described earlier, research information, the NIEHS Science Review Symposia reports (described below), the NIEHS Working Group Report (described below) and the public meeting comments received on these reports. There are links to other useful sites relating to ELF-EMF including the four regional exposure facilities. This site receives an average of 500 visits per day from approximately 21 countries. The requests come from individuals as well as commercial, educational, government, military and non-profit organizations.

The NIEHS actively recruited the inclusion of concerned citizens into the EMF-RAPID Program in several ways. Two scholarships were created to allow representatives from two citizen groups to attend an annual research review meeting conducted by the DOE. All EMF-RAPID Program sponsored meetings

were open to any interested parties and public comments at them were welcome. The NIEHS also set aside a two-month period for public comment and review on ELF-EMF and the meeting reports. In addition, costs for NEMFAC members to attend the Science Review Symposia, the chair of NEMFAC to attend the Working Group Meeting and one member of the NEMFAC to attend each of the public meetings were also provided. Finally, in cooperation with the EPA, a workshop was held in May 1995 to give policymakers current information on ELF-EMF and provide them with access to experts knowledgeable in communicating information on this topic.

After the EMF-RAPID Program ends, the documents from this program will continue to be publicly available through the National Technical Information Service. Also, copies of these materials are located in the Library of Congress and libraries of the EPA regional offices, the NIEHS and the National Academy of Sciences.

Literature Review and Health Risk Assessment

Recent scientific panels on methods for health risk assessment (*4-6*) have advocated open, participatory processes for the evaluation of health risks from environmental exposures. The strategy developed by the NIEHS for collecting and evaluating research information in preparation of the Director's report followed many of the recommendations of these recent panels. The resulting program, reviewed and accepted by both the IAC and NEMFAC, provides a blueprint for future risk assessments and is novel in the risk assessment community (*7, 8*). The program focused on a broad-based, scientific debate covering all of the diverse fields represented in ELF-EMF research and included scientists from both within and outside the EMF community. In addition, an aggressive outreach program was used to invite and include all interested parties in the debate. This program consisted of three basic tiers:

- A series of three science review symposia focused on 1) mechanistic research, 2) epidemiological research and 3) laboratory research (animals and humans). At each meeting participants considered the quality and reproducibility of the scientific evidence, suggested what literature provides the strongest scientific evidence for making a decision, suggested additional avenues for research and provided opinions on whether or not there is support for a causal linkage between exposure to ELF-EMF and an associated biological or health effect.
- A working group meeting where a select panel of scientists critically evaluated the entirety of research evidence on ELF-EMF health effects and determined the strength of the evidence for human health effects.
- A period of public review and comment on the reports from the symposia and working group prior to their use by NIEHS in preparing this report.

The Science Review Symposia were designed as open, public workshops aimed at including a broad spectrum of the research community in evaluating ELF-EMF health hazards. To minimize bias, outstanding research scientists from outside of the ELF-EMF research community were included in all reviews; these scientists provided an objective evaluation of the experimental methods used and the hypotheses underlying many of the studies. These EMF and non-EMF scientists were given the task of identifying key research findings and providing opinion on the quality of the research. The workshops were held 24-27 March 1997 in Durham, NC; 12-14 January 1998 in San Antonio, TX; and 6-9 April 1998 in Phoenix, AZ. Over 100 individuals attended each meeting and included representatives from the public, stakeholders, regulatory agencies, NEMFAC and IAC as well as scientists from varied disciplines including, but not limited to, medicine, epidemiology, molecular and cellular biology, physics, engineering, statistics, toxicology, pathology and neurobiology. The format for these meetings included plenary sessions with overview lectures to familiarize attendees about research findings and issues for specific ELF-EMF topics and small breakout discussion groups. The breakout group sessions (composed of 25-30 attendees per group) provided time for in-depth discussions on the quality and reproducibility of ELF-EMF research findings and possible linkages with health effects. The rapporteurs and facilitator for each session prepared a short report that was reviewed by attendees of that breakout group. The breakout group reports from each science review symposium are available as printed documents (*9-11*) or on the EMF-RAPID Program web-site.

The Working Group Meeting was held 16-24 June 1998 in Brooklyn Park, MN. Prior to this meeting, a group of select scientists was given the task of conducting a formal, comprehensive review of the literature for research areas identified from the symposia as being important to the assessment of ELF-EMF-related biological or health effects. At the Working Group Meeting, the panel of 30 international scientists, both from within and outside the field of ELF-EMF research, critically evaluated and rewrote the draft chapters into a single book (*12*). In addition to reviewing the literature, the Working Group also characterized the strength of the evidence in each category of research using the criteria developed by the International Agency for Research on Cancer (IARC). These criteria are given in Appendix A of the Working Group Report. The literature included in the report was limited to published, cited findings or novel work being prepared for publication that could be peer-reviewed by the Working Group members.

Following the Working Group Meeting, the NIEHS established a formal review period of 10 August – 9 October 1998 to receive comments on the Working Group Report and symposia reports. During this period, the NIEHS hosted four public meetings (14-15 September 1998, Tucson, AZ; 28 September 1998, Washington, DC; 1 October 1998, San Francisco, CA; and 5 October 1998, Chicago, IL) where individuals and groups could voice their comments orally and/or in writing to NIEHS officials and other scientists involved with preparation of this report. The meetings were recorded and a transcript was prepared.

Attendance at the public meetings varied from 32 to 101 attendees per meeting. Formal comments (8 to 21 per meeting) were provided by various groups including the general public, researchers, utility industry, advocacy groups and state governmental agencies. Written comments, independent of oral presentations, were also solicited during the comment period; 178 entries from individuals and groups were received. These transcripts and written comments were used by the NIEHS in preparing this report.

DO ELECTRIC AND MAGNETIC FIELDS POSE A HEALTH RISK?

The scientific evidence suggesting that ELF-EMF exposures pose any health risk is weak. The strongest evidence for health effects comes from associations observed in human populations with two forms of cancer: childhood leukemia and chronic lymphocytic leukemia in occupationally exposed adults. While the support from individual studies is weak, the epidemiological studies demonstrate, for some methods of measuring exposure, a fairly consistent pattern of a small, increased risk with increasing exposure that is somewhat weaker for chronic lymphocytic leukemia than for childhood leukemia. In contrast, the mechanistic studies and the animal toxicology literature fail to demonstrate any consistent pattern across studies although sporadic findings of biological effects (including increased cancers in animals) have been reported. No indication of increased leukemias in experimental animals has been observed.

The lack of connection between the human data and the experimental data (animal and mechanistic) severely complicates the interpretation of these results. The human data are in the "right" species, are tied to "real-life" exposures and show some consistency that is difficult to ignore. This assessment is tempered by the observation that given the weak magnitude of these increased risks, some other factor or common source of error could explain these findings. However, no consistent explanation other than exposure to ELF-EMF has been identified.

Epidemiological studies have serious limitations in their ability to demonstrate a cause and effect relationship whereas laboratory studies, by design, can clearly show that cause and effect are possible. Virtually all of the laboratory evidence in animals and humans and most of the mechanistic work done in cells fail to support a causal relationship between exposure to ELF-EMF at environmental levels and changes in biological function or disease status. The lack of consistent, positive findings in animal or mechanistic studies weakens the belief that this association is actually due to ELF-EMF, but it cannot completely discount the epidemiological findings.

The NIEHS concludes that ELF-EMF exposure cannot be recognized as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard. In our opinion, this finding is insufficient to warrant aggressive regulatory concern. However, because virtually everyone in the United States uses electricity and therefore is routinely exposed to ELF-EMF, passive regulatory action is warranted such as a continued emphasis on educating both the public and the regulated community on means aimed at reducing exposures. This is described in greater detail in the section, *Recommended Actions*. The NIEHS does not believe that other cancers or non-cancer health outcomes provide sufficient evidence of a risk to currently warrant concern.

Scientific Evidence Supporting This Conclusion

The reports from the Science Review Symposia (*9-11*) and the Working Group (*12*) provide detailed reviews of the literature in this area of science. What follows is a brief synopsis of this evidence. The reader should refer to the individual reports for greater detail.

Background on the Limitations of Epidemiology Studies

Epidemiological studies are used to investigate the associations between health effects and exposure to a presumed disease agent. A well-designed and conducted epidemiological study involves several steps including identification of a study population, definition of the exposure to be studied, choice of the type of study to conduct (e.g. cohort study versus case-control study) and description of the period over which the exposure is relevant. All of these factors influence the quality of a study and the limits that must be placed on interpretation of a study's findings.

In carefully controlled laboratory and clinical investigations, study subjects are typically assigned to a treatment or exposure regimen. In epidemiological investigations, the inability to randomly assign exposures means that investigators must design their study so that the individuals who develop the disease of interest (cases) resemble the individuals who are disease-free (controls) in all aspects except for exposure; this is intended to limit possible bias. Bias due to improper selection of cases and controls is introduced if exposure is related to characteristics that would make cases more or less likely to be sampled than controls, or once sampled, to participate.

In the Nordic countries, comprehensive national population registries are generally used for selecting controls. If all persons are listed in these population registries and participation rates are high, bias due to selection of improper controls is unlikely even if exposure is related to participation. In countries such as the United States where population registries do not exist, other methods must be used to study rare diseases like leukemia for which existing cohort studies are

inadequate. These methods lead to difficulties in identifying, contacting and recruiting controls that match the cases in all aspects other than exposure. For example, controls are sometimes identified through stratified random sampling of individual telephone numbers (random-digit dialing). Random-digit dialing may not properly identify controls of low socioeconomic status that do not have telephones; this could bias the results found in studies of childhood leukemias (*13*).

It is also possible to introduce bias through the selection of cases. For example, case selection bias may occur in studies that are based on mortality records (death certificates) if the survival rates of the exposed and unexposed subjects differ. This may occur if, for example, the exposure is related to socioeconomic status, and different socioeconomic groups have different survival rates for the studied disease (this might be due to a difference in the ability of cases to receive medical care). In addition, for diseases that are easily cured or allow patients to survive with the disease for a long period of time, persons who contract the disease and are treated properly may die of other causes and not appear as cases.

The inability to randomly assign exposures also introduces the possibility of confounding. Confounding occurs when the exposure of interest is associated with another factor that can increase (or decrease) the risk of getting the disease of interest (*14*). For example, smoking increases the risk of oral cancer; smoking is also associated with alcohol consumption, and there is a greater proportion of smokers among alcohol drinkers than among non-drinkers. Because smoking increases the risk of oral cancer and alcohol drinkers are more likely to smoke than non-drinkers are, alcohol drinkers will have a greater risk of oral cancer simply as a consequence of the greater percentage of smokers among alcohol drinkers. Thus, any study showing an increased risk of oral cancer associated with alcohol drinking will overstate that risk (resulting in a positive bias) if the effect of smoking is not carefully evaluated. Confounding can produce bias in either direction, artificially increasing or decreasing risks, depending on the direction of the association between the exposure, the disease and the confounder. When known, confounding can be controlled through statistical methods. Because there are very few known causes of childhood leukemias and chronic lymphocytic leukemia, it is difficult to identify and control potential confounders in these studies.

Another limitation of epidemiological studies is that exposure occurs through the natural course of events rather than being assigned and controlled by the investigator. Thus, a determination of the degree of exposure can be incorrect leading to what is known as “exposure misclassification.” Exposure misclassification may distort measures of association observed in a study. For example, in epidemiological studies aimed at exposures received on the job (occupational studies), it is common to define exposures by the type of job a person performs. Errors may occur in assigning job titles or the jobs themselves may have markedly different exposures for different individuals. It is also

possible that the exposure assignment may differ for diseased and non-diseased subjects. Information on exposure can be obtained either prospectively (before the disease has occurred) or retrospectively (after the disease has occurred). In the case where exposure is determined prior to disease onset, there is a reduced potential for misclassification of the exposure. In the case where exposure is determined after the onset of the disease, especially where it is obtained from questioning individuals with the disease, the recall of exposure may be influenced by the fact that the patient has a disease and is influenced by previous descriptions of potential causes of that disease.

Epidemiological studies have used various methods for estimating past ELF-EMF exposure to provide scientific evidence concerning the possibility of health effects from exposure to ELF-EMF. Residential exposures to ELF-EMF have been conducted in five basic ways: wire codes that are essentially based upon distance to major structures used for delivering electrical energy (e.g. high tension power lines and transformers); calculated magnetic fields that are based upon a theoretical calculation of the magnetic field emitted by certain types of power lines using historical electrical loads on those lines; spot measurements that generally give a single, instantaneous measurement of the magnitude of the magnetic field in one or more spots in a residence; average measured fields that are essentially spot measurements taken repeatedly every few seconds for 24 hours and averaged over time; and personal average measured fields where the subject wears a monitor and measurements are taken repeatedly every few seconds for 48 hours and averaged over time.

The validity of individual exposure assessment methods has been examined and each has its limitations (*12, 15-20*). Wire codes and calculated fields have the advantage of remaining fairly consistent over time making them more likely to be correctly determined during the time of cancer onset. However, their main disadvantage over measured fields is a lack of consideration of all possible sources of exposure, in particular fields from in-home appliances and ground currents. The relationship of wire codes to direct magnetic field measurements has been examined; the reliability of wire codes as a quantitative measure of magnetic field exposure is variable (*15, 17, 19, 20*).

Childhood Cancers

The hypothesis generated by the seminal study of Wertheimer and Leeper (*1*) used wire codes to evaluate residential exposures in children. Four additional epidemiological studies in which wire codes were used to assess exposure to ELF-EMF are of sufficient quality to be used in the evaluation of a causal association between the risk of childhood leukemia and exposure to magnetic fields. Two of the studies reported an association (*21, 22*), and two studies reported no association with the risk for childhood leukemia (*23, 24*). A trend of increasing risk with wire codes classification implying increased fields was

observed in the two positive studies (*21, 22*). All of these studies, including the seminal study, could have been affected by the types of biases described earlier including exposure bias (*1*), control selection (all five studies), and confounding from other risk factors (all five studies). In addition, the seminal study and the four subsequent studies differed in their groupings of leukemias ranging from evaluating all types of leukemias (*1, 21, 22, 24*) to evaluating only acute lymphoblastic leukemia (*23, 24*), the most common form of the disease in children. The most recent U.S. study (*23*) is the largest of the four subsequent studies for evaluating ELF-EMF exposure. Even though this study (*23*) shows a negative association when comparing Wertheimer-Leeper wire codes with leukemia risks, when combined with the remaining studies (*21, 22, 24*) in a meta-analysis (a form of statistical analysis in which like studies are combined to get a single answer), the results indicate a marginal association for the highest exposure group versus the lowest exposure groups. Removal of any of the three remaining studies (*21, 22, 24*) diminishes this association substantially. After removal of the one follow-up study with the most severe design limitations (*21*), the association is no longer present. Another study (*25*) was not included in the meta-analysis due to study limitations; this study showed no effect of wire codes.

Four epidemiological studies (*26-29*) assessed exposure using calculated fields; all four studies were conducted in Nordic countries. Three of the studies observed an increased leukemia risk in one or more exposure group (*26-28*) although only one (*26*) achieved statistical significance. All four studies were population-based, with minimal potential for selection bias both in terms of control selection and participation rates. The main limitations of all four studies are the small number of cases overall and the small number of cases and controls in the high exposure group. The general trend of these studies provides marginal support for a small, increased risk (*30*).

Four studies in which spot measurements were used to assess exposure to magnetic fields are clearly of greater quality than the remaining studies (*21, 22, 26, 31*). Two of these studies (*21, 22*) observed increased risks of marginal significance in one or more exposure groups and the other two (*26, 31*) showed no risk. Overall, spot measurements do not show an appreciable excess risk for leukemia when the four studies are combined (*30*).

Four studies used 24-hour measured magnetic fields to assess exposure (*22-24, 31*)[1]. The studies examined three different classifications of childhood leukemias: acute lymphocytic leukemia (*23, 24*), acute leukemia (*31*) and leukemia including nonlymphocytic leukemia (*22, 24*). The results of three of the studies showed an increased risk for children in higher exposure class(es); in two studies there were no statistically significant differences (*22, 24*), in the largest study only one experimental category out of many was statistically significant

[1] This publication (24) only provides a single odds ratio from their analysis of the 24-hour measurements. Additional information was obtained from the principal author.

(*23*), and depending on the grouping, the fourth study achieved statistical significance (*31*). The data reported for the largest study (*23*) suggest an exposure–response relationship that the original authors did not consider important. The pattern of dose versus response in this study was considerably different from the pattern in the other two studies with multiple dose groups (*22, 24*). The results of these studies, when combined, provide weak evidence for an association between exposure based on 24-hour measured magnetic fields and a small, increased incidence of childhood leukemia (*30*).

One study (*24*) assessed exposure using 48-hour personal monitors that measured both magnetic fields and electric fields. Analyses were done for all childhood leukemias and separately for acute lymphocytic leukemia. The general trend in the data indicated a negative association for both magnetic fields (current or predicted two years prior to diagnosis) and electric fields. No statistically significant positive associations were observed. This study, using personal exposure meters, does not support an association between ELF-EMF exposure and childhood leukemia.

Several of the same studies described earlier also looked at electrical appliance use and the risk of childhood leukemia (*22, 32, 33*). The results do not fit a coherent pattern.

None of the individual epidemiological studies provides convincing evidence linking magnetic field exposure with childhood leukemia. Hence, in making an assessment, one must rely upon the evaluation of the data as a whole using expert judgment and the meta-analyses as a guide. The pattern of response, for some methods of measuring exposure, suggests a weak association between increasing exposure and increasing risk. The small number of cases in these studies makes it impossible to firmly demonstrate this association. This level of evidence, while weak, is still sufficient to warrant limited concern.

