United States
Environmental Protection
Agency

Office of Research and
Development
Washington, DC 20460

EPA/600/6-90/005B
October 1990
External Review Draft

EPA

Evaluation of the Potential Carcinogenicity of Electromagnetic Fields

Review Draft

(Do Not
Cite or Quote)

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

NOTE TO REVIEWERS

The scientific issues concerning the relationship between EM fields and adverse health effects are very complex and difficult to interpret. Epidemiologic data are limited and many results to date are based on small studies with methodological limitations. As a result, there are large differences in the way that these studies are evaluated and interpreted, both within the scientific community in general, and among scientists and Agencies within the Federal government in particular. This draft document on electromagnetic (EM) fields reviews and evaluates published information pertaining to the potential carcinogenicity of EM fields. The information includes epidemiology studies, chronic lifetime animal tests, and laboratory studies of biological phenomena related to carcinogenesis. **While there are epidemiological studies that indicate an association between EM fields or their surrogates and certain types of cancer, other epidemiological studies do not substantiate this association. There are insufficient data to determine whether or not a cause and effect relationship exists.** The document clearly reveals the need for further research.

The draft document on EM fields has been reviewed previously by scientists with EPA's Office of Research and Development, and, at a June 1990 workshop, by a panel of scientists from outside the Agency. The draft document is now being sent for review by both the EPA Science Advisory Board (SAB) and the Federal Coordinating Council for Science, Engineering, and Technology's (FCCSET) Committee on Interagency Radiation Research and Policy Coordination (CIRRPC).

The document stating the Agency's findings and conclusions will consider and address comments made by these groups. Currently, there is disagreement among the reviewers from various Agencies about the weight of evidence and the conclusions presented in the Executive Summary. EPA will provide an opportunity for public review and comment before developing the final version of the report.

Given the controversial and uncertain nature of the scientific findings of this report and other reviews of this subject, this review draft should not be construed as representing Agency policy or position.

Erich Bretthauer

Erich W. Bretthauer
Assistant Administrator for
Research and Development
12-13-90

U.S. ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

NONIONIZING ELECTRIC AND MAGNETIC FIELDS SUBCOMMITTEE

Open Meeting

January 14, 15, 16, 1991

AGENCY : U.S. Environmental Protection Agency

ACTION: Pursuant to the Federal Advisory Committee Act, Public Law 92-463, notice is hereby given that the Nonionizing Electric and Magnetic Fields Subcommittee of the Science Advisory Board's Radiation Advisory Committee will meet January 14-16, 1991, at the National Museum for Women in the Arts, 1250 New York Avenue, N.W., Washington, DC, in the Auditorium. The meeting will begin at 9:00 a.m. Monday and adjourn on Wednesday no later than 5:00 p.m.

SUMMARY: On January 14, 1991, the Subcommittee will begin its review of a draft document prepared by the EPA's Office of Health and Environmental Assessment entitled "Evaluation of the Potential Carcinogenicity of Electromagnetic Fields" (EPA/600/6-90-005B). The draft document on EM fields reviews and evaluates published information pertaining to the potential carcinogenicity of EM fields. The information includes epidemiology studies, chronic lifetime animal tests, and laboratory studies of biological phenomena related to carcinogenesis. **While there are epidemiological studies that indicate an association between EM fields or their surrogates and certain types of cancer, other epidemiological studies do not substantiate this association. There are insufficient data to determine whether or not a cause and effect relationship exists.** The document clearly reveals the need for further research.

DATES: The meeting will be held January 14, 15, and 16, 1991. In accordance with Public Law 92-463, the meeting is open to the public, and members of the public may provide comments to the SAB

Subcommittee. However, seating is limited and is on a first-come basis.

ADDRESSES: To obtain a single copy of the draft document on EM fields, interested parties should contact the ORD Publications Office, CERI-FRN, U.S. Environmental Protection Agency, 26 W. Martin Luther King Drive, Cincinnati, OH 45268, telephone (513) 569-7562 or FTS/684-7562. FAX: (513) 569-7566 or FTS/684-7566. Please provide your name and mailing address and request the document by title and EPA number. A copy of the document will be sent to those individuals who have previously requested it.