Two other childhood cancers have been sufficiently studied to warrant comment. Two early studies observed an increased risk of brain cancers using wire codes as the exposure measure (*1, 21*). Later studies using wire codes (*34, 35*), calculated fields (*26-28, 36*) and measured fields (*35*) failed to support this finding. The association between exposure to ELF-EMF and childhood lymphomas was considered in several epidemiological investigations (*1, 21, 26-28, 36*). In all studies, the number of cases of lymphoma in the high exposure groups was too small for any reliable inference to be drawn. In general, these data do not support the concern that exposure to magnetic fields may increase the risk of brain cancers or lymphomas in children.

Adult Cancers

Epidemiological reports of diseases associated with occupational exposure to ELF-EMF preceded concerns about residential exposure. Reports of various health problems in high-voltage substations in the former USSR initially focused attention on ELF electric fields (*37*). Initial studies in the United States (*38, 39*) led to over 100 epidemiological investigations of workplace exposure to ELF-EMF and various diseases. The early studies were based on workers in jobs assumed to entail exposure, and more recent studies used measured fields.

Recent studies evaluating the association between exposure to magnetic fields and chronic lymphocytic leukemia (*40-44*) show mixed results. The two studies in the United States (*43, 44*) reported no association, but one (*44*) used death certificates to identify the cases (chronic lymphocytic leukemia has a rather long survival time that can confound the diagnosis of the cases). One of the remaining studies (*42*) indicated increased risk, which did not achieve statistical significance, and the two Scandinavian studies (*40, 41*) showed significantly elevated risks in one or more exposure groups. Both of the Scandinavian studies had consistently increasing risks with increasing exposure. Each of these studies has its limitations and the limitations are different across studies, as are the designs and exposure assessment methods. Taken together, the studies provide weak evidence for an association between occupational exposure to magnetic fields and chronic lymphocytic leukemia.

Acute myelogenous leukemia was considered in these same epidemiological studies. The results, which were observed from these studies, are not sufficiently compelling to support an association.

The association between exposure to magnetic fields and a variety of other cancers has also been considered in occupational settings. Included are brain cancers, breast cancers (in both males and females), testicular cancers, cancers in offspring of workers, lymphoma, multiple myeloma, melanoma, non-Hodgkin's lymphoma, thyroid cancers and many others. Some evidence exists for an association between brain cancers and exposure to ELF-EMF and between female breast cancers and ELF-EMF exposure; however, the studies evaluating these associations are inconsistent and have limits to their interpretation making them inadequate for supporting or refuting an effect. In the remaining cases, the evidence supporting an association is negative or too weak to warrant concern.

The risks of adult cancer based on residential exposure to ELF-EMF have been evaluated in a number of studies. Risks of leukemia (of all types and of specific sub-types) from residential exposures were evaluated in several recent studies (*40, 45-50*). The calculated field studies (*40, 47-50*) showed mixed results for the different sub-types of leukemia studied and for changes in the definition of the exposure category. Specifically, when chronic lymphocytic leukemias was

examined separately (this was done in only two of the studies), the results were inconsistent with one study (*40, 48*) showing no increased risk and with the other (*49*) showing fairly consistent dose-response with increasing cumulative exposure. The remaining studies, using wire codes (*46*) and measured fields (*46, 48*), demonstrated no increased risk. These data are inadequate for evaluating the association between exposure to ELF-EMF and leukemias. Specifically, for chronic lymphocytic leukemia, which demonstrated a weak association in the occupational studies, there are mixed results for adults in the residential studies.

The risk for leukemia associated with use of electrical appliances was also considered in two studies (*45, 51*). These studies resulted in inconsistent findings and generally do not support an association between appliance use and increased leukemia risk.

Limited data are available on risks of male and female breast cancer associated with residential exposure to ELF-EMF. A small, non-significant association between use of electric blankets and the risk for breast cancer was observed in one, large U.S. study (*52*) but not in another (*53*). Both found no evidence for an association with duration of exposure. Three studies, using exposure measured by calculated fields (*50, 54, 55*), identified no association between exposure to magnetic fields and the risk of breast cancer. These same scientists (*40, 47, 48, 50, 55*) also looked at exposures to ELF-EMF and cancers of the central nervous system (such as brain cancers); no associations were found.

None of the associations between cancer and residential exposure to magnetic fields in adults were indicative of a positive association. However, the specific adult cancer showing weak evidence of a positive association with occupational exposure to ELF-EMF, chronic lymphocytic leukemia, was inadequately studied in residential settings. It cannot, therefore, be concluded that there is no association.

Non-Cancer Findings in Humans

The relationship between spontaneous abortion and exposure to ELF-EMF has been considered in several studies. Recent occupational and residential studies were the focus of this assessment. In the first occupational study (*56*), no association was observed. In a second occupational study (*57*), a significant association was found with exposure to high ELF-EMF; however, the response rate was very poor, particularly among controls, which could have biased this result upward. Pregnancy loss was investigated in two residential cohort studies (*58, 59*). In one study (*58*), an increased risk was observed in the highest exposure category but not in the intermediate category. In the other (*59*), no association was observed for any measure of exposure. In a carefully designed prospective study in the United States (*60*), no association was reported between

measured fields (including personal exposure monitoring) and intrauterine growth, birth weight or gestational age.

Low birth weight (*60, 61*), intrauterine growth retardation (*60*), preterm birth (*61*) and congenital anomalies arising from the father's exposure (*62*) were not associated with occupational exposures to ELF-EMF. The risk for congenital anomalies in relation to the mother's use of heated waterbeds and electric blankets around the time of conception was evaluated in three studies (*63-65*); no association was observed for heated waterbeds in any study, and inconsistent results were reported for electric blanket use.

The association between occupational exposure to ELF-EMF and Alzheimer's disease was considered in five studies (*66-70*). All five studies showed increases in one or more exposure groups with four studies (*66-69*) showing statistically significant increases and one (*70*) showing non-statistically significant increases. All of these studies suffer from design limitations that make it inappropriate to use them for addressing a causal association between ELF-EMF exposure and Alzheimer's disease. Two of these (*66, 67*) are based on diagnoses from death certificates (Alzheimer's disease is not consistently noted on death certificates). Two studies (*68, 69*) used different groups of cases and controls; some of the control groups included persons with other types of dementia, and proxy information was used to define the exposure of cases. The one remaining study (*70*) was evaluated using data for twins and also suffered many limitations. These data are inadequate for interpreting the possibility of an association.

The association between exposure to magnetic fields and amyotrophic lateral sclerosis was assessed in three studies (*66, 71, 72*). One study (*71*) showed an increased risk in the highest exposure group and the other two studies were negative. Adequate adjustment could not be made for known risk factors (electric shocks or a family history of amyotrophic lateral sclerosis) making these studies difficult to interpret.

Suicide and depression were studied in three occupational epidemiological studies (*72-74*). These studies do not support an association with ELF-EMF exposure.

Two occupational studies (*75, 76*) assessed possible adverse cardiovascular outcomes that may result from exposure to magnetic fields. In the first study (*75*), a significant decrease in risk using a broadly defined cardiovascular grouping was observed. In the second (*76*), data from five utilities were examined. This study was motivated *a priori* by a biological hypothesis based on the results of human clinical studies on heart rate variability (*77*) for increased numbers of deaths due to arrhythmia and acute myocardial infarct. Significant, exposure-dependent associations were reported. Lacking additional epidemiological studies to

collaborate these results, these data are inconclusive regarding an association between cardiovascular disease and exposure to ELF-EMF.

Human clinical studies of ELF-EMF exposures were carried out mainly through three major research initiatives. These include a long series of studies of utility workers begun in the 1960s in the former USSR (*37*), human laboratory research conducted in the 1970s in Germany (*78, 79*) and the human laboratory research program started in 1982 at the Midwest Research Institute in the United States (*80*). Dedicated facilities for human exposure testing were designed and constructed in Australia (*81*), Canada (*82*), England (*83*), France (*84*), Germany (*78*), New Zealand (*85*), the Russian Federation (*86*) and the United States (*87, 88*). Research with human volunteers is currently under way in many of these facilities.

A large number of clinical end-points were evaluated in these laboratories. Several effects reported at high exposures warrant little concern as health dangers such as hair standing on end in very strong electric fields and flickering visual sensations in very strong magnetic fields. However, a number of measurements potentially linked to health effects have been studied. The central nervous system was one of the first areas investigated as a potential site of interaction with ELF-EMF. Studies of changes in brain wave patterns (electroencephalography) during waking hours were generally negative showing little or no effect of ELF-EMF, especially in the range of power-line frequencies (*79, 80, 86, 89-94*). Several studies (*95-97*) showed decreased sleep and reduced sleep efficiency during ELF-EMF exposure. These studies all had deficiencies (e.g. disturbance of subjects by drawing blood and incomplete adaptation of study subjects to the laboratory environment) making them inconclusive.

Changes in human pulse as a function of exposure to ELF-EMF fall into two categories: changes in the number of beats per minute (pulse rate) and changes in the variability of the electro-chemical signals going to the heart (heart-rate variability). Two research groups examined changes in pulse rate following exposure to ELF-EMF (*80, 91-93, 98, 99*). All five clinical studies (*80, 91-93, 99*) from the same laboratory showed a decrease in pulse rate in at least one exposure group; however, all exposures represented rather large, combined electric and magnetic fields (6 to 12 kV/m and 10 to 30 μT, respectively). The remaining study (*98*) was a field trial under a high-tension power line and no effect was observed. The biological mechanism is unknown, and the general effect is very small making it unlikely that this is a health risk at lower doses.

Changes in heart-rate variability were evaluated in a retrospective analysis of three previous studies (*77*). Some changes in heart-rate variability were observed, which according to the authors, could indicate a potential for increased risk of sudden cardiovascular death. However, even though decreased heart-rate

variability is associated with increased risk of cardiovascular death, it is not clear that transiently induced changes in healthy individuals will carry any risk. While these findings are inconclusive, the recent epidemiological result (*76*) discussed earlier suggests this area may warrant additional study.

Two possible mechanistic explanations for cancer findings from exposure to ELF-EMF, changes in melatonin (a hormone associated with sleep) and changes in the immune system, have been studied. The potential for ELF-EMF exposure to alter nighttime melatonin levels was addressed in 11 studies (*81, 84, 96, 100-106*). The clinical studies (*81, 84, 96, 102, 103*) demonstrated no consistent pattern of melatonin reduction (one study saw a marginal effect in men with already reduced melatonin levels and one saw a reduction in onset of the nightly increase in melatonin). In the occupational studies (*100, 101, 105, 106*), some changes were reported in urinary excretion of melatonin metabolites (the result of degradation of melatonin in the body) following workplace exposure (when melatonin levels are generally low), but not in evening melatonin levels. In the one residential study (*104*), significant dose-related reductions were associated with measured fields in bedrooms, but not with other measures (e.g. wire codes and total 72-hour exposure). All combined, these studies provide little support that exposure to ELF-EMF is altering melatonin levels in humans. A number of other hormones were also studied such as testosterone, thyroid hormones and several stress hormones; no effects of ELF-EMF exposure on these levels were observed.

Few laboratories studied the effects of ELF-EMF on the immune system. Three studies investigated effects of ELF-EMF exposure on the immune system (*80, 107, 108*) and all were negative.

Finally, there have been a number of case reports of mood changes and hypersensitivity thought attributable to ELF-EMF exposure (manifested as physiological reactions, disturbed sleep, fatigue, headaches, loss of concentration, dizziness, eye strain and skin problems). These symptoms generally seem to be intermittent and difficult to study clinically. Several carefully designed studies (*109-113*) were performed to evaluate the response of persons with these symptoms to ELF-EMF. In general, these studies were negative with the exception of one (*112*) that reported an increased incidence of skin rashes in persons exposed to high ambient electric fields (>31 V/m) relative to control fields (<10 V/m). These data are insufficient to support an association between ELF-EMF and hypersensitivity.

Animal Cancer Data

Animal carcinogenicity studies are routinely used to identify environmental agents that may increase cancer risk in humans. Many areas of biological investigation are more efficiently studied in animal models than in human beings,

because the agent can be studied invasively and under carefully controlled environmental conditions. The use of animal models in studying effects of ELF-EMF exposure is limited by two problems: extrapolation of experimental findings across species and extrapolation of laboratory exposure patterns to environmental exposure patterns. Animal carcinogenic studies of ELF-EMF were done at levels of exposure generally much higher and having greater uniformity in frequency and intensity than would appear in environmental settings. These experimental conditions were chosen to maximize the ability of a researcher to detect an effect, if one exists, for a clearly defined exposure.

The laboratory data in animal models are inadequate to conclude that exposure to ELF-EMF alters the rate or pattern of cancer. There are some sporadic findings (including increased cancers) with no clear interpretation; however, it is noteworthy that these data provide no support for the reported epidemiological findings (discussed earlier) of increased risk for leukemia from ELF-EMF exposure.

Only a few lifetime bioassay studies (*114-116*) have been performed for ELF-EMF exposure. These studies exposed large groups of animals generally for periods of up to two years at magnetic field intensities considerably higher than elevated residential exposures. No consistent effects of ELF-EMF exposure on cancer rates in bioassay animals were found. The most comprehensive study conducted through the National Toxicology Program (*115*) used four exposure groups (control, 2, 200 and 1000 μT continuous exposure for 18.5 hours per day and 1000 μT intermittent exposure) and four gender/species groups. There were no exposure-related clinical findings for rats or mice. The two-year study found no evidence of carcinogenicity in female rats and male or female mice at any exposure level and equivocal evidence for carcinogenicity in male rats based upon an increased incidence of thyroid gland C-cell tumors.

A similar study (*114*) was conducted in female rats where exposure to 60 Hz linearly polarized magnetic fields (control, 2, 20, 200 and 2000 μT continuous exposure) began *in utero* two days before birth and continued for 20 hours per day for two years. No consistent, exposure-related clinical findings or evidence of carcinogenic activity from 60 Hz magnetic fields were reported. In another study (*116*) male and female rats were exposed to control, 500 or 5000 μT 50 Hz magnetic fields for 22.6 hours per day for two years. No differences in cancer rates between field-exposed and sham-exposed animals were found.

Epidemiological findings have suggested a possible association between magnetic field exposure and breast cancer in men (*117, 118*) or women (*119*). In addition, a hypothesis was proposed that magnetic field exposure might lower nocturnal melatonin levels that could increase risk for breast cancer (*120*). Animal studies using chemically induced mammary cancer followed by magnetic field promotion

of carcinogenesis were undertaken to test whether mammary cancer was affected by ELF-EMF exposure.

Following an initial report that magnetic fields promoted mammary tumor development in rodents (*121*), a comprehensive series of studies on ELF-EMF exposure and mammary tumor initiation and promotion in the rodent model was conducted (*122-124*). In these studies, female Sprague-Dawley rats were used and cancer was initiated by intragastric administration of four weekly doses of 7,12-dimethylbenz[a]anthracene (DMBA) followed by promotion with 50 Hz ELF magnetic fields, 24 hours per day for 13 weeks. One of the early studies in this series (*122*), where the data were subsequently examined histologically (*125*), provided evidence that magnetic fields of low flux density (100 μT) promoted increased growth and size of mammary tumors but did not affect tumor incidence. The same laboratory repeated this work, and in additional studies testing different magnetic flux densities, examined the question of whether a dose-response relationship exists with field intensity (*126-128*). Over the range of 10 to100 μT magnetic fields (50 Hz), a higher (not statistically significant) number of total tumors was found in the field-exposed groups. Magnetic field exposure was not associated with more tumors per tumor-bearing animal. Effects on tumor latency and size were not consistent across the studies.

The National Toxicology Program (*129*) conducted similar studies. Animals were exposed to magnetic fields at both European frequency (50 Hz, 100 or 500 μT) and American frequency (60 Hz, 100 μT) 18.5 hours per day, seven days per week for 13 weeks following intragastric administration of four weekly doses of DMBA as the initiator. There was no difference in size or incidence of mammary gland tumors between control and exposed groups. However, the tumor incidence was high in all groups, and sensitivity was reduced for detecting a promoting effect of magnetic fields. The study was repeated at a lower dose of DMBA. Tumor incidence, latency and size, total number of tumors and number of tumors per tumor-bearing animal were not affected by magnetic field exposure; in the exposure groups there were slightly fewer total mammary neoplasms (not statistically significant) than in controls. A 26-week study, where animals received a single initiating dose of DMBA, gave similar results (*129*); there were significantly fewer tumors for the two exposed groups. However, the tumor incidence was high in all groups, and sensitivity was reduced for detecting promoting effects of magnetic fields. This collection of studies (*129*) provides strong evidence of no effect of magnetic fields on the promotional development of mammary cancer.

Another laboratory (*130*) also examined the effects of magnetic field exposure, which included transients, on mammary tumor development in female Sprague-Dawley rats. This study differed slightly in experimental design from the ones described earlier, but used DMBA as initiator and examined similar magnetic fields, 250 and 500 μT, at 50 Hz. No effects of magnetic fields were observed.

The explanation for the observed difference among these studies is not readily apparent. However, within the limits of the experimental rodent model of multistage mammary carcinogenesis, the findings do not provide consistent evidence for a promoting effect of ELF-EMF on chemically induced mammary cancer.

Animal models of skin carcinogenesis are well established for the study of the initiation, promotion and progression of cancer (*131*). Several laboratories examined whether 50 and 60 Hz magnetic fields promoted or co-promoted development of cancer using this model (*132-137*). Skin tumors were initiated by topical treatment of the animals with a known chemical carcinogen (e.g. DMBA) followed by exposure to various intensities of magnetic fields or combinations of magnetic fields plus a known chemical promoter (e.g. 12-*O*-tetradecanoyl phorbol 13-acetate, TPA). The findings from these studies demonstrated no significant promotional effect of magnetic fields on skin tumor development.

Rat liver is a most commonly used experimental model for investigating multistage carcinogenesis in tissues other than the skin (*138*). Several experiments from a single laboratory used this model to investigate ELF-EMF exposure effects and reported no evidence of a promotional or co-promotional role of magnetic fields in cancer development (*139, 140*).

Several epidemiological studies have suggested a possible association between ELF-EMF exposure and an increased risk for leukemia. Two types of animal models were used for determining whether magnetic fields can alter the time of onset or incidence of leukemia: 1) initiation with X-rays or chemical carcinogen followed by ELF-EMF exposure and 2) progression of leukemia by injection of leukemia cells into the animal followed by ELF-EMF exposure.

The largest ELF-EMF study using an agent to initiate disease involved over 2000 mice with different doses of ionizing radiation to initiate lymphoma followed by either exposure to 1400 μT magnetic fields or no exposure for up to 30 months. Exposure to magnetic fields did not affect the incidence or time of onset of leukemia/lymphoma, the rate of death among animals with leukemia/lymphoma or the leukemia sub-types (*141*). In another study (*142*), no promotional effects of a 1000 μT 50 Hz magnetic field in mice were found following initiation of lymphoma/leukemia with DMBA.

A study of leukemia progression was conducted in Fischer rats inoculated with large granular lymphocytic leukemia cells (*143, 144*). In the first study (*144*), treatment with a 1000 μT continuous 60 Hz magnetic field did not significantly alter the clinical progression of the disease in exposed versus ambient-field controls. In the second study (*143*), an additional, lower inoculum of leukemia cells was included to increase sensitivity as well as intermittent magnetic field presentation (3 min on, 3 min off). No significant effects were observed for the

continuous field exposure at either inoculum; however, with intermittent fields at the higher inoculum, latency to disease was slightly decreased.

The findings from the lifetime bioassay study ((*115*), discussed earlier) with ELF-EMF exposure are also consistent with the absence of an effect on leukemia/lymphoma. When animals exposed to a range of magnetic fields for up to two years were examined, no increases in leukemias or lymphomas were found in the 16 gender/species groups.

Two studies were conducted in genetically altered mice that are prone to leukemia (*145, 146*). These studies showed no evidence of magnetic field effects on lymphoma incidence.

Based upon some evidence from occupational and residential studies suggesting an increased risk for brain cancer with ELF-EMF exposure, several animal studies examined this question. Rodent models are relatively insensitive to the induction of brain cancer by chemicals, and as such, caution should be used in interpreting the findings from studies with ELF-EMF exposure. The lifetime studies in rodents (*114-116*) demonstrated no effect of magnetic field exposure on brain cancer. In the large initiation/promotion leukemia study in female mice ((*141*), discussed earlier), sections of the brain were prepared and reviewed for primary proliferative lesions (*147*). No evidence of an effect of magnetic field exposure on primary brain tumors was found.

Non-Cancer Health Effects in Experimental Animals

A number of non-cancer end-points were investigated for possible adverse effects of ELF-EMF exposure. In general, the experimental models used to study interactions with ELF-EMF have been guided by methods and end-points that were developed to assay the effects of other physical and chemical agents such as drugs, chemicals and ionizing radiation.

The effects of ELF-EMF exposure on the immune system were investigated in multiple animal models including baboons and rodents, and there is no consistent evidence in experimental animals for effects from ELF-EMF exposure. Reports of effects in baboons (*148*) were not confirmed when the study was repeated. Some studies had methodological difficulties making interpretation of the findings difficult (*127, 149*). Other studies found no or inconsistent effects of ELF-EMF exposure on immune system indices and function (*150, 151*).

Seven studies examined standard measurements of hematological and clinical chemistry indices following ELF-EMF exposure (*152-158*); several included a limited number of animals and were of short duration. These studies provide no

evidence that exposure to ELF-EMF affects hematological or clinical chemistry parameters in rodents.

A variety of animal models including non-human primates, pigeons and rodents were exposed to high intensity electric or magnetic fields to study the behavior and physiology of the nervous system. Detection of electric fields by animals is a well-established phenomenon, and the sensitivity thresholds for animals appear to be similar.

Various neuro-behavioral responses including avoidance and aversion and learning and performance were tested for effects from exposure to ELF-EMF. The data from studies including baboons and rodents suggest that exposure to strong electric fields can be perceived (*159-162*), but there is no evidence that these fields are harmful at environmental intensities. The addition of a magnetic field to the electric field appears to modulate the acute behavioral response of animals to perceptible electric fields (*163, 164*).

Relatively little evidence is available for evaluating whether exposure to ELF electric fields can affect performance of learned behavior. The studies in baboons (*160, 161*) suggest that any effects are minimal. In contrast, exposure to ELF magnetic fields was associated with several effects: adverse (*165, 166*), beneficial (*167*) or absent (*168, 169*) depending upon the task being performed and the timing of the magnetic field exposure. Studies in non-human primates with combined exposure to electric fields and magnetic fields detected no impact on operant performance (*164, 170*).

Epidemiological studies have addressed the question of whether ELF-EMF exposure affects reproduction and development. Studies using avian species were conducted, but their relevance to mammalian systems is not clear. Studies examining teratogenic and reproductive end-points were also done in mammalian systems. An extensive evaluation of magnetic field exposure (control, 2, 200 and 1000 μT continuous exposure and 1000 μT intermittent exposure) on fetal development and reproductive toxicity in the rodent was conducted (*171*). There was no evidence of any maternal or fetal toxicity or malformation. A further study examined multi-generational reproductive toxicity using a continuous breeding experiment. The results suggested no evidence of altered reproductive performance or developmental toxicity in the rat (*172*).

At the onset of the EMF-RAPID Program, one hypothesis was that magnetic fields acting through the retina as a sensitive receptor reduce melatonin levels. It was thought that this depression might act as a risk factor for cancer (*120, 173*). Studies examining effects of ELF-EMF exposure on circulating melatonin levels were conducted in a variety of mammalian species. Overall, the experimental evidence is lacking in consistency and quality across the studies. The data in rodents is weak, but suggests that when effects do occur, the result is a decrease in

melatonin concentration. There is no evidence for ELF-EMF effects on melatonin in sheep and baboons. These findings parallel those reported from clinical investigations in humans and population studies (discussed earlier).

Long-term exposure to electric fields decreases melatonin concentrations slightly in rats (*174-177*); the biological significance of this effect is not understood. In a series of studies of acute magnetic field exposure in hamsters (*178-180*), a suppression of pineal and plasma melatonin levels reported in the earliest study was not replicated in later studies. Studies in rats with different magnetic field exposures, field intensities and times of exposure relative to the dark cycle have not shown consistent effects of magnetic fields on melatonin levels. Some laboratories reported that long-term exposure to magnetic fields in rats can reduce nocturnal pineal or blood concentrations of melatonin (*123, 181-184*), but other laboratories did not find similar results (*127, 129, 185, 186*). Interpretation of the findings from this large data set is complicated by variability across studies in confounding factors such as species, strain, gender, co-exposure to chemicals, field characteristics and measured outcomes. Long-term studies of ELF-EMF exposure in lambs (*187, 188*) and baboons (*189*) showed no effects on melatonin levels.

Studies of Cellular Effects of ELF-EMF

The number of cellular components, processes and systems that can possibly be affected by ELF-EMF is large. Historically, testing of potentially toxic substances has relied on the use of carefully controlled *in vitro* experimental systems. In an attempt to identify potentially carcinogenic or toxic effects of an agent, these studies have typically exposed cells to the agent over a range of doses including levels above those encountered in the environment. Measurements are then made of cellular end-points as a means to detect alterations in processes such as differentiation, proliferation, gene expression and signal transduction pathways. This toxicological approach was applied to ELF-EMF in general through exposure of cultured cells over a range of doses. Because nothing is known about the potential mechanistic action of ELF-EMF on biological end-points, careful consideration must be given to the range over which the experimental doses of ELF-EMF is varied. The extrapolation of observed effects to lower field intensities may be inappropriate as ELF-EMF may have different mechanistic actions over different patterns of field intensity. Likewise, the actual agents responsible for the ELF-EMF "dose" to which individuals are exposed are not clear. Environmental ELF-EMF exposure is complex being composed of not only pure 60 Hz electric fields and magnetic fields, but also possibly transients (intermittent spikes and changes in the frequency of the field) and harmonics (multiples of the pure 60 Hz exposure: 120, 180, 240, etc.). To understand this complexity, careful control of laboratory exposure conditions also becomes important to ensure that the exposure being tested is known.

The breadth of *in vitro* data on ELF-EMF produced over the last two decades is enormous. Many of these investigations were done using unique experimental protocols in single laboratories. Under the EMF-RAPID Program, a major focus was research that targeted examination of *in vitro* effects that might clarify potential mechanistic actions of ELF-EMF in order to explain reported epidemiological associations with magnetic fields. Because of the noted complexity of ELF-EMF exposures, efforts were also made to standardize the exposure systems used in these studies to allow for comparability of findings across laboratories. Through oversight by the DOE, on-site quality assurance evaluations were made of laboratories funded by this program. In addition, four regional ELF-EMF exposure facilities were established and made available for use by investigators (discussed earlier).

Through the EMF-RAPID Program, considerable progress was made in the area of *in vitro* research on ELF-EMF. Many of these studies of ELF-EMF exposure focused on end-points commonly associated with cancer (e.g. cell proliferation, disruption of signal transduction pathways and inhibition of differentiation). Convincing evidence for causing effects is only available for magnetic flux densities greater than 100 μT or internal electric field strengths greater than approximately 1 mV/m. To date, there is no generally accepted biophysical mechanism by which actions of lower intensity ELF-EMF exposures, including those reported to be of concern in epidemiological studies, might be explained.

Given the concern about whether ELF-EMF exposure is carcinogenic, considerable effort was undertaken to investigate whether ELF-EMF exposures can damage DNA or induce mutations. It has been generally believed that the energy associated with ELF-EMF is not sufficient to cause direct damage to DNA; however, it has been postulated that indirect effects might be possible by ELF-EMF altering processes within cells that could subsequently lead to changes in DNA structure. Overall, there was considerable variability in experimental design and methodology used in these studies resulting in no conclusive evidence that genotoxic effects result from ELF-EMF exposures.

Studies also examined the potential cytogenetic effects of power-frequency sine wave or pulsed magnetic fields using model systems of human cells isolated directly from peripheral blood and amniotic fluid or cultured human lymphocytes and leukemia cells. Overall, the studies varied considerably, and in general, there is no evidence of chromosomal damage even when cells were exposed to relatively strong magnetic fields (*190, 191*). Chromosomal aberrations were reported in one study (*192*) using pulsed magnetic fields; however, the exposures tested were within the range of exposures reported in other studies to have no effect.

Relatively few studies have addressed the question of whether ELF-EMF exposures cause genetic mutations (*193*). Studies using bacteria or yeast cells

(*194, 195*) to investigate possible mutational changes in DNA reported no damage from ELF-EMF exposure at levels less than 1000 μT. However, at higher field strength (400,000 μT, 50 Hz), well above environmental field intensities, enhanced mutagenicity was reported in two cell lines (*196, 197*). Exposure to ELF-EMF (magnetic field strengths ≥500 μT) following exposure to ionizing radiation was reported to produce significant enhancement of mutagenicity (*197, 198*); ELF-EMF exposure alone had no effect. Several investigators examined the ability of ELF-EMF to alter the repair of DNA strand breaks caused by hydrogen peroxide or radiation; no effects with exposure to either magnetic or electric fields were observed (*199-201*).

The concept that ELF-EMF might be carcinogenic through effects on gene transcription was stimulated by an extensive series of studies in human leukemia cells (*202, 203*). It was initially reported that high-intensity ELF-EMF exposure increased expression of several genes important in carcinogenesis. The presence of this effect was later reported to occur at field intensities more characteristic of environmental levels (*204*) and in three types of human cell lines (*203, 205, 206*). Because some of these genes may have a central role in controlling cancer, these findings were of great significance. Intense efforts by several laboratories failed to confirm the reported findings (*207-210*). Follow-up studies by the original investigators demonstrated strain-specific responsiveness to ELF-EMF of the cell line (*211*), although this does not appear to explain the inability of other laboratories to confirm the reported findings (*209*).

Several investigations were undertaken to determine whether cells might respond to ELF-EMF with transcriptional or translational changes of heat-shock proteins, which are important in control of stress within a cell. Exposure of cells to ELF-EMF was reported from a single laboratory to result in increases in some of these proteins (*212-214*).

Signal transduction processes aid cells in receiving signals from their environment and from other cells. These signals help to regulate cellular processes such as gene expression, metabolic activity, differentiation and proliferation. Signals received by the cell membrane, which control processes within the cell, have been proposed as a means by which ELF-EMF might affect cellular function. In the case of electrical signals, these are not expected to penetrate the cell's outer membrane but may signal release of proteins on the cell membrane that could alter cellular function.

Numerous laboratories performed studies to evaluate potential ELF-EMF effects on cellular end-points related to signal transduction pathways, which if altered, might be carcinogenic. Overall the body of evidence suggests that ELF-EMF exposures at magnetic field intensities greater than 100 μT and electric fields greater than 1 mV/m have shown effects on signal transduction pathways. Studies at lower exposures are inconclusive.

Recent studies investigated whether ELF-EMF exposure might play a role in B-cell leukemogenesis (the major form of childhood leukemia) through signaling pathways. A series of studies, which focused on one particular signal (the protein kinase C-linked signaling cascade), provided preliminary evidence that *in vitro* exposure to ELF-EMF (100 μT) can affect this pathway (*215-217*). This finding was not reproduced by a second independent laboratory (*218*).

Because of concern about ELF-EMF possibly being carcinogenic, studies were initiated to investigate whether there were effects on ornithine decarboxylase (ODC), an enzyme activated during carcinogenesis. An early study (*219*) reported increased ODC activity in three cell lines in response to a sinusoidal 60 Hz electric field (10 mV/cm). Subsequent work by others demonstrated effects of ELF magnetic fields (field strengths ≤ 100 μT) on ODC although the experimental conditions (e.g. cell line/tissue, field intensity, time of exposure) varied among laboratories (*220-222*). One study reported increased ODC activity in mouse lymphoma cells exposed to 10 μT 60 Hz magnetic fields (*220*). Attempts to reproduce this finding were not successful (*223, 224*).

Abnormal cellular proliferation is a hallmark of carcinogenesis. This complex process is under control of numerous signal transduction pathways. Several laboratories studied *in vitro* cellular proliferation as an end-point for ELF-EMF effects. Alterations in proliferation were observed in a number of laboratories using a variety of exposure conditions (magnetic fields strengths of 1000 to 5000 μT) and cell lines (*225-227*). Two studies (*228, 229*) did not confirm an earlier report (*227*) of increased colony growth for cells exposed to 60 Hz magnetic fields, although one study (*229*) used a similar experimental protocol. Another study, which used several methods for independently assessing proliferation, reported increased growth over an exposure range of 50 to100 Hz and 100 to 700 μT (*230*).

Disruption of the normal circadian rhythm of melatonin, a hormone produced by the pineal gland, has been postulated as a possible mechanism whereby ELF-EMF exposure might increase risk for breast cancer (*120*). Studies in a human breast cancer cell line (*231*) showed that cellular proliferation *in vitro* was decreased by treatment with physiological levels of melatonin; exposure to a sinusoidal ELF magnetic field (1.2 μT) could overcome this effect. These studies were extended and the anti-proliferative effects of tamoxifen (an anti-cancer therapy) were also reported to be reversed by a 1.2 μT field (*232*). Another laboratory presented similar findings (*233*). The original laboratory also reported finding comparable effects using a second human breast cancer cell line (*234*) and a human glioma cell line (*235*). There is some concern about the experimental design of these studies and further work is underway. In addition, because the observed effect is small, the importance of these findings for human health is not clear (*236*).

Numerous investigations have examined ELF-EMF exposure effects on markers characteristics of cellular differentiation (e.g. matrix protein synthesis; cell surface characteristics; cell morphology, size and orientation). Several of these studies demonstrated a role of electric fields in affecting cellular behavior. Two investigations of alterations in matrix protein production studied effects of electric fields (*237*, *238*) and found a positive correlation between dose and the differentiated state of the cells. Studies examining ELF-EMF effects on alterations of cell surface markers used a variety of cell types. In two of these investigations, the observed cellular effects were attributed to the induced electric fields (*239*, *240*). Exposure to 60 Hz electric fields was also found to suppress formation of osteoclast-like cells in marrow culture (*241*).

Biophysical Theory

The physics governing the interactions of ELF-EMF with matter were elucidated over a century ago and succinctly stated in the Maxwell equations. Years of successful application of these principles for practical advances have left little doubt about our ability to understand and predict electromagnetic biophysical phenomena when details of the system and fields are completely described. Given the complexity, dynamics and organization in living organisms, it is difficult to apply this knowledge. Living organisms function through the use of biochemical and electrical signals carefully controlled by the organism's structure. Early attempts to explain the biological effects of ELF-EMF focused on simple application of electromagnetic theory to calculate the forces on biological molecules and the energies transferred to them by weak ELF-EMF. The extremely small magnitude of these interactions led many investigators to conclude that they would not occur at normally encountered field strengths. This has not fundamentally changed; calculations still strongly suggest that the small electric fields and magnetic fields associated with ELF-EMF in environmental settings cannot be expected to supply, by themselves, the energies necessary for chemical changes.

The complexity and structure of biological systems make uniform application of these findings difficult. For example, even very small fields might act as control signals to modify processes that depend on metabolically supplied energy. This would be analogous to extremely weak radio signals, such as those transmitted over thousands of miles, that control locally supplied energy or power a loud-speaker or a large-screen television set. The exact nature of biological signal processing systems and their susceptibility to control by time-varying ELF-EMF is of continuing interest. Biological systems contain complex feedback loops and amplification sequences in which very small changes at one point may ultimately lead to very large changes further along the communication chain. In considering ELF-EMF changes on the nature of biological signals, it is essential to recognize that all aspects of a field (frequency, amplitude and pattern) may be involved. These considerations make definitive statements based upon biophysical theory difficult to apply to living organisms.