The draft document will be available for public inspection and copying in the Public Information Reference Unit of the EPA Library, U.S. Environmental Protection Agency Headquarters, Waterside Mall, 401 M Street, S.W., Washington, DC 20460.

A limited number of copies will be available at the meeting. The document is not available from the SAB.

FOR FURTHER INFORMATION CONTACT: Members of the public wishing to provide written comments or to present oral comments at the meeting should contact Mrs. Kathleen Conway, Designated Federal Official, at (202) 382-2552 by 3:20 p.m., January 2, 1991. Written comments to be mailed to the Subcommittee in advance of the meeting must be given to Mrs. Conway by noon Friday, January 4, 1991. Written comments may also be submitted at the Subcommitteee meeting. If possible, please provide at least 20 copies for distribution to the Subcommittee. Oral comments should not duplicate written materials and opportunity for oral comment is limited.

SUPPLEMENTARY INFORMATION: The draft document on EM fields has been reviewed previously by scientists within EPA's Office of Research and Development and several federal agencies, and, at a

June 1990 workshop, by a panel of scientists from outside the Agency. These reviewers' comments have been addressed and many incorporated into the current draft. There are no changes in the conclusions between the workshop review draft and the current draft. There is, however, disagreement among the reviewers from various Agencies about the weight of evidence and the conclusions presented in the Executive Summary. This report is now being submitted to the Agency's SAB for review. In addition, the Agency is requesting comments from the Federal Coordinating Council for Science, Engineering and Technology's (FCCSET) Committee on Interagency Radiation Research and Policy Coordination (CIRRPC). Based on these reviews, the draft report will be revised as necessary and EPA will provide an opportunity for public review and comment before developing the final version of the document.

The scientific issues concerning the relationship between electromagnetic (EM) fields and adverse health effects are very complex and difficult to interpret. The final document stating the Agency's findings and conclusions will consider and address comments made by the groups mentioned above. **Given the controversial and uncertain nature of the scientific findings of this report and other reviews of this subject, the external review draft should not be construed as representing Agency policy or position.**

December 13, 1990
Date

Staff Director
Science Advisory Board

December 13, 90
Date

Assistant Administrator
for Research and Development

DRAFT
DO NOT QUOTE OR CITE

EPA/600/6-90/005B
October 1990
External Review Draft

EVALUATION OF THE POTENTIAL CARCINOGENICITY OF ELECTROMAGNETIC FIELDS

NOTICE

THIS DOCUMENT IS A PRELIMINARY DRAFT. It has not been formally released by the US. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

DISCLAIMER

This document is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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PREFACE

This document was prepared by the Human Health Assessment Group of the Office of Health and Environmental Assessment (part of the Office of Research and Development, U.S. Environmental Protection Agency) at the request of the Office of Radiation Programs. It summarizes and evaluates the available literature relating to the potential carcinogenicity of electromagnetic fields in the frequency range from 3 Hz to 30 GHz (3×10^{10} Hz). Topics evaluated are human epidemiologic studies relating in some way to carcinogenesis, chronic animal studies, and short-term and in vitro studies related to the carcinogenic effects of these fields. The literature search supporting this review was completed in mid-1989.

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The Human Health Assessment Group (HHAG) of the Office of Health and Environmental Assessment (OHEA) was responsible for the preparation of this document.

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*Prepared under interagency agreement No. DW8932701.

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This document has been reviewed, either in whole or in part, by the following individuals within the U.S. Environmental Protection Agency. In addition, reviews have been carried out by interested individuals from the U.S. Department of Energy, Centers for Disease Control, and the National Cancer Institute.