Several mechanisms for explaining ELF-EMF effects on biological systems have been proposed. One set of theories (*242-248*) predicts effects of ELF-EMF on chemical reactions due to resonances that depend on complex interactions between constant and oscillating magnetic fields. There is limited experimental support for these theories (*12*); the validity of the assumptions used in the theories has been questioned (*249*).

Modification of the transfer of electrons from one molecule to another has also been suggested as a theoretical mechanism for the effects of ELF-EMF (*250-255*). However, the energies involved in electron binding are many orders of magnitude larger than those contained in weak, externally applied electric fields or magnetic fields (*256-260*) making these theories difficult to accept.

It is also possible that ELF-EMF could interact with magnetic particles in human cells (*261-264*). However, work with this theory (*263-265*) would suggest that such effects can occur only with large magnetic fields and are not applicable to the normal human environment; these conclusions may be premature (*12, 266*).

Magnetic fields are capable of altering specific types (e.g. radical pair formation) of chemical reactions (*267-273*). Potential effects of ELF-EMF have been predicted by analytical work (*274-278*). Such reaction effects have been shown for strong fields (*279*), but there are few studies of the effects in biological systems with moderate to low field intensities.

Biochemical and biomechanical processes are generally dynamic. It has been suggested that rather than causing changes in the usual state of the system, ELF-EMF may induce slight changes in the frequency of events that trigger other processes, especially for effects on chemicals that oscillate within cells and between cells and their environments (*250, 277, 280-286*). Both theoretical (*287-291*) and biological (*292-294*) studies exist that support this suggestion. However, there is open debate about whether this phenomenon is applicable for ELF-EMF exposures that are generally found in the human environment.

All of the theories for biological effects of ELF-EMF suffer from a lack of detailed, quantitative knowledge about the processes to be modeled. Nevertheless, theoretical models are useful, even in the absence of critical data, because they can indicate what data are needed, suggest previously uncontemplated experiments, suggest bounds on risks under defined situations and provide nonlinear methods of analysis of critical data based upon presumed mechanisms. The current biophysical theories for ELF-EMF would suggest little possibility for biological effects below exposures of 100 μT. However, considering the complexity of biological systems and the limitations required by the assumptions used to mathematically model these theories, this finding has to be viewed with caution.

HOW HIGH ARE EXPOSURES IN THE U.S. POPULATION?

An evaluation of the importance of any environmental agent requires knowledge of both the potential health impacts associated with exposure and the exposure levels encountered by the population. For any environmental exposure, a clear estimate of risk is made more difficult by the lack of a well-defined measure of dose. For ELF-EMF, it is unknown whether time-averaged fields, time above a threshold, the electric current induced by the field, the magnetic field itself, or specific temporal characteristics of the field (e.g. frequency, waveform, or intermittency) are relevant to human health.

Recognizing this uncertainty and faced with practical limitations, investigators have employed several different methods to estimate human exposure to ELF-EMF. Most of these approaches provide an estimate of the 24-hour time-average of the 60 Hz magnetic field. The first ELF-EMF epidemiological study, as well as several subsequent studies, estimated exposure by developing a code to describe power-line wiring near homes. More recent studies performed actual measurements of magnetic fields using either survey instruments in homes or miniature monitors worn by an individual for periods of up to 24 hours or more (personal exposure measurements). Another approach was to calculate time-average magnetic field exposures based on electric current in nearby power lines and distance of homes to the lines. This report focuses entirely on recent studies that measured magnetic fields, and highlights single spot measurements and 24-hour, time-weighted averages.

Several studies measured magnetic fields in either homes (*22, 26, 295-298*) or personal exposures (*297, 299*). These studies and others (*16, 18, 20, 300-309*) compared different types of measurements in an attempt to relate the results across various epidemiological studies. Two of the studies (*297, 299*) attempted to evaluate nationwide exposures in the U.S. population. One study (*297*) measured magnetic fields in various locations within homes using fixed meters. This survey, although not designed to describe individual exposures, provides a snapshot of residential fields, and the results are probably reasonably representative of residential conditions. An extensive measurement protocol (*297*) was used including spot measurements inside rooms, field recordings in the

home, measurements of field profiles from wiring outside the home, measurements of household appliances and measurement of fields from currents in the electrical grounding system. The other study (*299*) relied entirely upon personal monitors mailed to participants along with a questionnaire that addressed characteristics of the individual wearing the monitor. These two studies form the basis for most of the discussion that follows.

Measured magnetic field exposures to individuals and measurements in homes tend to have an asymmetric distribution with the bulk of their values in the low range with fewer values in the range of higher exposures. Therefore, the central tendency of the values is better represented as a geometric mean (log-weighted average) and the variation around that mean given as a geometric standard deviation. Another measure commonly used is the median, which denotes the estimate of exposure for which 50% of the population have smaller exposures and 50% have larger exposures. In addition, estimates are also presented for the portion of the population in the upper range of exposure. This report presents averages as geometric means with geometric standard deviations given in parenthesis beside the average estimate.

Average 24-hour personal magnetic field exposure for individuals in the U.S. population (*299*) is about 0.09 µT (geometric standard deviation of approximately 2.2). About 44% of the population have 24-hour exposures above 0.1 µT, about 14% above 0.2 µT, about 2.5% above 0.5 µT and less than 1% above 0.75 µT. The median measured fields using monitors located for 24 hours in several places in the homes (*297*) was 0.06 µT with about 28% of the homes exceeding 0.1 µT, about 11% of the homes exceeding 0.2 µT and about 2% exceeding 0.5 µT. The main difference between the home and personal exposure measurements pertains to exposures incurred outside of the home and the movement of individuals within the home near ELF-EMF sources.

Personal exposures measured within the home (*299*) averaged 0.08 µT (2.5) for time not in bed and 0.05 µT (3.52) for time spent in bed. In comparison, personal exposures at work averaged 0.1 µT (2.57), exposure at school averaged 0.06 µT (2.1) and exposure during travel measured 0.1 µT (2.0). Approximately 38% of the personal measurements in the home (not in bed) were above 0.1 µT, about 14% were above 0.2 µT and about 3.5% were above 0.5µT. Personal measurements at home and in bed were slightly different in the low exposure range with approximately 30% of the measurements above 0.1 µT, but similar in the high exposure region with about 14% above 0.2 µT and about 4% above 0.5 µT. It is clear from these numbers that personal exposures tend to be somewhat larger than those observed by fixed measurement of fields in homes.

Personal exposures do not appear to differ by gender, but do differ by age (*299*) with young children (less than five years of age) having an average exposure of 0.08 µT (2.1), school-aged children (five to 17 years of age) having an average

exposure of 0.08 μT (2.2), working-aged adults (18 to 64 years of age) having an average exposure of 0.1 μT (2.2) and retirement-aged adults (greater than 64 years of age) having an average exposure of 0.09 μT (2.2). There are some regional differences in exposure across the United States, but these are differences that are likely to change based upon the seasons and are not likely to have a major impact upon exposure considerations. Residents of apartments and duplexes seem to have higher average exposures (approximately 0.1 μT) compared to residents of other dwelling types (0.05 to 0.07 μT) (*297*).

The presence of overhead power lines near homes contributes to both personal exposures and fixed home measurements. In a large study using fixed monitors in homes (*297*), estimates of fields due to power-line fields were determined independent of exposures measured in the homes. Both the power-line and grounding system fields were combined and compared to the short-term field levels measured in the centers of rooms. Combined, the two sources add up to much of the spot residential fields in homes having higher than usual magnetic field levels.

A comparison was made between different types of power lines to determine which ones produced the greatest fields. Transmission lines and certain types of distribution lines produced the greatest fields (medians ranging from 0.09 to 0.38 μT, although the number of residences exposed to these fields was small), and several types of primary distribution lines produced the lowest median fields (medians ranging from 0.01 to 0.02 μT). The majority of homes were associated with underground distribution lines that still generated fields with a median of 0.03 μT and with 5% exceeding 0.13 μT (roughly 75% of the median for all homes).

The effect of power lines on personal exposures was also assessed (*299*), but in contrast to the previous discussion, self-reporting was used to classify the types of power lines. Persons reporting three-phase primary distribution lines (average exposure at home 0.083 μT), multiple three-phase primary distribution lines (average exposure at home 0.1 μT) and transmission lines (average exposure at home 0.1 μT) had the highest average exposures, while those reporting single phase (average exposure of 0.07 μT) and two-phase primary distribution lines (average exposure of 0.05 μT) had the lowest exposure. For all types of lines, 25% of the population had exposures greater than 0.1 to 0.2 μT and 5% had exposures greater than 0.3 to 0.5 μT. At distances of greater than 50 feet, the type of power lines appeared to have little impact on the average exposure and only a minor impact on the number of individuals with the highest exposures.

Several other factors contributed to increased personal exposure and/or increased residential exposure. These included type of home (single family homes had smaller average exposures than multi-family homes), size of the home (smaller homes had higher fields), age of the home (older homes had higher fields), water-

line type inside the home (homes with metal pipes tended to have higher fields) and location of the home (urban and suburban homes had higher fields than rural homes).

Magnetic fields generated by appliances were also studied (*297*). Exposures tend to vary greatly by distance to the appliance and type of appliance. In general, microwave ovens, toaster ovens, ceiling heat and refrigerators generated the highest fields. However, the contributions of these fields to personal exposure will depend upon placement of the appliance, distance from the appliance, frequency of use, manufacturer, etc. Any observations on exposures from appliances are not easily generalized.

Occupational exposures have been evaluated in a large number of studies (see Table 2.4 (*12*)). The list of occupations with ELF-EMF exposure is quite large and will not be repeated here. In general, electrical workers, persons working near machines with electric motors and welders tend to have the highest exposures with time-weighted average magnetic field exposure levels in the range of 0.1 to 4.0 μT.

CONCLUSIONS AND RECOMMENDATIONS

Previous Panel Reviews

Since 1990, more than 60 reports and literature reviews written by various expert panels, individual researchers or governmental officials have examined the ELF-EMF scientific evidence worldwide. While most of these documents are one-time assessments, some U.S. states (including Connecticut, Maryland, Virginia) have recognized public concern for this topic and monitored this issue on a yearly or periodic basis (*310*). A number of national reviews of ELF-EMF research have also been prepared.

The most recent panel reviews (*19, 311-316*) used a variety of evaluation criteria and differing types of information to evaluate potential health effects from ELF-EMF exposures. Several groups concluded that the epidemiological evidence for childhood and adult cancers was inconsistent and inconclusive and was insufficient to address risks (*19, 311, 312, 315, 316*). Several noted that there existed some associations between exposures and cancers, but without mechanistic and animal evidence to support the effect, concluded it was still basically a hypothesis to be studied further (*19, 313-315*). For all of these reviews, the conduct of additional research was suggested.

NIEHS Conclusion

As part of the EMF-RAPID Program's assessment of ELF-EMF-related health effects, an international panel of 30 scientists met in June 1998 to review and evaluate the weight of the ELF-EMF scientific evidence (*12*). Using criteria developed by the International Agency for Research on Cancer, none of the Working Group considered the evidence strong enough to label ELF-EMF exposure as a "known human carcinogen" or "probable human carcinogen." However, a majority of the members of this Working Group (19/28 voting members) concluded that exposure to power-line frequency ELF-EMF is a "possible" human carcinogen. This decision was based largely on "limited evidence of an increased risk for childhood leukemias with residential exposure

and an increased occurrence of CLL (chronic lymphocytic leukemia) associated with occupational exposure." For other cancers and for non-cancer health endpoints, the Working Group categorized the experimental data as providing much weaker evidence or no support for effects from exposure to ELF-EMF.

The NIEHS agrees that the associations reported for childhood leukemia and adult chronic lymphocytic leukemia cannot be dismissed easily as random or negative findings. The lack of positive findings in animals or in mechanistic studies weakens the belief that this association is actually due to ELF-EMF, but cannot completely discount the finding. The NIEHS also agrees with the conclusion that no other cancers or non-cancer health outcomes provide sufficient evidence of a risk to warrant concern.

The ultimate goal of any risk assessment is to estimate the probability of disease in an exposed population. In general, this involves the combination of three basic pieces of information: the probability that the agent causes the disease, the response as a function of exposure given that the exposure does cause disease and the distribution of exposures in the population being studied. The NIEHS believes that the probability that ELF-EMF exposure is truly a health hazard is currently small. The weak epidemiological associations and lack of any laboratory support for these associations provide only marginal, scientific support that exposure to this agent is causing any degree of harm.

The NIEHS concludes that ELF-EMF exposure cannot be recognized as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard. In our opinion, this finding is insufficient to warrant aggressive regulatory concern. However, because virtually everyone in the United States uses electricity and therefore is routinely exposed to ELF-EMF, passive regulatory action is warranted such as a continued emphasis on educating both the public and the regulated community on means aimed at reducing exposures. The NIEHS does not believe that other cancers or non-cancer health outcomes provide sufficient evidence of a risk to currently warrant concern.

Several groups have attempted to determine the risk of childhood leukemia in the general population under the unproven assumption that ELF-EMF is truly causing this disease (*317-319*). If this assumption were correct, these calculations generally suggest, on average, that between 5% and 15% of childhood leukemias could be caused by exposures to ELF-EMF with confidence intervals including 0%. Based upon this assumption, our own evaluations using the most current data and several different methods of analysis do not disagree with these percentages. The risk of getting leukemia prior to age 15 in the United States is about 0.05% (5/10,000 people) (*320*). This would make the lifetime risk of childhood leukemia attributable to ELF-EMF (again, conditional on the risk being real) between 2.5 to 7.5 per 100,000 people. On a yearly basis, this conditional risk is

approximately 15 times less than the lifetime risk or 2 to 6 additional cases per million children per year.

The National Toxicology Program routinely examines environmental exposures to determine the degree to which they constitute a human cancer risk and produces the "Report on Carcinogens" listing agents that are "known human carcinogens" or "reasonably anticipated to be human carcinogens." It is our opinion that based on evidence to date, ELF-EMF exposure would not be listed in the "Report on Carcinogens" as an agent "reasonably anticipated to be a human carcinogen." This is based on the limited epidemiological evidence and the findings from the EMF-RAPID Program that did not indicate an effect of ELF-EMF exposure in experimental animals or a mechanistic basis for carcinogenicity.

Recommended Actions

Regulatory action on any environmental exposure can be multifaceted and proceed by any of a number of options. In general, if regulatory action is to be taken, the types of controls can be broken down into restrictions placed on the production of the hazard and those placed on individuals who might come in contact with the hazard. In the case of ELF-EMF, there are several issues that complicate any regulatory action. First, there is only marginal, scientific support that exposure to ELF-EMF is a health hazard. Second, it is unclear what aspect of the exposure, if any, may be the active component of the field resulting in the increased cancer risk. While the association observed is with average magnetic field measures, controls resulting in reductions in these field levels may not alleviate the risk. Third, it is impossible to remove all ELF-EMF exposure and remain a modern, technologically advanced society. Finally, considering the weak degree of evidence involved, it is critical that the potential risks from any alternatives to our current methods of using electricity be carefully evaluated.

Regulatory actions prompted by this review of ELF-EMF are not the purview of the NIEHS. The Interagency Committee (IAC, described earlier) has been involved in all aspects of both our research program and the process of reviewing these data. The agencies that compose the IAC employ experts who have greater experience and knowledge concerning mitigation of ELF-EMF exposure than the NIEHS. However, it is important that the strength of the evidence reported here be placed in a context that is clear to the regulatory authorities. Therefore, the NIEHS is providing the following suggestions that are intended to give scope for future regulatory actions.

The NIEHS suggests that the level and strength of evidence supporting ELF-EMF exposure as a human health hazard are insufficient to warrant aggressive regulatory actions; thus, we do not recommend actions such as stringent standards on electric appliances and a national program to bury all transmission and distribution lines. Instead, the evidence suggests passive measures such as a

continued emphasis on educating both the public and the regulated community on means aimed at reducing exposures. NIEHS suggests that the power industry continue its current practice of siting power lines to reduce exposures and continue to explore ways to reduce the creation of magnetic fields around transmission and distribution lines without creating new hazards. We also encourage technologies that lower exposures from neighborhood distribution lines provided that they do not increase other risks, such as those from accidental electrocution or fire.

Exposures in individual residences are linked to certain characteristics. Their chief causes are improper grounding and improper wiring, which if addressed by properly following current electrical codes, can be mitigated and exposures reduced. Older homes may also have higher ambient exposures, but these must be assessed on a case-by-case basis. Many of the U.S. electric utility companies will measure fields in their customers' homes and help them to identify sources of high fields; we encourage continuation of this practice. Finally, the NIEHS would encourage the manufacturers of household and office appliances to consider alternatives that reduce magnetic fields at a minimal cost. We feel that the risks do not warrant major and expensive redesign of modern electrical appliances, but inexpensive modifications should be sought to reduce exposures.

Certain occupations result in high field exposures. The NIEHS encourages the National Institute for Occupational Safety and Health and the Occupational Safety and Health Administration to review these findings and carefully evaluate if current occupational exposure standards are adequate.

In summary, the NIEHS believes that there is weak evidence for possible health effects from ELF-EMF exposures, and until stronger evidence changes this opinion, inexpensive and safe reductions in exposure should be encouraged.

Future Research

The NIEHS is committed to the support of hypothesis-driven research on any environmental exposure that is of concern for human beings. Exposure to ELF-EMF is no different. These exposures warrant continued monitoring because ELF-EMF exposure is ubiquitous and the use of electromagnetic technology is growing in our society.

The characteristics of ELF-EMF and their possible interactions with biological systems have been investigated for several decades. The EMF-RAPID Program successfully contributed to the scientific knowledge on ELF-EMF through its support of high quality, hypothesis-based research. While some questions were answered, others remain. Building upon the knowledge base developed under the EMF-RAPID Program, meritorious research on ELF-EMF through carefully designed, hypothesis-driven studies should continue for areas warranting

fundamental study including leukemia. The NIEHS will continue to support research in this area. Certain areas of research, however, warrant noting.

There are several epidemiological studies of ELF-EMF exposures and childhood leukemia underway that may help clarify this issue. Any new epidemiological studies of ELF-EMF exposure are not warranted unless, in some unique manner, the studies differ from existing ones and can test new hypotheses. Very little is known about the mechanisms and causes of childhood leukemias and chronic lymphocytic leukemia in adults. Many agencies, including the National Institutes of Health, have ongoing programs in these areas aimed at improving our understanding of these diseases. As risk factors are identified, we strongly recommend re-analysis of the existing ELF-EMF epidemiology data to determine if these risk factors reduce or strengthen the reported findings of concern expressed in this document. Where currently available studies cannot adequately address newly discovered risk factors, the NIEHS encourages new studies.

Several non-cancer health areas including neurodegenerative and cardiovascular diseases have been identified as being of national concern, but for which there are few, high quality studies to evaluate adequately whether ELF-EMF exposure might have effects. Preliminary work suggests that ELF-EMF exposure may be linked to cardiovascular deaths resulting from arrhythmia and acute myocardial infarction. The mechanism for such an effect, if true, is not known, but possibly occurs through exposure-related effects on autonomic nervous system control of cardiac function. Also, several exploratory studies have suggested possible associations between occupational ELF-EMF exposure and neurodegenerative diseases specifically amyotrophic lateral sclerosis and Alzheimer's disease. The data on these end-points are inadequate for interpreting the possibility of an association. Research in these areas should cover all aspects of scientific investigation including epidemiology, laboratory and mechanistic studies.

Preliminary studies in transformed breast cancer cells suggest that ELF-EMF exposures can overcome effects of melatonin and tamoxifen in regulating cell growth. This effect of ELF-EMF appears to occur at magnetic field exposures that may be encountered in the environment. Several other laboratories have presented similar, unpublished findings at national meetings. The importance of this finding for human health is unclear, but considering the magnitude of the incidence of breast cancer, this area warrants further investigation.

There is a continued need for more biologically realistic mathematical models to evaluate the biophysics of ELF-EMF and for biological systems specifically developed to evaluate the validity and utility of these mathematical models. While it is clearly established that certain animals can sense weak magnetic fields for navigation and homing, the physical basis for these processes is unknown. More remains to be learned about the physics of magnetic field interactions with biological systems.

The interaction of humans with ELF-EMF is complicated and will undoubtedly continue to be an area of public concern. The World Health Organization through its own international program on ELF-EMF will review this field in the year 2003. The NIEHS is a partner in this process.

REFERENCES

1. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. American Journal of Epidemiology 109:273-284(1979).

2. Galvin MJ, Bernheim NJ, Boorman GA, Portier CJ, Wolfe MS, eds. Research and Communication Project Summaries, September 1994 - December 1998. Research Triangle Park: National Institute of Environmental Health Sciences, National Institutes of Health, 1999.

3. Bracken TD, Montgomery JH, eds. Proceedings of EMF Engineering Review Symposium, Status and Summary of EMF Engineering Research (Draft). Charleston: U.S. Department of Energy, 1998.

4. NRC National Research Council, Committee on the International Means for Assessment of Risk to Public Health. Risk Assessment in the Federal Government: Managing the Process. Washington:National Academy Press, 1983.

5. NRC National Research Council, Committee on Risk Assessment of Hazardous Air Pollutants. Science and Judgment in Risk Assessment. Washington:National Academy Press, 1994.

6. Presidential/Congressional Commission on Risk Assessment and Risk Management. Framework for Environmental Health Risk Management. Final Report. Washington, 1997.

7. Portier CJ, Wolfe MS. Risk communication: Focus in the NIEHS RAPID review of EMF hazards. In: Proceedings of the ICNIRP/WHO Symposium on Communicating Risks from Exposure to EMF, Australia, December 1997.

8. Portier CJ, Wolfe MS. Linking science to decisions: A strategy for electric and magnetic fields. In: Proceedings of the ICNIRP/WHO Symposium on Research Priorities for Evaluating Risks from Exposure to EMF, Bologna, June 1997.

9. Portier CJ, Wolfe MS, eds. EMF Science Review Symposium Breakout Group Reports for Theoretical Mechanisms and *In Vitro* Research Findings. Research Triangle Park: National Institute of Environmental Health Sciences, 1997.

10. Portier CJ, Wolfe MS, eds. EMF Science Review Symposium Breakout Group Reports for Epidemiological Research Findings. San Antonio: National Institute of Environmental Health Sciences, 1998.

11. Portier CJ, Wolfe MS, eds. EMF Science Review Symposium Breakout Group Reports for Clinical and *In Vivo* Laboratory Findings. NIH Publication No. 98-4400. Research Triangle Park: National Institute of Environmental Health Sciences, 1998.

12. Portier CJ, Wolfe MS, eds. Assessment of Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields - NIEHS Working Group Report NIH Publication No. 98-3981. Research Triangle Park: National Institute of Environmental Health Sciences, 1998.

13. Poole C, Trichopoulos D. Extremely low-frequency electric and magnetic fields and cancer. Cancer Causes and Control 2:267-276(1991).

14. Rothman KR. Causal inference in epidemiology. In: Modern Epidemiology. Boston:Little, Brown and Company, 1986;7-21.

15. Kaune WT. Assessing human exposure to power-frequency electric and magnetic fields. Environmental Health Perspectives 101:121-133(1993).

16. Feychting M, Kaune WT, Savitz DA, Ahlbom A. Estimating exposure in studies of residential magnetic fields and cancer: Importance of short-term variability, time interval between diagnosis and measurement, and distance to power line. Epidemiology 7:220-224(1996).

17. Kheifets LI, Kavet R, Sussman SS. Wire codes, magnetic fields, and childhood cancer. Bioelectromagnetics 18:99-110(1997).

18. Neutra RR, DelPizzo V. When 'wire codes' predict cancer better than spot measurements of magnetic fields. Epidemiology 7:217-218(1996).

19. NRC National Research Council, Committee on the Possible Effects of Electromagnetic Fields on Biologic Systems. Possible Health Effects of Exposure to Residential Electric and Magnetic Fields. Washington:National Academy Press, 1997.

20. Tarone RE, Kaune WT, Linet MS, Hatch EE, Kleinerman RA, Robison LL, Boice JD, Wacholder S. Residential wire codes: Reproducibility and relation with measured magnetic fields. Occupational and Environmental Medicine 55:333-339(1998).

21. Savitz DA, Wachtel H, Barnes FA, John EM, Tvrdik JG. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. American Journal of Epidemiology 128:21-38(1988).

22. London SJ, Thomas DC, Bowman JD, Sobel E, Cheng T-C, Peters JM. Exposure to residential electric and magnetic fields and risk of childhood leukemia. American Journal of Epidemiology 134:923-937(1991).

23. Linet MS, Hatch EE, Kleinerman RA, Robison LL, Kaune WT, Friedman DR, Severson RK, Haines CM, Hartsock CT, Niwa S, Wacholder S, Tarone RE. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. New England Journal of Medicine 337:1-7(1997).

24. McBride ML, Gallagher RP, Thériault G, Armstrong BG, Tamaro S, Spinelli JJ, Deadman JE, Fincham B, Robson D, Chaoi W. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. American Journal of Epidemiology 149:831-842(1999).

25. Fulton JP, Cobb S, Preble L, Leone L, Forman E. Electrical wiring configurations and childhood leukemia in Rhode Island. American Journal of Epidemiology 111:292-296(1980).

26. Feychting M, Ahlbom A. Magnetic fields and cancer in children residing near Swedish high-voltage power lines. American Journal of Epidemiology 138:467-481(1993).

27. Olsen JH, Nielsen A, Schulgen G. Residence near high voltage facilities and risk of cancer in children. British Medical Journal 307:891-895(1993).

28. Verkasalo PK, Pukkala E, Hongisto MY, Valjus JE, Jarvinen PJ, Heikkila KV, Koskenvuo M. Risk of cancer in Finnish children living close to power lines. British Medical Journal 307:895-898(1993).

29. Tynes T, Andersen A, Langmark F. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. American Journal of Epidemiology 136:81-88(1992).

30. Wartenberg D, Dietrich F, Goldberg R, Poole C, Savitz D. A meta-analysis of studies of childhood cancer and residential exposure to magnetic fields PR-702871. Research Triangle Park: Report for the National Institute of Environmental Health Sciences, 1998.

31. Michaelis J, Schuz H, Meiner R, Zemann E, Grigat J-P, Kaatsch P, Kaletsch U, Miesner A, Brinkmann K, Kalkner W, Karner H. Combined risk estimates for two German population-based case-control studies on residential magnetic fields and childhood acute leukemia. Epidemiology 9:92 - 94(1998).

32. Hatch EE, Linet MS, Kleinerman RA, Tarone RE, Severson RK, Hartsock CT, Haines C, Kaune WT, Friedman D, Robison LL, Wacholder S. Association between childhood acute lymphoblastic leukemia and use of electric appliances during pregnancy and childhood. Epidemiology 9:234-245(1998).

33. Savitz DA, John EM, Kleckner RC. Magnetic field exposure from electric appliances and childhood cancer. American Journal of Epidemiology 131:763-773(1990).

34. Gurney JG, Mueller BA, Davis S, Schwartz SM, Stevens RG, Kopecky KJ. Childhood brain tumor occurrence in relation to residential power line configuration, electric heating sources, and electric appliance use. American Journal of Epidemiology 143:120-128(1996).

35. Preston-Martin S, Navidi W, Thomas D, Lee P-J, Bowman J, Pogoda J. Los Angeles study of residential magnetic fields and childhood brain tumors. American Journal of Epidemiology 143:105-119(1996).

36. Tynes T, Haldorsen T. Electromagnetic fields and cancer in children residing near Norwegian high-voltage power lines. American Journal of Epidemiology 145:219-226(1997).

37. Asanova TP, Rakov AN. The health status of people working in the electric field of open 400-500 KV switching structures. Gigiena Truda I Professionalnye Zabolevaniia 10:50-52(1966).

38. Wertheimer N, Leeper E. Magnetic field exposure related to cancer subtypes. Annals of the New York Academy of Science 502:43-54(1987).

39. Milham S. Mortality from leukemia in workers exposed to electrical and magnetic fields (Letter to the editor). New England Journal of Medicine 307:249(1982).

40. Feychting M, Forssen U, Floderus B. Occupational and residential magnetic field exposure and leukemia and central nervous system tumors. Epidemiology 8:384-389(1997).

41. Floderus B, Persson T, Stenlund C, Wennberg A, Ost A, Knave B. Occupational exposure to electromagnetic fields in relation to leukemia and brain tumors: A case-control study in Sweden. Cancer Causes and Control 4:465-476(1993).

42. Thériault G, Goldberg M, Miller AB, Armstrong B, Guénel P, Deadman J, Imbernon E, To T, Chevalier A, Cyr D, Wall C. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France:1970-1989. American Journal of Epidemiology 139:550-572(1994).

43. London SJ, Bowman JD, Sobel E, Thomas DC, Garabrant DH, Pearce N, Bernstein L, Peters JM. Exposure to magnetic fields among electrical workers in relation to leukemia risk in Los Angeles County. American Journal of Industrial Medicine 26:47-60(1994).

44. Savitz DA, Loomis DP. Magnetic field exposure in relation to leukemia and brain cancer mortality among electric utility workers. American Journal of Epidemiology 141:123-134(1995).

45. Preston-Martin S, Peters JM, Yu MC, Garabrant DH, Bowman JD. Myelogenous leukemia and electric blanket use. Bioelectromagnetics 9:207-213(1988).

46. Severson RK, Stevens RG, Kaune WT, Thomas DB, Heuser L, Davis S, Sever LE. Acute nonlymphocytic leukemia and residential exposure to power frequency magnetic fields. American Journal of Epidemiology 128:10-20(1988).

47. Feychting M, Ahlbom A. Magnetic fields and cancer in people residing near Swedish high voltage power lines: Institutet for Miljomedicin (IMM), 1992.

48. Feychting M, Ahlbom A. Magnetic fields, leukemia, and central nervous system tumors in Swedish adults residing near high-voltage power lines. Epidemiology 5:501-509(1994).

49. Verkasalo PK. Magnetic fields and leukemia -- Risk for adults living close to power lines. Scandinavian Journal of Work, Environment and Health 22:1-56(1996).

50. Li C-Y, Thériault G, Lin RS. Residential exposure to 60-Hertz magnetic fields and adult cancers in Taiwan. Epidemiology 8:25-30(1997).

51. Lovely RH, Buschbom RL, Slavich AL, Anderson LE, Hansen NH, Wilson BW. Adult leukemia risk and personal appliance use: A preliminary study. American Journal of Epidemiology 140:510-517(1994).

52. Vena JE, Graham S, Hellmann R, Swanson M, Brasure J. Use of electric blankets and risk of postmenopausal breast cancer. American Journal of Epidemiology 134:180-185(1991).

53. Gammon MD, Schoenberg JB, Britton JA, Kelsey JL, Stanford JL, Malone KE, Coates RJ, Brogan DJ, Potischman N, Swanson CA, Brinton LA. Electric blanket use and breast cancer risk among younger women. American Journal of Epidemiology 148:556-563(1998).

54. Feychting M, Forssen U, Rutqvist LE, Ahlbom A. Magnetic fields and breast cancer in Swedish adults residing near high-voltage power lines. Epidemiology 9:392-397(1998).

55. Verkasalo PK, Pukkala E, Kaprio J, Heikkila KV, Koskenvuo M. Magnetic fields of high voltage power lines and risk of cancer in Finnish adults: Nationwide cohort study. British Medical Journal 313:1047-1051(1996).

56. Schnorr TM, Grajewski BA, Hornung RW, Thun MJ, Egeland GM, Murray WE, Conover DL, Halperin WE. Video display terminals and the risk of spontaneous abortion. New England Journal of Medicine 324:727-733(1991).

57. Lindbohm M-L, Hietanen M, Kyyronen P, Sallmen M, Von Nandelstadh P, Taskinen H, Pekkarinen M, Ylikoski M, Hemminki K. Magnetic fields of video display terminals and spontaneous abortion. American Journal of Epidemiology 136:1041-1051(1992).

58. Juutilainen J, Matilainen P, Saarikoski S, Laara E, Suonio S. Early pregnancy loss and exposure to 50-Hz magnetic fields. Bioelectromagnetics 14:229-236(1993).

59. Belanger K, Leaderer B, Kellenbrand K, Holford T, McSharry J-E, Power M-E, Bracken M. Spontaneous abortion and exposure to electric blankets and heated water beds. Epidemiology 9:36-42(1998).

60. Bracken MB, Belanger K, Hellenbrand K, Dlugosz L, Holford TR, McSharry J-E, Addesso K, Leaderer B. Exposure to electromagnetic fields during pregnancy with emphasis on electrically heated beds: Association with birthweight and intrauterine growth retardation. Epidemiology 6:263-270(1995).

61. Grajewski B, Schnorr TM, Reefhuis J, Roeleveld N, Salvan A, Mueller C, Murray WE, Conover DL. Work with video display terminals and the risk of reduced birthweight and preterm birth. American Journal of Industrial Medicine 32:681-688(1997).

62. Tornqvist S. Paternal work in the power industry: Effects on children at delivery. Journal of Occupational and Environmental Medicine 40:111-117(1998).

63. Wertheimer N, Leeper E. Possible effects of electric blankets and heated waterbeds on fetal development. Bioelectromagnetics 7:13-22(1986).

64. Dlugosz L, Vena J, Byers T, Sever L, Bracken M, Marshall E. Congenital defects and electric bed heating in New York state: A register-based case-control study. American Journal of Epidemiology 135:1000-1011(1992).

65. Li D-K, Checkoway H, Mueller BA. Electric blanket use during pregnancy in relation to the risk of congenital urinary tract anomalies among women with a history of subfertility. Epidemiology 6:485-489(1995).

66. Savitz D, Checkoway H, Loomis D. Magnetic field exposure and neurodegenerative disease mortality among electric utility workers. Epidemiology 9:398-404(1998).

67. Savitz D, Loomis D, Chiu-Kit T. Electrical occupations and neurodegenerative disease: Analysis of U.S. mortality data. Archives of Environmental Health 53:1-5(1998).

68. Sobel E, Davanipour Z, Sulkava R, Erkinjuntti T, Wikstrom J, Henderson VW, Buckwalter G, Bowman JD, Lee P-J. Occupations with exposure to electromagnetic fields: A possible risk factor for Alzheimer's disease. American Journal of Epidemiology 142:515-524(1995).

69. Sobel E, Davanipour Z. Electromagnetic field exposure may cause increased production of amyloid beta and may eventually lead to Alzheimer's disease. Neurology 47:1594-1600(1996).

70. Feychting M, Pedersen N, Svedberg P, Floderus B, Gatz M. Dementia and occupational exposure to magnetic fields. Scandinavian Journal of Work, Environment and Health 24:46-53(1998).

71. Davanipour Z, Sobel E, Bowman JD, Qian Z, Will AD. Amyotrophic lateral sclerosis and occupational exposure to electromagnetic fields. Bioelectromagnetics 18:28-35(1997).

72. Johansen C, Olsen JH. Mortality from amyotrophic lateral sclerosis, other chronic disorders and electric shocks among utility workers. American Journal of Epidemiology 148:362-368(1998).

73. Savitz DA, Boyle CA, Holmgreen P. Prevalence of depression among electrical workers. American Journal of Industrial Medicine 25:165-176(1994).