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The document was reviewed by a panel of scientists at a Peer Review Workshop held in Morrisville, North Carolina, on June 28, 1990. Comments and recommendations made by the panel at the workshop and in written post-meeting comments were incorporated into this draft. The peer panel members were:

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1. EXECUTIVE SUMMARY

This review and evaluation of the potential carcinogenicity of electromagnetic (EM) fields has been carried out by the Office of Health and Environmental Assessment within the Office of Research and Development at the request of the Office of Air and Radiation (OAR) at the US. Environmental Protection Agency (EPA). The Office of Radiation Programs within OAR is responsible for the radiation protection activities of the Agency. The purpose of the document is to evaluate the likelihood that exposure to nonionizing electromagnetic radiation (NIEMR) poses a risk or is a risk factor for the development of cancer in humans. Although the entire NIEMR spectrum is of interest, the emphasis in this document is on time-varying electric and magnetic fields in the extremely low frequency (ELF) range [approximately 3 to 3000 hertz (Hz)] and on radiofrequency (RF) radiation [approximately 0.003 to 30,000 megahertz (MHz)]. These two regions of the spectrum are emphasized because they are of regulatory concern to the Agency and because the preponderance of information is in these regions,

The evaluation of the likelihood of human cancer risk is based on a judgment as to the overall weight of evidence that a carcinogenic response is causally related to specific levels or types of exposure. Since the establishment of causality is often difficult, the weight-of-evidence approach relies on the combination of empirical observations and inferences founded in reasonable scientific judgment. Under this approach, the evidence from human studies is considered most important, with lesser importance being attached, respectively, to chronic lifetime animal studies and ancillary evidence, such as short-term tests of genetic toxicity, mechanistic studies, and evidence of carcinogenicity for chemical analogues to the agent under study. Accordingly, this document considers human, animal, and supporting evidence in separate chapters.

There are four essential elements in a risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This document deals largely with hazard identification, with a brief section (Section 2.3) devoted to exposure. Dose-response assessment is not attempted because the nature of the interaction between the body and electric and magnetic fields is not well enough understood to be able to specify the relevant aspects of exposure. In the absence of critical information about both exposure and dose-response, an overall risk characterization is not developed in this document. In its entirety, this document represents an analysis of the state-of-the-science supporting a concern for the potential carcinogenic hazard of EM fields.

The two basic sources of information that furnish evidence of the relationship between exposure to EM fields and cancer are human evidence and laboratory studies. Human evidence is observational in nature and cannot account for or control all of the potentially relevant factors. Laboratory studies with biological models of the human disease search for explanations of the human findings by evaluating the effects of the various controllable factors. It is necessary to have both types of information in order to be able to specify what measures are likely to reduce the hazard. However, if the laboratory studies are not able to provide adequate explanations, the human observations still furnish a basis for concern.

A large number of human studies are available in which the relationship between human cancer incidence or mortality and exposure to EM fields has been investigated. From these studies the strongest relative evidence that exposure to EM fields is causally related to human cancer comes from case-control studies of cancer in children. Seven of these have examined residential exposure from electric power transmission and distribution lines and two others have examined cancer in children in relation to father's occupation. These studies have consistently found modestly elevated risks (some statistically significant) of leukemia, cancer of the nervous system and, to a lesser extent, lymphomas. These findings are associated with magnetic fields in homes where children reside which were estimated after the diagnosis with both magnetic field measurements and with surrogate indicators of magnetic fields, i.e., wiring codes. Electric fields were not found to be a critical factor thus far. In two studies in which magnetic fields measurements were made, significant elevated risks were observed in those exposed at or above 2 to 3 milligauss (mG) [0.2 to 0.3 microtesla (μT)]. In contrast with adults, children probably have relatively few confounding factors other than EM fields that could explain the association because of their shorter lifespan and lack of occupational exposure. In fact, potential confounders and biases that might have affected the results were examined by one of the authors in some detail and found not to explain the results. As yet, no other agents have been identified that could explain this association. Although a dose-response relationship with respect to surrogate measures of exposure is suggested in two studies, reliable dose-response information is not available due to the use of dichotomized exposure categories and small numbers of cases within the exposure groupings. Issues pertaining to personal exposure and latency have not been addressed.