74. Baris D, Armstrong BG, Deadman J, Thériault G. A case cohort study of suicide in relation to exposure to electrical and magnetic fields among electrical utility workers. Occupational and Environmental Medicine 53:17-24(1996).

75. Baris D, Armstrong BG, Deadman J, Thériault G. A mortality study of electrical utility workers in Quebec. Occupational and Environmental Medicine 53:25-31(1996).

76. Savitz DA, Liao D, Sastre A, Kleckner RC. Magnetic field exposure and cardiovascular disease mortality among electric utility workers. American Journal of Epidemiology 149:135-142(1999).

77. Sastre A, Cook MR, Graham C. Nocturnal exposure to intermittent 60 Hz magnetic fields alter human cardiac rhythm. Bioelectromagnetics 19:98-106(1998).

78. Hauf R, Wiesinger J. Biological effects of technical electric and electromagnetic VLF fields. International Journal of Biometeorology 17:213-215(1973).

79. Silny J. The influence thresholds of the time-varying magnetic field in the human organism. In: Proceedings of the Symposium on Biological Effects of Static and ELF-Magnetic Fields, Neuherberg, May 1986;1-11.

80. Graham C, Cohen HD, Cook MR. Immunological and biochemical effects of 60-Hz electric and magnetic fields in humans MRI Project No. RA-338-C. Kansas City: Midwest Research Institute, 1990.

81. Wood AW, Armstrong SM, Sait ML, Devine L, Martin MJ. Changes in human plasma melatonin profiles in response to 50 Hz magnetic field exposure. Journal of Pineal Research 25:116-127(1998).

82. Blondin J-P, Nguyen D-C, Sbeghen J, Goulet D, Cardinal C, Maruvada PS, Plante M, Bailey WH. Human perception of electric fields and ion currents associated with high-voltage DC transmission lines. Bioelectromagnetics 17:230-241(1996).

83. Stollery BT. Effects of 50 Hz electric currents on mood and verbal reasoning skills. British Journal of Industrial Medicine 43:339-349(1986).

84. Selmaoui B, Lambrozo J, Touitou Y. Magnetic fields and pineal function in humans: Evaluation of nocturnal acute exposure to extremely low frequency magnetic fields on serum melatonin and urinary 6-sulfatoxymelatonin circadian rhythms. Life Science 58:1539-1549(1996).

85. Podd JV, Whittington CJ, Barnes GRG, Page WH, Rapley BI. Do ELF magnetic fields affect human reaction time? Bioelectromagnetics 16:317-323(1995).

86. Lyskov EB, Juutilainen J, Jousmaki V, Partanen J, Medvedev S, Hanninen O. Effects of 45-Hz magnetic Fields on the functional state of the human brain. Bioelectromagnetics 14:87-95(1993).

87. Cohen HD, Graham C, Cook MR, Phelps JW. ELF exposure facility for human testing. Bioelectromagnetics 13:169-182(1992).

88. Doynov P, Cohen HD, Cook MR, Graham C. Test facility for human exposure to AC and DC magnetic fields. Bioelectromagnetics In press(1999).

89. Lyskov E, Juutilainen V, Jousmaki V, Hanninen O, Medvedev S, Partanen J. Influence of short-term exposure of magnetic field on the bioelectrical processes of the brain and performance. International Journal of Psychophysiology 14:227-231(1993).

90. Bell GB, Marino AA, Chesson AL. Alterations in brain electrical activity caused by magnetic fields: detecting the detection process. Electroencephalography and Clinical Neurophysiology 83:389-397(1992).

91. Cook MR, Graham C, Cohen HD, Gerkovich MM. A replication study of human exposure to 60-Hz fields: Effects on neurobehavioral measures. Bioelectromagnetics 13:261-285(1992).

92. Graham C, Cohen H, Cook M, Phelps J, Gerkovich M, Fotopoulos S. A double-blind evaluation of 60-Hz field effects on human performance, physiology, and subjective state. In: Interaction of Biological Systems with Static and ELF Electric and Magnetic Fields (Anderson LE, ed). Springfield, 1987;471-486.

93. Graham C, Cook MR, Cohen HD, Gerkovich MM. A dose response study of human exposure to 60 Hz electric and magnetic fields. Bioelectromagnetics 15:447-463(1994).

94. Graham C, Cook M, Hoffman S, Gerkovich M. An electrophysiological study of human EEG activity in 60-Hz magnetic fields. In: Bioelectromagnetics Society, 17th Annual Meeting, Boston, MA, 18-22 June 1995;84.

95. Akerstedt T, Arnetz B, Ficca G, Lars-Eric P. Low frequency electromagnetic fields suppress slow wave sleep. Sleep Research 26:260(1997).

96. Akerstedt T, Arnetz T, Picca G, Paulsson LE, Kallner A. Effects of low frequency electromagnetic fields on sleep and some hormones (summary). Stress Research Reports 275(1997).

97. Graham C, Cook MR. Human sleep in 60 Hz magnetic fields. Bioelectromagnetics In press(1999).

98. Korpinen L, Partanen J, Uusitalo A. Influence of 50 Hz electric and magnetic fields on the human heart. Bioelectromagnetics 14:329-340(1993).

99. Maresh CM, Cook MR, Cohen HD, Graham C, Gunn WS. Exercise testing in the evaluation of human responses to powerline frequency fields. Aviation, Space, and Environmental Medicine 59:1139-1145(1988).

100. Arnetz BB, Berg M. Melatonin and adrenocorticotropic hormone levels in video display unit workers during work and leisure. Journal of Occupational Medicine 38:1108-1110(1996).

101. Burch JB, Reif JS, Yost MG, Keffe TJ, Pitrat CA. Nocturnal excretion of a urinary melatonin metabolite in electric utility workers. Scandinavian Journal of Work, Environment and Health 24:183-189(1998).

102. Graham C, Cook MR, Riffle DW, Gerkovich MM, Cohen HD. Nocturnal melatonin levels in human volunteers exposed to intermittent 60 Hz magnetic fields. Bioelectromagnetics 17:263-273(1996).

103. Graham C, Cook MR, Riffle DW. Human melatonin during continuous magnetic field exposure. Bioelectromagnetics 18:166-171(1997).

104. Kaune W, Davis S, Stevens R. Relation between residential magnetic fields, light-at-night and nocturnal urine melatonin levels in women TR-107242-V1. Palo Alto: EPRI, Fred Hutchinson Research Center, 1997.

105. Pfluger DH, Minder CE. Effects of exposure to 16.7 Hz magnetic fields on urinary 6-hydroxymelatonin sulfate excretion of Swiss railway workers. Journal of Pineal Research 21:91-100(1996).

106. Wilson BW, Wright CW, Morris JE, Buschbom RL, Brown DP, Miller DL, Sommers-Flannigan R, Anderson LE. Evidence for an effect of ELF electromagnetic fields on human pineal gland function. Journal of Pineal Research 9:259-269(1990).

107. Selmaoui B, Bogdan A, Auzeby A, Lambrozo J, Touitou Y. Acute exposure to 50 Hz magnetic field does not affect hematologic or immunologic functions in healthy young men: A circadian study. Bioelectromagnetics 17:364-372(1996).

108. Hauf R. Electric and magnetic fields at power frequencies with particular reference to 50 and 60 Hz. In: Nonionizing Radiation Protection (Suess M, ed). Copenhagen:World Health Organization, 1982.

109. Andersson B, Berg M, Arnetz BB, Melin L, Langlet I, Liden S. A cognitive-behavioral treatment of patients suffering from 'electric hypersensitivity.' Subjective effects and reactions in a double-blind provocation study. Journal of Occupational and Environmental Medicine 38:752-758(1996).

110. Arnetz BB. Technological stress: Psychophysiological aspects of working with modern information technology. Scandinavian Journal of Work, Environment and Health. 23:97-103(1997).

111. Arnetz BB, Berg M, Arnetz J. Mental strain and physical symptoms among employees in modern offices. Archives of Environmental Health 52:63-67(1997).

112. Sandström M, Lyskov E, Berglund A, Medvedev S, Mild K. Neurophysiological effects of flickering light in patients with perceived electrical hypersensitivity. Journal of Occupational and Environmental Medicine 39:15-22(1997).

113. Swanbeck G, Bleeker T. Skin problems from visual display units. Acta Dermatologica Venereologica 69:46-51(1989).

114. Mandeville R, Franco E, Sidrac-Ghali S, Paris-Nadon L, Rocheleau N, Mercier G, Desy M, Gaboury L. Evaluation of the potential carcinogenicity of 60 Hz linear sinusoidal continuous-wave magnetic fields in Fisher F344 rats. FASEB Journal 11:1127-1136(1997).

115. NTP. Toxicology and Carcinogenesis Studies of 60-Hz Magnetic Fields in F344/N Rats and B6C3F1 Mice (Whole Body Exposure Studies). Technical Report Series No. 488 NIH Publication No. 98-3978. Research Triangle Park: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, 1998.

116. Yasui M, Kikuchi T, Ogawa M, Otaka Y, Tsuchitani M, Iwata H. Carcinogenicity test of 50 Hz sinusoidal magnetic fields in rats. Bioelectromagnetics 18:531-540(1997).

117. Matanoski GM, Breysse PN, Elliott EA. Electromagnetic field exposure and male breast cancer. Lancet 337:737(1991).

118. Demers PA, Thomas DB, Rosenblatt KA, Jimenez LM, McTiernan A, Stalsberg H, Stemhagen A, Thompson WD, Curnen MGM, Satanano W, Austin DF, Isacson P, Greenberg RS, Key C, Kolonel LN, West DW. Occupational exposure to electromagnetic fields and breast cancer in men. American Journal of Epidemiology 134:340-347(1991).

119. Coogan PF, Clapp RW, Newcomb PA, Wenzl TB, Bogdan G, Mittendorf R, Baron JA, Longnecker MP. Occupational exposure to 60-Hertz magnetic fields and risk of breast cancer in woman. Epidemiology 7:459-464(1996).

120. Stevens RG. Electic power use and breast cancer: A hypothesis. American Journal of Epidemiology 125:556-561(1987).

121. Beniashvili DS, Bilanishvili VG, Menabde MZ. Low-frequency electromagnetic radiation enhances the induction of rat mammary tumors by nitrosomethyl urea. Cancer Letters 61:75-79(1991).

122. Löscher W, Mevissen M, Lehmacher W, Stamm A. Tumor promotion in a breast cancer model by exposure to a weak alternating magnetic field. Cancer Letters 71:75-81(1993).

123. Löscher W, Wahnschaffe U, Mevissen M, Lerchl A, Stamm A. Effects of weak alternating magnetic fields on nocturnal melatonin production and mammary carcinogenesis in rats. Oncology 51:288-295(1994).

124. Mevissen M, Stamm A, Buntenkotter S, Zwingelberg R, Wahnschaffe U, Löscher W. Effects of magnetic fields on mammary tumor development induced by 7,12-dimethylbenz(a)anthracene in rats. Bioelectromagnetics 14:131-143(1993).

125. Baum A, Mevissen M, Kamino K, Mohr U, Löscher W. A histopathological study on alterations in DMBA-induced mammary carcinogenesis in rats with 50 Hz, 100 μT magnetic field exposure. Carcinogenesis 16:119-125(1995).

126. Mevissen M, Lerchl A, Löscher W. Study on pineal function and DMBA-induced breast cancer formation in rats during exposure to a 100-mg, 50-Hz magnetic field. Journal of Toxicology and Environmental Health 48:169-185(1996).

127. Mevissen M, Lerchl A, Szamel M, Löscher W. Exposure of DMBA-treated female rats in a 50-Hz, 50 microtesla magnetic field: Effects on mammary tumor growth, melatonin levels and T-lymphocyte activation. Carcinogenesis 17:903-910(1996).

128. Mevissen M, Haubler M, Lerchl A, Löscher W. Acceleration of mammary tumorigenesis by exposure of 7,12-dimethylbenz(a)anthracene-100-μt magnetic field: Replication study. Journal of Toxicology and Environmental Health, Part A 53:401-418(1998).

129. NTP. Studies of Magnetic Field Promotion in Sprague-Dawley Rats. Technical Report Series No. 489 NIH Publication No. 98-3979. Research Triangle Park: US Department of Health and Human Services, Public Health Service, National Institute of Environmental Health Sciences, National Toxicology Program, 1998.

130. Ekström T, Mild KH, Homberg B. Mammary tumours in Sprague-Dawley rats after initiation with DMBA followed by exposure to 50 Hz electromagnetic fields in a promotional scheme. Cancer Letters 123:107-111(1998).

131. DiGiovanni J. Multistage carcinogenesis in mouse skin. Pharmaceutical Therapy 54:63-128(1992).

132. Stuchly MA, McLean JRN, Burnett R, Goddard M, Lecuyer DW, Mitchel REJ. Modification of tumor promotion in the mouse skin by exposure to an alternating magnetic field. Cancer Letters 65:1-7(1992).

133. McLean J, Thansandote A, Lecuyer D, Goddard M, Tryphonas L, Scaiano JC, Johnson F. A 60-Hz magnetic field increases the incidence of squamous cell carcinomas in mice previously exposed to chemical carcinogens. Cancer Letters 92:121-125(1995).

134. McLean JRN, Thansandote A, Lecuyer D, Goddard M. The effect of 60-Hz magnetic fields on co-promotion of chemically induced skin tumors on SENCAR mice: A discussion of three studies. Environmental Health Perspectives 105:94-96(1997).

135. Rannug A, Ekström T, Mild KH, Holmberg B, Gimenez-Conti I, Slaga TJ. A study on skin tumour formation in mice with 50 Hz magnetic field exposure. Carcinogenesis 14:573-578(1993).

136. Rannug A, Holmberg B, Ekström T, Mild KH, Gimenez-Conti I, Slaga TJ. Intermittent 50 Hz magnetic field and skin tumor promotion in SENCAR mice. Carcinogenesis 15:153-157(1994).

137. Sasser LB, Anderson LE, Morris JE, Miller DL, Walborg EF, Jr., Kavet R, Johnston DA, DiGiovanni J. Lack of co-promoting effect of a 60 Hz magnetic field on skin tumorigenesis in SENCAR mice. Carcinogenesis 19:1617-1621(1998).

138. Dragan YP, Pitot HC. The role of the stages of initiation and promotion in phenotypic diversity during hepatocarcinogenesis in the rat. Carcinogenesis 13:739-750(1992).

139. Rannug A, Holmberg B, Ekström T, Mild KH. Rat liver foci study on coexposure with 50 Hz magnetic fields and known carcinogens. Bioelectromagnetics 14:17-27(1993).

140. Rannug A, Holmberg B, Mild KH. A rat liver foci promotion study with 50-Hz magnetic fields. Environmental Research 62:223-229(1993).

141. Babbitt JT, Kharazi AI, Taylor JMG, Rafferty CN, Kovatch R, Bonds CB, MIrell SG, Frumkin E, Dietrich F, Zhuang D, Hahn TJM. Leukemia/lymphoma in mice exposed to 60-Hz magnetic fields: Results of the chronic exposure study TR-110338. Los Angeles: EPRI, 1998.

142. Shen YH, Shao BJ, Chiang H, Fu YD, Yu M. The effects of 50 Hz magnetic field exposure on dimethylbenz(alpha)anthracene induced thymic lymphoma/leukemia in mice. Bioelectromagnetics 18:360-364(1997).

143. Anderson LE, Sasser LB, Morris JE, Miller DL. Large granular lymphocytic (LGL) leukemia in rats exposed to 60 Hz magnetic fields: results of the second study using continuous and intermittent fields TR-109469. Palo Alto: EPRI, 1997.

144. Sasser LB, Morris JE, Miller DL, Rafferty CN, Ebi KL, Anderson LE. Exposure to 60 Hz magnetic fields does not alter clinical progression of LGL leukemia in Fischer rats. Carcinogenesis 17:2681-2687(1996).

145. McCormick DL, Ryan BM, Findlay JC, Gauger JR, Johnson TR, Morrissey RL, Boorman GA. Exposure to 60 Hz magnetic fields and risk of lymphoma in PIM transgenic and TSG-p53 (p53 knockout) mice. Carcinogenesis 19:1649-1653(1998).

146. Harris AW, Basten A, Gebski V, Noonan D, Finnie J, Bath ML, Bangay MJ, Repacholi MH. A test of lymphoma induction by long-term exposure of Eμ−Pim1 transgenic mice to 50 Hz magnetic fields. Radiation Research 149:300-307(1998).

147. Kharazi AI, Babbitt JT, Boorman GA, Hahn TJ. Brain tumors in mice exposed to 60 Hz magnetic fields No. 97-B: EPRI, UCLA, 1998.

148. Murthy KK, Rogers WR, Smith HD. Initial studies on the effects of combined 60 Hz electric and magnetic field exposure on the immune system of nonhuman primates. Bioelectromagnetics Supplement 3:93-102(1995).

149. Mevissen M, Haussler M, Szamel M, Emmendorffer A, Thun-Battersby S, Löscher W. Complex effects of long-term 50 Hz magnetic field exposure *in vivo* on immune functions in female Sprague-Dawley rats depend on duration of exposure. Bioelectromagnetics 19:259-270(1998).

150. Tremblay L, Houde M, Mercier G, Gagnon J, Mandeville R. Differential modulation of natural and adaptive immunity in Fischer rats exposed for 6 weeks to 60 Hz linear sinusoidal continuous-wave magnetic fields. Bioelectromagnetics 17:373-383(1996).

151. House RV, Ratajczak HV, Gauger JR, Johnson TR, Thomas PT, McCormick DL. Immune function and host defense in rodents exposed to 60-Hz magnetic fields. Fundamental Applied Toxicology 34:228-239(1996).