Additional, but weaker, evidence that there is an elevated risk of leukemia, cancer of the nervous system, and perhaps other sites comes from occupational studies of EM-field exposure. Although many of these studies have found an excess risk of these forms of cancer to be associated with employment in certain jobs that have a high potential for exposure to EM

fields, few or no measurements have actually been taken in those occupations. Furthermore, the available sources of information concerning these occupations do not provide a reliable indication of actual exposure to electromagnetic fields. The likelihood that misclassification or information bias is present in these studies is high. However, exposure misclassification, if random, tends to bias risks toward the null. Despite these weaknesses, the occupational studies tend to support the results of the childhood cancer studies, and excesses occur at the same sites.

The studies of residential adult exposures to EM fields provide mixed evidence of a risk of leukemia, but due to a lack of statistical power and a lack of definite information on precise EM-field exposures, these findings are not as strong as those for childhood cancer. These studies cannot be interpreted as evidence either for or against a causal association between cancer and EM-field exposures. On the other hand, the case-control study of cancer in Colorado residents does support an association of central nervous system cancer and lymphoma if proximity to high-current electrical wiring configurations is assumed to be an adequate surrogate for exposure.

The studies of adults exposed to RF radiation produced mixed results, primarily because of limited sample size, inadequate length of follow-up, imprecise exposure data, and lack of information on potential confounders. These problems prevent conclusions to be made about causal relationships with RF exposures. However, the statistically significant excess risks of leukemia in amateur radio operators requires further examination.

There have been very few lifetime animal carcinogenicity studies of EM fields, and none at power line frequencies. One study in mice of unmodulated 2450-MHz RF radiation at power levels low enough to cause only moderate body heating showed an enhancement of the growth rate of spontaneous mammary tumors and of skin tumors initiated by benzo[a]pyrene, a chemical carcinogen. One rat study of pulse-modulated 2450-MHz RF radiation designed to simulate human exposure to medium-range radar showed the induction of benign adrenal medulla tumors and an increased incidence of carcinomas at all tissue sites combined, with no increase at any one site; the latter finding was not accompanied by the induction of benign tumors.

A large number of biological phenomena related in some way to known mechanisms of carcinogenesis have been affected by EM fields under controlled laboratory exposure situations. ELF fields of relatively high intensity producing induced tissue currents on the order of 10 microamperes per square centimeter (μA/cm2) have enhanced DNA synthesis, altered the transcription of DNA into mRNA, altered the molecular weight distribution during

protein synthesis, delayed the mitotic cell cycle, induced chromosome aberrations, blocked the action of parathyroid hormone at the site of its plasma membrane receptor, induced enzymes normally active during cell proliferation, inhibited differentiation and stimulated the growth of carcinoma cell lines, inhibited the cytotoxicity of T-lymphocytes (which indicates an impairment of the immune system) in vitro but not in vivo, inhibited the synthesis of melatonin (a hormone that suppresses the growth of several types of tumors), and caused alterations in the binding of calcium to brain tissues. The large variety of exposure conditions and the lack of detail on the geometry of the biological samples in these studies precludes a systematic evaluation of the actual induced currents and field strengths at the tissue and cellular levels that are causing these effects. In addition, the lack of reproducible results between laboratories limits the interpretation of much of this literature.

RF fields modulated at the same extremely low frequencies that cause some of the effects noted above also result in the same responses, indicating that the ELF component may be responsible for these effects. Unmodulated RF radiation has not caused any of the effects noted above except for chromosome aberrations. None of the EM fields have caused gene mutations, sister chromatid exchanges, or DNA damage (as measured by DNA breaks, DNA repair, or differential killing of repair defective organisms) in a large number of studies.

Only three ELF effects have been induced at field strengths comparable to the low environmental exposures at which human cancer has putatively been caused: (1) the calcium efflux from brain tissue preparations using 16-Hz electric and magnetic fields that were perpendicular to each other; (2) calcium efflux from chick brain tissues after exposure of the developing embryo to electric fields; and (3) the inhibition of melatonin synthesis by the pineal gland when a static magnetic field of approximately the strength of the earth's magnetic field is changed through a small angle of rotation. The results of this first experiment are one of several phenomena that show a complex dependence of frequency, intensity, and orientation with respect to the earth's magnetic fields.

In view of these laboratory studies, there is reason to believe that the findings of carcinogenicity in humans are biologically plausible. However, the explanation of which biological processes are involved and the way in which these processes causally relate to each other and to the induction of malignant tumors is not understood. Most of the effects have been observed at field strengths that are many times higher than the ambient fields which are the putative cause of the childhood cancers in residential situations; as a consequence, many of the candidate mechanisms may not be really involved in the response to low environmental fields. The same issue arises in the evaluation of chemical agents.

In conclusion, several studies showing leukemia, lymphoma, and cancer of the nervous system in children exposed to magnetic fields from residential 60-Hz electrical power distribution systems, supported by similar findings in adults in several occupational studies also involving electrical power frequency exposures, show a consistent pattern of response which suggests a causal link. Frequency components higher than 60 Hz cannot be ruled out as contributing factors. Evidence from a large number of biological test systems shows that ELF electric and magnetic fields induce biological effects that are consistent with several possible mechanisms of carcinogenesis. However, none of these processes has been experimentally linked to the induction of tumors, either in animals or in humans by EM-field exposure. The particular aspects of exposure to the ELF fields that cause these events are not known.

In evaluating the potential for carcinogenicity of chemical agents, the U.S. EPA has developed an approach that attempts to integrate all of the available information into a summary classification of the weight of evidence that the agent is carcinogenic in humans. At this time, such a characterization regarding the link between cancer and exposure to EM fields is not appropriate because the basic nature of the interaction between EM fields and biological processes leading to cancer is not understood. For example, if induced electrical currents were the causative factor, then exposure to electric as well as magnetic fields would be important and the effect would be more severe as the frequency increases. But if the direct magnetic field interaction were the critical factor, then the ambient static magnetic field, as well as the alternating magnetic field, would be critical, and the effect may be confined to specific frequencies, resulting in an extremely complicated dose-response relationship. In addition, if they were shown to be causative agents, these fields probably exert their effects via other chemical and environmental factors rather than directly causing events known to be causally related to carcinogenic processes, as with genotoxic chemical agents.

Because of these uncertainties, it would be inappropriate at this time to classify the carcinogenicity of EM fields in the same way as the Agency does for chemical carcinogens. As additional studies with more definitive exposure assessment become completed, a better understanding of the nature of the hazard will be gained. With our current understanding, we can identify 60-Hz magnetic fields from power lines and perhaps other sources in the home as a possible, but not proven, cause of cancer in humans. The absence of key information summarized above makes it difficult to make quantitative estimates of risk. Such quantitative estimates are necessary before judgments about the degree of safety or hazard of a given exposure can be made. This situation indicates the need to continue to evaluate the

information from ongoing studies and to further evaluate the mechanisms of carcinogenic action and the characteristics of exposure that lead to these effects.

2. MECHANISMS OF ELECTROMAGNETIC INTERACTION

Electromagnetic (EM) fields with certain exposure parameters do affect biological systems, as demonstrated by the studies described in this report. These experimental findings raise a number of pressing questions. Primarily, how can the effects of an arbitrary EM-field exposure be predicted? In the present context, can environmental EM-field exposures be carcinogenic? Experimental data directly addressing the latter question are extremely limited. The biological effects described in this report have served mainly to indicate that present biological models are incomplete and to stimulate the development of new theories. Bioeffects have been found to result from induced currents far weaker than normal physiological currents, and at imparted energy levels a fraction of the average thermal energy (per particle). Only by identifying the mechanisms through which EM fields interact with biological systems can the larger questions, such as the potential for carcinogenicity, be fully addressed. This section will briefly review several major interaction mechanism theories. In preparation for this review, a discussion of the properties of EM fields and field coupling with the body is presented.