152. Boorman GA, Gauger JR, Johnson TR, Tomlinson MJ, Findlay JC, Travlos GS, McCormick DL. Eight-week toxicity study of 60 Hz magnetic fields in F344 rats and B6C3 F1 mice. Fundamental and Applied Toxicology 35:55-63(1997).

153. Lorimore SA, Kowalczuk CI, Saunders RD, Wright EG. Lack of acute effects of 20 mT, 50 Hz magnetic fields on murine hematopoiesis. International Journal of Radiation Biology 58:713-723(1990).

154. Margonato V, Veicsteinas A, Conti R, Nicolini P, Cerretelli P. Biologic effects of prolonged exposure to ELF electromagnetic fields in rats. I. 50 Hz electric fields. Bioelectromagnetics 14:479-493(1993).

155. Margonato V, Nicolini P, Conti R, Zecca L, Veicsteinas A, Cerretelli P. Biologic effects of prolonged exposure to ELF electromagnetic fields in rats: II. 50 Hz magnetic fields. Bioelectromagnetics 16:343-355(1995).

156. Picazo ML, Vallejo D, Bardasano JL. An introduction to the study of ELF magnetic field effects on white blood cells in mice. Electro- and Magnetobiology 13:77-84(1994).

157. Picazo ML, Sanz P, Vallejo D, Alvarez-Ude JA, Bardasano JL. Effects of ELF magnetic fields on hematological parameters: an experimental model. Electro- and Magnetobiology 14:75-89(1995).

158. Zecca L, Mantegazza C, Margonato V, Cerretelli R, Caniatti M, Piva R, Dondi D, Hagino N. Biological effects of prolonged exposure to ELF electromagnetic fields in rats: III. 50 Hz electromagnetic fields. Bioelectromagnetics 19:57-66(1998).

159. Creim JA, Lovely RH, Kaune WT, Phillips RD. Attempts to produce taste-aversion learning in rats exposed to 60-Hz electric fields. Bioelectromagnetics 5:271-282(1984).

160. Rogers WR, Orr JL, Smith HD. Initial exposure to 30 kV/m or 60 kV/m 60 Hz electric fields produces temporary cessation of operant behavior of nonhuman primates. Bioelectromagnetics Supplement 3:35-47(1995).

161. Rogers WR, Orr JL, Smith HD. Nonhuman primates will not respond to turn off strong 60 Hz electric fields. Bioelectromagnetics Supplement 3:48-60(1995).

162. Stern S, Laties VG. 60-Hz electric fields: Detection by female rats. Bioelectromagnetics 6:99-103(1985).

163. Coelho AM, Jr., Easley SP, Rogers WR. Effects of exposure to 30 kV/m, 60-Hz electric fields on the social behavior of baboons. Bioelectromagnetics 12:117-135(1991).

164. Orr JL, Rogers WR, Smith HD. Exposure of baboons to combined 60 Hz electric and magnetic fields does not produce work stoppage or affect operant performance on a match-to-sample task. Bioelectromagnetics Supplement 3:61-70(1995).

165. Sienkiewicz ZJ, Haylock RGE, Saunders RD. Deficits in spatial learning after exposure of mice to a 50 Hz magnetic field. Bioelectromagnetics 19:79-84(1998).

166. Lai H. Spatial learning deficit in the rat after exposure to a 60 Hz magnetic field. Bioelectromagnetics 17:494-496(1996).

167. Kavaliers M, Ossenkopp K-P, Prato FS, Innes DGL, Galea LAM, Kinsella DM, Perrot-Sinal TS. Spatial learning in deer mice: Sex differences and the effects of endogenous opioids and 60 Hz magnetic fields. Journal of Comparative Physiology A - Sensory Neural and Behavioral Physiology 179:715-724(1996).

168. Sienkiewicz ZJ, Robbins L, Haylock RGE, Saunders RD. Effects of prenatal exposure to 50 Hz magnetic fields on development in mice: II. Postnatal development and behavior. Bioelectromagnetics 15:363-375(1994).

169. Sienkiewicz ZJ, Larder S, Saunders RD. Prenatal exposure to a 50 Hz magnetic field has no effect on spatial learning in adult mice. Bioelectromagnetics 17:249-252(1996).

170. Coelho AM, Jr., Rogers WR, Easley SP. Effects of concurrent exposure to 60 Hz electric and magnetic fields on the social behavior of baboons. Bioelectromagnetics Supplement 3:71-92(1995).

171. Ryan BM, Mallett E, Johnson TR, Gauger JR, McCormick DL. Developmental toxicity study of 60 Hz (power frequency) magnetic fields in rats. Teratology 54:73-83(1996).

172. Ryan BM, Symanski RR, Pomeranz LE, Johnson TR, Gauger JR, McCormick DL. Multi-generation reproductive toxicity assessment of 60 Hz magnetic fields using a continuous breeding protocol in rats. Teratology 56:159-162(1999).

173. Baldwin WS, Barrett JC. Melatonin: Receptor-mediated events that may affect breast and other steroid hormone-dependent cancers. Molecular Carcinogenesis 21:149-155(1998).

174. Wilson BW, Anderson LE, Hilton DI, Phillips RD. Chronic exposure to 60-Hz electric fields: Effects on pineal function in the rat. Bioelectromagnetics 2:371-380(1981).

175. Wilson BW, Chess EK, Anderson LE. 60-Hz electric-field effects on pineal melatonin rhythms: Time course for onset and recovery. Bioelectromagnetics 7:239-242(1986).

176. Reiter RJ, Anderson LE, Buschbom RL, Wilson BW. Reduction of the nocturnal rise in pineal melatonin levels in rats exposed to 60-Hz electric fields *in utero* and for 23 days after birth. Life Science 42:2203-2206(1988).

177. Grota LJ, Reiter RJ, Keng P, Michaelson S. Electric field exposure alters serum melatonin but not pineal melatonin synthesis in male rats. Bioelectromagnetics 15:427-437(1994).

178. Yellon SM. Acute 60 Hz magnetic field exposure effects on the melatonin rhythm in the pineal gland and circulation of the adult Djungarian hamster. Journal of Pineal Research 16:136-144(1994).

179. Truong H, Yellon SM. Effect of various acute 60 Hz magnetic field exposures on the nocturnal melatonin rise in the adult Djungarian hamster. Journal of Pineal Research 22:177-183(1997).

180. Yellon SM, Truong HN. Melatonin rhythm onset in the adult Siberian hamster: Influence of photoperiod but not 60-Hz magnetic field exposure on melatonin content in the pineal gland and in circulation. Journal of Biological Rhythms 13:52-59(1998).

181. Kato M, Honma K, Shigemitsu T, Shiga Y. Effects of exposure to a circularly polarized 50-Hz magnetic field on plasma and pineal melatonin levels in rats. Bioelectromagnetics 14:97-106(1993).

182. Kato M, Honma K, Shigemitsu T, Shiga Y. Circularly polarized 50-Hz magnetic field exposure reduces pineal gland melatonin and blood concentrations of long-evans rats. Neuroscience Letters 166:59-62(1994).

183. Kato M, Honma K, Shigemitsu T, Shiga Y. Horizontal or vertical 50-Hz, 1-μT magnetic fields have no effect on pineal gland or plasma melatonin concentration of albino rats. Neuroscience Letters 168:205-208(1994).

184. Selmaoui B, Touitou Y. Sinusoidal 50-Hz magnetic fields depress rat pineal NAT activity and serum melatonin. Role of duration and intensity of exposure. Life Science 57:1351-1358(1995).

185. John TM, Liu G-Y, Brown GM. 60 Hz magnetic field exposure and urinary 6-sulphatoxymelatonin levels in the rat. Bioelectromagnetics 19:172-180(1998).

186. Kato M, Honma K, Shigemitsu T, Shiga Y. Recovery of nocturnal melatonin concentration takes place within one week following cessation of 50 Hz circularly polarized magnetic field exposure for six weeks. Bioelectromagnetics 15:489-492(1994).

187. Lee JM, Jr., Stormshak F, Thompson JM, Thinesen P, Painter LJ, Olenchek EG, Hess DL, Forbes R, Foster DL. Melatonin secretion and puberty in female lambs exposed to environmental electric and magnetic fields. Biology of Reproduction 49:857-864(1993).

188. Lee JM, Jr., Stormshak F, Thompson JM, Hess DL, Foster DL. Melatonin and puberty in female lambs exposed to EMF: A replicate study. Bioelectromagnetics 16:119-123(1995).

189. Rogers WR, Reiter RJ, Smith HD, Barlow-Walden L. Rapid-onset/offset, variably scheduled 60 Hz electric and magnetic field exposure reduces nocturnal serum melatonin concentration in nonhuman primates. Bioelectromagnetics Supplement 3:119-122(1995).

190. Scarfi MR, Lioi MB, Zeni O, Franceschetti G, Franceschi C, Bersani F. Lack of chromosomal aberration and micronucleus induction in human lymphocytes exposed to pulsed magnetic fields. Mutation Research 306:129-133(1994).

191. Paile W, Jokela K, Koivistoinen A, Salomaa S. Effects of 50 Hz sinusoidal magnetic fields and spark discharges on human lymphocytes *in vitro*. Bioelectrochemistry and Bioenergetics 36:15-22(1995).

192. Khalil AM, Qassem W. Cytogenetic effects of pulsing electromagnetic field on human lymphocytes *in vitro*: chromosome aberrations, sister-chromatid exchanges and cell kinetics. Mutation Research 247:141-146(1991).

193. McCann J, Dietrich F, Rafferty C. The genotoxic potential of electric and magnetic fields - An update. Mutation Research 411:45-86(1998).

194. Ager DD, Radul JA. Effect of 60-Hz magnetic fields on ultraviolet light-induced mutation and mitotic recombination in *Saccharomyces cerevisiae*. Mutation Research 283:279-286(1992).

195. Morandi MA, Pak CM, Caren RP, Caren LD. Lack of an EMF-induced genotoxic effect in the Ames assay. Life Science 59:263-271(1996).

196. Miyakoshi J, Ohtsu S, Shibata T, Takebe H. Exposure to magnetic field (5 mT at 60 Hz) does not affect cell growth and *c-myc* gene expression. Journal of Radiation Research (CHIBA) 37:185-191(1996).

197. Miyakoshi J, Mori Y, Yamagishi N, Yagi K, Takebe H. Suppression of high-density magnetic field (400 mT at 50 Hz)-induced mutations by wild-type p53 expression in human osteosarcoma cells. Biochemical and Biophysical Research Communications 243:579-584(1998).

198. Walleczek J, Shiu E, Hahn GM. Increase in radiation-induced HPRT gene mutation frequency from nonthermal exposure to non-ionizing 60-Hz electromagnetic fields. Radiation Research In press(1999).

199. Cantoni O, Sestili P, Fiorani M, Dacha M. The effect of 50 Hz sinusoidal electric and/or magnetic fields on the rate of repair of DNA single/double strand breaks in oxidatively injured cells. Biochemistry and Molecular Biology International 37:681-689(1995).

200. Frazier ME, Reese JA, Morris JE, Jostes RF, Miller DL. Exposure of mammalian cells to 60-Hz magnetic or electric fields: analysis of DNA repair of induced, single-strand breaks. Bioelectromagnetics 11:229-234(1990).

201. Whitson GL, Carrier WL, Francis AA, Shih CC, Georghiou S, Regan JD. Effects of extremely low frequency (ELF) electric fields on cell growth and DNA repair in human skin fibroblasts. Cell and Tissue Kinetics 19:39-47(1986).

202. Goodman R, Wei L-X, Xu J-C, Henderson A. Exposure of human cells to low-frequency electromagnetic fields results in quantitative changes in transcripts. Biochimica et Biophysica Acta 1009:216-220(1989).

203. Goodman R, Shirley-Henderson A. Transcription and translation in cells exposed to extremely low frequency electromagnetic fields. Bioelectrochemistry and Bioenergetics 25:335-355(1991).

204. Goodman R, Bumann J, Wei L-X, Shirley-Henderson A. Exposure of human cells to electromagnetic fields: Effect of time and field strength on transcript levels. Electro- and Magnetobiology 11:19-28(1992).

205. Gold S, Goodman R, Shirley-Henderson A. Exposure of Simian virus-40-transformed human cells to magnetic fields results in increased levels of T-antigen mRNA and protein. Bioelectromagnetics 15:329-336(1994).

206. Lin H, Goodman R, Henderson AS. Specific region of the *c-myc* promoter is responsive to electric and magnetic fields. Journal of Cellular Biochemistry 54:281-288(1994).

207. Desjobert H, Hillion J, Adolphe M, Averlant G, Nafziger J. Effects of 50 Hz magnetic fields on *c-myc* transcript levels in nonsynchronized and synchronized human cells. Bioelectromagnetics 16:277-283(1995).

208. Lacy-Hulbert A, Wilkins RC, Hesketh TR, Metcalfe JC. No effect of 60 Hz electromagnetic fields on *myc* or *beta-actin* expression in human leukemic cells. Radiation Research 144:9-17(1995).

209. Owen RD. *MYC* mRNA abundance is unchanged in subcultures of HL60 cells exposed to power-line frequency magnetic fields. Radiation Research 150:23-30(1998).

210. Saffer JD, Thurston SJ. Short exposure to 60 Hz magnetic fields do not alter *myc* expression in HL60 or Daudi cells. Radiation Research 144:18-25(1995).

211. Jin M, Lin H, Han L, Opler M, Maurer S, Blank M, Goodman R. Biological and technical variables in *myc* expression in HL60 cells exposed to 60 Hz electromagnetic fields. Bioelectrochemistry and Bioenergetics 44:111-120(1997).

212. Goodman EM, Greenebaum B, Marron MT. Magnetic fields alter translation in *Escherichia coli*. Bioelectromagnetics 15:77-83(1994).

213. Weisbrot DR, Khorkova O, Lin H, Henderson AS, Goodman R. The effect of low frequency electric and magnetic fields on gene expression in *Saccharomyces cerevisiae*. Bioelectrochemistry and Bioenergetics 31:167-177(1993).

214. Lin H, Opler M, Head M, Blank M, Goodman R. Electromagnetic field exposure induces rapid, transitory heat shock factor activation in human cells. Journal of Cellular Physiology 66:482-488(1997).

215. Dibirdik I, Kristupaitis D, Kurosaki T, Tuel-Ahlgren L, Chu A, Pond D, Tuong D, Luben R, Uckun F. Stimulation of *Src* family protein-tyrosine kinases as a proximal and mandatory step for SYK kinase-dependent phospholipase C(gamma)2 activation in lymphoma B-cells exposed to low energy electromagnetic fields. Journal of Biological Chemistry 273:4035-4039(1998).

216. Kristupaitis D, Dibirdik I, Vassilev A, Mahajan S, Kurosaki T, Chu A, Tuel-Ahlgren L, Tuong D, Pond D, Luben R, Uckun FM. Electromagnetic field-induced stimulation of Bruton's tyrosine kinase. Journal of Biological Chemistry 273:12397-12401(1998).

217. Uckun FM, Kurosaki T, Jin J, Jun X, Morgan A, Takata M, Bolen J, Luben R. Exposure of B-lineage lymphoid cells to low energy electromagnetic fields stimulates lyn kinase. Journal of Biological Chemistry 270:27666-27670(1995).

218. Miller SC, Furniss MJ. Bruton's tyrosine kinase activity and inositol-1,4,5-trisphosphate production are not altered in the DT40 lymphoma B cells exposed to power line frequency magnetic fields. Journal of Biological Chemistry 273:32618-32626(1998).

219. Byus CV, Pieper SE, Adey WR. The effects of low-energy 60-Hz environmental electromagnetic fields upon the growth-related enzyme ornithine decarboxylase. Carcinogenesis 8:1385-1389(1987).

220. Litovitz TA, Krause D, Mullins JM. Effect of coherence time of the applied magnetic field on ornithine decarboxylase activity. Biochemical and Biophysical Research Communication 178:862-865(1991).

221. Mevissen M, Kietzmann M, Löscher W. *In vivo* exposure of rats to a weak alternating magnetic field increases ornithine decarboxylase activity in the mammary gland by a similar extent as the carcinogen DMBA. Cancer Letters 90:207-214(1995).

222. Valtersson U, Mild KH, Mattsson M-O. Ornithine decarboxylase activity and polyamine levels are different in Jurkat and CEM-CM3 cells after exposure to a 50 Hz magnetic field. Bioelectrochemistry and Bioenergetics 43:169-172(1997).

223. Azadniv M, Klinge CM, Gelein R, Carstensen EL, Cox C, Brayman AA, Miller MW. A test of the hypothesis that a 60-Hz magnetic field affects ornithine decarboxylase activity in mouse l929 cells *in vitro*. Biochemical and Biophysical Research Communications 214:627-631(1995).

224. Cress LW, Owen RD, Desta AB. Ornithine decarboxylase activity in L929 cells following exposure to 60 Hertz magnetic fields. Carcinogenesis In press(1999).

225. Antonopoulos A, Yang B, Stamm A, Heller W-D, Obe G. Cytological effects of 50 Hz electromagnetic fields on human lymphocytes *in vitro*. Mutation Research 346:151-157(1995).

226. Rosenthal M, Obe G. Effects of 50-Hertz electromagnetic fields on proliferation and on chromosomal alterations in human peripheral lymphocytes untreated or pretreated with chemical mutagens. Mutation Research 210:329-335(1989).

227. West RW, Hinson WG, Lyle DB, Swicord ML. Enhancement of anchorage-independent growth in JB6 cells exposed to 60 Hertz magnetic fields. Bioelectrochemistry and Bioenergetics 34:39-43(1994).

228. Saffer JD, Chen G, Colburn NH, Thurston SJ. Power frequency magnetic fields do not contribute to transformation of JB6 cells. Carcinogenesis 18:1365-1370(1997).

229. Snawder JE, Edwards RM, Conover DL, Lotz WG. Effect of magnetic field exposure on anchorage-independent growth of a promoter sensitive mouse epidermal cell line (JB6). Environmental Health Perspectives In press(1999).

230. Katsir G, Baram S, Parola A. Effect of sinusoidally varying magnetic fields on cell proliferation and adenosine deaminase specific activity. Bioelectromagnetics 19:46-52(1998).

231. Liburdy RP, Sloma TR, Sokolic R, Yaswen P. ELF magnetic fields, breast cancer, and melatonin: 60 Hz fields block melatonin's oncostatic action on ER+ breast cancer cell proliferation. Journal of Pineal Research 14:89-97(1993).

232. Harland JD, Liburdy RP. Environmental magnetic fields inhibit the antiproliferative action of tamoxifen and melatonin in a human breast cancer cell line. Bioelectromagnetics 18:555-562(1997).

233. Blackman CF, Benane SG, House DE. The influence of magnetic fields on tamoxifen-induced inhibition of MCF-7 cell growth. Submitted(1999).

234. Harland JD, Levine GA, Liburdy RP. Differential inhibition of tamoxifen's oncostatic functions in a human breast cancer cell line by a 12 mG (1.2 μT) magnetic field. In: Electricity and Magnetism in Biology and Medicine (Bersani F, ed). Bologna:Plenum Press, 1998.

235. Afzal SMJ, Liburdy RP. Magnetic fields reduce the growth inhibitory effects of tamoxifen in a human brain tumor cell line. In: Electricity and Magnetism in Biology and Medicine. (Bersani F, ed). Bologna:Plenum Press, 1998.

236. Baldwin WS, Travlos GS, Risinger JI, Barrett JC. Melatonin does not inhibit estradiol-stimulated proliferation in MCF-7 and BG-1 cells. Carcinogenesis 19:1895-1900(1998).

237. Fitzsimmons RJ, Farley J, Adey WR, Baylink DJ. Embryonic bone matrix formation is increased after exposure to a low-amplitude capacitively coupled electric field, *in vitro*. Biochimica et Biophysica Acta 882:51-56(1986).

238. McLeod KJ, Lee RC, Ehrlich HP. Frequency dependence of electric field modulation of fibroblast protein synthesis. Science 236:1465-1469(1987).

239. Horton P. Stimlution of neuronal differentiation proteins in PC12 cells by combined AC/DC magnetic fields. In: Electricity and Magnetism in Biology and Medicine. (Blank M, ed). San Francisco:San Francisco Press, Inc., 1993;619-622.

240. McLeod KJ, Rubin CT. *In vivo* sensitivity of bone tissue to electromagnetic field exposure. Science Submitted(1998).

241. Rubin J, McLeod KJ, Titus L, Nanes MS, Catherwood BD, Rubin CT. Formation of osteoblast-like cells is suppressed by low frequency, low intensity electric fields. Journal of Orthopaedic Research 14:7-15(1996).

242. Chiabrera A, Bianco B, Caratozzolo F, Giannetti G, Grattarola M, Viviani R. Electric and magnetic field effects on ligand binding to the cell membrane. In: Interactions Between Electromagnetic Fields and Cells (Chiabrera A, Nicolini C, Schwan HP, eds). London:Plenum Press, 1985.

243. Liboff AR. Cyclotron resonance in membrane transport. In: Interactions Between Electromagnetic Fields and Cells (Chiabrera A, Nicolini C, Schwann HP, eds). London:Plenum Press, 1985;281-296.

244. Lednev VV. Possible mechanism for the influence of weak magnetic fields on biological systems. Bioelectromagnetics 12:71-75(1991).

245. Lednev VV. Possible mechanism for the effect of weak magnetic fields on biological systems: Correction of the basic expression and its consequences. In: Electricity and Magnetism in Biology and Medicine (Blank M, ed). San Francisco:San Francisco Press, Inc., 1993;550-552.

246. Lednev VV. Interference with the vibrational energy sublevels of ions bound in calcium-binding proteins as the basis for the interaction of weak magnetic fields with biological systems. In: On the Nature of Electromagnetic Field Interactions with Biological Systems (Frey AH, ed). Austin:R. G. Landes Company, 1994;59-72.

247. Blanchard JP, Blackman CF. Clarification and application of an ion parametric resonance model for magnetic field interactions with biological systems. Bioelectromagnetics 15:217-238(1994).

248. Blanchard JP, Blackman CF. A mechanistic model for biological effects of magnetic fields. Biological Effects of Nonionizing Electromagnetic Radiation Digest Update 5:11-16(1995).

249. Adair RK. Criticism of Lednev's mechanism for the influence of weak magnetic fields on biological systems. Bioelectromagnetics 13:231-235(1992).

250. Grundler W, Kaiser F, Keilmann F, Walleczek J. Mechanisms of electromagnetic interaction with cellular systems. Naturwissenschaften 79:551-559(1992).

251. Blank M. Na, K-ATPase function in alternating electric fields. FASEB Journal 6:2434-2438(1992).

252. Blank M, Soo L. Temperature dependence of electric field on Na, K-ATPase. Bioelectrochemistry and Bioenergetics 28:291-299(1992).

253. Blank M, Soo L, Papstein V. Effects of low frequency magnetic fields on Na, K-ATPase activity. Bioelectrochemistry and Bioenergetics 38:267-273(1995).

254. Derenyi I, Astumian RD. Spontaneous onset of coherence and energy storage by membrane transporters in an RLC electric circuit. Physical Review Letters 80:4602-4605(1998).

255. Polk C. Can static magnetic fields affect proton and electron transfer within the inner mitochondrial membrane? In: The Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery & Use of Electricity., San Diego, CA, 9-13 November 1997.

256. Pethig R. Dielectric and Electronic Properties of Biological Materials. New York:John Wiley & Sons, 1979.

257. Arkin MR, Stemp EDA, Holmlin RE, Barton JK, Hormann A, Olson EC, Barbara PF. Rates of DNA-mediated electron transfer between metallonintercalators. Science 273:475-480(1996).

258. Meade TJ, Kayyem JF. Electron transfer through DNA: Site-specific modification of duplex DNA with ruthenium donors and acceptors. Angewandte Chemie International Edition (English) 34:352-354(1995).

259. Murphy JC, Kaden DA, Warren J, Sivak A. Power frequency electric and magnetic fields: A review of genetic toxicity. Mutation Research 296:221-240(1993).

260. Stemp EDA, Arkin MR, Barton JK. Electron transfer between metallointercalators bound to DNA: Spectral identification of the transient intermediate. Journal of the American Chemical Society 117:2375-2376(1995).

261. Kirschvink JL. Comment on "Constraints on biological effects of weak extremely-low-frequency electromagnetic fields". Physiological Review 46:2178-2184(1992).

262. Kirschvink JL, Kobayasi-Kirschvink A, Diaz-Ricci JC, Kirschvink SJ. Magnetite in human tissues: A mechanism for the biological effects of weak ELF magnetic fields. Bioelectromagnetics Supplement 1:101-113(1992).

263. Vaughan TE, Weaver JC. Energetic constraints on the creation of cell membrane pores by magnetic particles. Biophysical Journal 71:616-622(1996).

264. Vaughan TE, Weaver JC. Molecular change due to biomagnetic stimulation and transient magnetic fields: Mechanical interference constraints on possible effects by cell membrane pore creation via magnetic particles. Bioelectrochemistry and Bioenergetics 46:121-128(1998).

265. Adair RK. Effect of ELF magnetic fields on biological magnetite. Bioelectromagnetics 14:1-4(1993).

266. Polk C. Effects of extremely-low frequency magnetic fields on biological magnetite. Bioelectromagnetics 15:261-270(1994).

267. Blankenship RE, Schaafsma TJ, Parson WW. Magnetic field effects on radical pair intermediates in bacterial photosynthesis. Biochimica et Biophysica Acta 461:297-305(1977).

268. Hoff AJ, Rademaker H, Van Grondelle R, Duysens LNM. On the magnetic field dependence of the yield of the triplet state in reaction centers of photosynthetic bacteria. Biochimica et Biophysica Acta 460:547-554(1977).

269. Werner H, Schulten K, Weller A. Electron transfer and spin exchange contributing to the magnetic field dependence of the primary phototchemical reaction of bacterial photosynthesis. Biochimica et Biophysica Acta 502:255-268(1978).

270. Cozens FL, Scaiano JC. A comparative study of magnetic field effects on the dynamics of geminate and random radical pair processes in micelles. Journal of the American Chemical Society 115:5204-5211(1993).

271. Hamilton CA, Hewitt JP, McLauchlan KA, Steiner UE. High resolution studies of the effects of magnetic fields on chemical reactions. Molecular Physics 65:423-438(1988).

272. McLauchlan KA. Magnetokinetics, mechanistics and synthesis. Chemistry in Britain 25:895-898(1989).

273. Walleczek J. Magnetokinetic effects on radical pairs: A paradigm for magnetic field interactions with biological systems at lower than thermal energy. In: Advances in Chemistry Series. Electromagnetic Fields: Biological Interactions and Mechanisms, vol 250 (Blank M, ed). Washington:American Chemical Society, 1995;395-420.

274. Adair RK. Effects on radical pair reformation of very weak magnetic fields. In: The Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery & Use of Electricity, San Diego, CA, 9-13 November 1997;20-22.

275. Brocklehurst B, McLauchlan KA. Free radical mechanism for the effects of environmental electromagnetic fields on biological systems. International Journal of Radiation Biology 69:3-24(1996).

276. Canfield JM, Belford RL, Debrunner PG, Schulten KJ. A perturbation theory treatment of oscillating magnetic fields in the radical pair mechanism. Chemical Physics 182:1-18(1994).

277. Eichwald C, Kaiser F. Model for external influences on cellular signal transduction pathways including cytosolic calcium oscillations. Bioelectromagnetics 16:75-85(1995).

278. Grissom CB. Magnetic field effects in biology: A survey of possible mechanisms with emphasis on radical-pair recombination. Chemical Reviews 95:3-24(1995).

279. Chignell CF, Sik RH. The effect of static magnetic fields on the photohemolysis of human erythrocytes by ketoprofen. Photochemistry and Photobiology 67:591-595(1998).

280. Kaiser F. Explanation of biological effects of low-intensity electric, magnetic and electromagnetic fields by nonlinear dynamics. In: Ninth Annual Review of Progress in Applied Computational Electromagnetics, Monterey, 22-26 March 1993;425-431.

281. Barnes FS. Interaction of DC and ELF electric fields with biological materials and systems. In: Handbook of Biological Effects of Electromagnetic Fields. Second Edition (Polk C, Postow E, eds). Boca Raton:CRC Press, 1996;103-147.

282. Eichwald C, Kaiser F. Model for receptor-controlled cytosolic calcium oscillations and for external influences on the signal pathway. Biophysical Journal 65:2047-2058(1993).

283. Eichwald C, Walleczek J. Activation-dependent and biphasic electromagnetic field effects: Model based on cooperative enzyme kinetics in cellular signaling. Bioelectromagnetics 17:427-435(1996).

284. Eichwald C, Walleczek J. Model for magnetic field effects on radical pair recombination in enzyme kinetics. Biophysical Journal 71:623-631(1996).

285. Sevcikova H, Marek M, Muller SC. The reversal and splitting of waves in an excitable medium caused by an electrical field. Science 257:951-954(1992).

286. Wachtel H. Firing-pattern changes and transmembrane currents produced by extremely low frequency fields in pacemaker neuron. In: Hanford Life Sciences Symposium, 18th Annual Meeting, Richland, 16-18 October 1978.

287. Bezrukov SM. The status of 1/f noise research in biological systems: Empherical picture and theories. In: Proceedings of the First International Conference on Unsolved Problems of Noise, Szeged, Hungary, 1996.

288. Bezrukov SM, Vodyanoy I. Stochastic resonance in non-dynamical systems without response thresholds. Nature 385:319-321(1997).

289. Astumian RD, Adair RK, Weaver JC. Stochastic resonance at the single-cell level (letter). Nature 388:632-633(1997).

290. Bezrukov SM, Vodyanoy I. Stochastic resonance at the single-cell level. Nature 388:632-633(1997).

291. Galvanoskis J, Sandblom J. Amplification of electromagnetic signals by ion channels. Biophysical Journal 73:3056-3065(1997).

292. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced information transmission in rat SA1 cutaneous mechanoreceptors via aperiodic stochastic resonance. Journal of Neurophysiology 76:642-645(1996).

293. Douglass JK, Wilkens L, Pantazelou E, Moss F. Noise enhancement of information transfer in crayfish mechanoreceptors by stochastic resonance. Nature 365:337-340(1993).

294. Gluckman BJ, Netoff TI, Neel EJ, Ditto WL, Spano ML, Schiff SJ. Stochastic resonance in a neuronal network from mammalian brain. Physical Review Letters 77:4098-4101(1996).

295. Silva M, Hummon N, Rutter D, Hooper C. Power frequency magnetic fields in the home. IEEE Transactions on Power Delivery 4:465-478(1989).

296. Yost MG, Lee GM, Duane BD, Fisch J, Neutra RR. California protocol for measuring 60 Hz magnetic fields in residences. Applied Occupational and Environmental Hygiene 7:772-777(1992).

297. Zaffanella L. Survey of Residential Magnetic Field Sources. Volume 1: Goals, Results and Conclusions. Volume 2: Protocol, Data analysis, and Management TR-102759-V1, TR-102759-V2. Palo Alto: EPRI, 1993.

298. Kleinerman RA, Linet MS, Hatch EE, Wacholder S, Tarone RE, Severson RK, Kaune WT, Friedman DR, Haines CM, Muirhead CR, Boice JD, Jr., Robison LL. Magnetic field exposure assessment in a case-control study of childhood leukemia. Epidemiology 8:575-583(1997).

299. Zaffanella LE, Kalton GW. Survey of Personal Magnetic Field Exposure Phase II: 1000-Person Survey EMF*RAPID* Program Engineering Project #6. Oak Ridge, TN: Lockheed Martin Energy Systems, Inc., 1998.

300. Kaune WT, Stevens RG, Callahan NJ, Severson RK, Thomas DB. Residential magnetic and electric fields. Bioelectromagnetics 8:315-335(1987).

301. DelPizzo V, Salzberg MR, Farish SJ. The use of 'spot' measurements in epidemiological studies of the health effects of magnetic field exposure. International Journal of Epidemiology 20:448-455(1991).

302. Kavet R, Silva JM, Thornton D. Magnetic field exposure assessment for adult residents of Maine who live near and far away from overhead transmission lines. Bioelectromagnetics 13:35-55(1992).

303. DelPizzo V, Salzberg MR. Relative-risk-estimate bias and loss of power in the Mantel test for trend resulting from the use of magnetic-field point-in-time ("spot") measurements in epidemiological studies based on an ordinal exposure scale. Bioelectromagnetics 13:363-378(1992).

304. Dovan T, Kaune WT, Savitz DA. Repeatability of measurements of residential magnetic fields and wire codes. Bioelectromagnetics 14:145-159(1993).

305. Kaune WT, Darby SD, Gardner SN, Hrubec Z, Iriye RN, Linet MS. Development of a protocol for assessing time-weighted-average exposures of young children to power-frequency magnetic fields. Bioelectromagnetics 15:33-51(1994).

306. Kaune WT, Zaffanella LE. Assessing historical exposures of children to power-frequency magnetic fields. Journal of Exposure Analysis Environmental Epidemiology 4:149-170(1994).

307. Friedman DR, Hatch EE, Tarone R, Kaune WT, Kleinerman RA, Wacholder S, Boice JD, Linet MS. Childhood exposure to magnetic fields: Residential area measurements compared to personal dosimetry. Epidemiology 7:151-155(1996).

308. Bowman J, Thomas D, Jiang L, Jiang F, Peters J. Residential magnetic fields predicted from wiring configurations: I. Exposure model. Bioelectromagnetics Submitted(1999).

309. Kheifets L, Afifi AA, Buffler P, Zhang Z, Matkin C. Occupational electric and magnetic field exposure and leukemia. Journal of Occupation and Environmental Health 39:1074-1091(1997).

310. Lynch CG. EMF Literature Reviews and Reports: 1990-1998. Minneapolis: Robert S. Banks Associates, Inc., 1998.

311. ORAU Oak Ridge Associated Universities Panel. Health Effects of Low-Frequency Electric and Magnetic Fields: Prepared for the Committee on Interagency Radiation Research and Policy Coordination: Oak Ridge Associated Universities, 1992.

312. NRPB National Radiation Protection Board. Electromagnetic Fields and the Risk of Cancer: Report of an Advisory Group on Non-Ionising Radiation. Oxon, 1992.

313. NRPB National Radiation Protection Board. Electromagnetic Fields and the Risk of Cancer: Supplementary Report by the Advisory Group on Non-Ionizing Radiation. Chilton: National Radiological Protection Board, 1994.

314. Hardell L, Holmberg B, Malker H, Paulsson L-E. Exposure to extremely low frequency electromagnetic fields and the risk of malignant diseases - An evaluation of epidemiological and experimental findings. European Journal of Cancer Prevention 4:3-107(1995).

315. European Commission Directorate V. Public Health and Safety at Work - Non ionizing radiation: Sources, Exposure and Health Effects ISBN 92-827-5492-8. Luxembourg, 1996.

316. ICNIRP International Commission on Non-Ionizing Radiation Protection. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Physics 74:494-522(1998).

317. SNBOSH Swedish National Board of Occupational Safety and Health. Low-Frequency Electrical and Magnetic Fields: The Precautionary Principle for National Authorities. Guidance for Decision-Makers. Solna, 1996.

318. Banks RS, Carpenter DO. AC electric and magnetic fields: A new health issue (article and commentary). Health Environmental Digest 2:1-4(1988).

319. Grandolfo M. Extremely low frequency magnetic fields and cancer. European Journal of Cancer Prevention 5:379-381(1996).

320. Gurney JG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States. Cancer 75:2186-2195(1995).