2.1. PHYSICAL PROPERTIES OF ELECTRIC AND MAGNETIC FIELDS

Although electric and magnetic fields are used widely in modern technology, most persons outside of the scientific and engineering community have few reference points with which to understand them. The most common experiences include static electric fields produced indoors in dry climates and static magnetic fields around permanent magnets. Electromagnetic radiation, or at least the effect of it, is familiar to almost everyone in the form of visible light, radio transmission, and x-rays. The purpose of this section is to provide a brief description of the properties of electric and magnetic fields and of how they interact with matter. This knowledge has been applied to human exposures to electric and magnetic fields for several decades, and many of the details of interaction at certain levels are now understood. Specific knowledge of how these interactions affect living organisms, on the other hand, is very limited and the subject of much investigation.

Electric fields occur when electric charges are present. The matter we experience commonly consists of almost equal numbers of positively charged and negatively charged particles, so even though intense electric fields are occurring on a microscopic or atomic level, the matter is practically neutral on the macroscopic scale of which we are aware (inches, feet, etc.). When some of the positive and negative charges are separated over distances on our scale, we may experience obvious effects of an electric field. For example, the movement of

certain shoe materials across some carpet materials separates positive and negative charges by a process called triboelectricity. The large separation of charges as one moves across a room can produce a substantial static electric field. This field may cause the hair on the hands or arms to stand up as the subject moves near a grounded conductive object and result in a physical sensation. If the conductor is physically contacted, a shock may occur as electric current (the movement of charges) flows, returning the separated electric charges to a more neutral condition.

This example demonstrates several of the principles of electric field theory. Separating opposite charges results in a potential difference that is measured in the unit of volts (V). All units described in this chapter, unless otherwise specified, are in the Standard International (SI) system, which is now almost universally accepted. For a given system, the voltage increases as more charges are separated. In the above example, increased movement across the carpet separates more charge and results in a larger potential difference. The electric field is a description of the force that a unit charge will experience at any point in space. Electric charges attract more strongly as they are moved closer together in a way similar to bar magnets.

If a conducting path is provided between areas of separated charge, the charges, usually in the form of electrons or ions (atoms with an unequal number of positive and negative electric charges), will flow between the two regions. This flow of charge is called electric current and is measured in units of amperes (A). Electric charge is measured in coulombs (C). Current is simply the number of coulombs of charge that flow through a given region per second.

The relationship between some of the above quantities is easier to describe using a different example. Imagine two large parallel sheets of a conductive material such as copper separated by a small distance, d. If charges from one sheet are removed and placed on the other, a potential difference, V, will be produced. The strength or magnitude of the electric field between the plates is given by,

$$E=V/d.$$

The unit for electric fields is volts/meter. Note that either increasing the potential difference or decreasing the separation between plates results in an increase in the electric field strength.

Electric fields are known as vector fields, meaning that they specify a magnitude and a direction for each point in space. The direction of an electric field at a given point is defined as

the direction in which a small positive charge will move if placed at that point. For a parallel plate system, the electric field points from the positive plate towards the negative plate. No current can flow between the plates because they are separated by air, which is an insulator or dielectric. Parallel plates are often used in laboratory experiments because they create a relatively large region where the direction of the electric field is uniform. In general, and often in environmental exposures, the direction of the electric field can vary for each point in space.

Magnetic fields occur whenever charges are in motion, as in the case of an electric current. Permanent magnets may appear to be an exception to this principle, but the field of these magnets is caused by the orbital motion of the electrons in the magnetic material. Magnetic fields exert a force on electric charges, but only charges that are in motion. Thus, a magnetic field will exert a force on a current carrying conductor, or on ions or electrolytes moving through the bloodstream. A simple example can be used to describe the units of magnetic field. Imagine a long thin wire carrying a current, I. The magnitude of the magnetic field (H) at a distance, d, from the wire is

$$H = I/(2 \pi d).$$

Note that the quantity ($2 \pi d$) is the circumference of the circle with a radius equal to the distance from the wire to the measurement point. The magnitude of the magnetic field is the magnitude of the current divided by the circumference of this circle. The field is directed in a circle around the wire such that the field vector at any point is tangent to the circle. As for the case of electric fields, the direction of a magnetic field can vary for each point in space, but special configurations are often used in the laboratory to produce fields with a relatively uniform direction throughout the exposure area. Standard International units for magnetic fields are amperes per meter (A/m).

Besides free charges and currents, electric and magnetic fields also act on certain materials. The electric and magnetic properties of materials are described by their conductivity, σ, permittivity, ε, and permeability, μ. Dielectrics are materials in which charge separation, or polarization, occurs when they are exposed to an electric field. Another vector field, the electric flux density (or electric displacement), D, can be used when dielectrics are present.

$$D = \varepsilon E$$

The permittivity of air is close to that of a vacuum, ε_0, so that when describing an exposure in air, a fixed relationship exists between E and D. In most bioeffects experiments, the exposure field, E, is described before the subject is placed in the field. Similarly, magnetic materials have induced magnetic moments when exposed to a magnetic field. The magnetic flux density is related to the magnetic field by

$$B = \mu H .$$

The permittivity or dielectric constant of biological materials is significantly different from that of a vacuum. Further complicating matters is the fact that different tissues and even different microscopic structures within the tissues have widely different dielectric properties. These properties have been studied in some detail (Schwan and Foster, 1980). The permeability of most biological materials, on the other hand, is very close to that of air or a vacuum. Thus, in these materials, B and H can be used somewhat interchangeably. The SI unit for B, the magnetic flux density, is tesla (T). Another commonly used unit for B is gauss (G), which is a cgs unit. The conversion from gauss to tesla is 1 tesla = 10^4 gauss.

Normally, we think of an electric current confined to a thin conductor and simply specify a value of the total current. Because of the structure and widely differing electrical properties of the body, currents flowing through the body are not uniform. In this case, it is more descriptive to specify the current density or current per unit area flowing through certain regions of biological specimens, When a conductive material, such as a biological substance, is subjected to an electric field, electric currents are induced according to

$$J = \sigma E$$

where J is the current density (A/m^2 in SI units), and E is the electric field at the point of interest inside the material.

Field theory becomes more complicated when time-varying fields are considered. Electric and magnetic fields which vary in time are described by a frequency, the number of times that the field oscillates per second. The unit for frequency is cycles per second or hertz (Hz). Phenomena such as radio waves, visible light, x-rays, gamma rays, etc., are all electromagnetic fields of different frequencies (see Figure 2-1). The dielectric properties of biological substances, for example, vary with the frequency of electric field exposure.

Extremely low frequency (ELF) fields range from 3 Hz to 300 Hz. In this range, the electric and magnetic fields are considered separately for purposes of biological effects experiments. The radiofrequency (RF) range is generally defined as 10,000 Hz to 300 gigahertz (GHz) (1 GHz = one billion Hz). In this range, a significant portion of field exposures may occur in the form of electromagnetic radiation, where a fixed relationship exists between the electric and magnetic fields. ELF and RF fields interact differently with the body and are discussed below in separate sections for clarity.

2.1.1. Extremely Low Frequency Fields

An ELF electric field can be imagined by referring to the parallel plate example and alternating the potential on the plates so that the field constantly reverses direction. The most prevalent man-made ELF field in the environment is that resulting from power lines. In this case, the direction of the field oscillates (changes direction and returns to its beginning direction) 60 times per second. The electric field in the parallel plate system connected to a 60-Hz voltage source will reach a maximum value, gradually drop to zero, climb to a maximum in the other direction, return to zero, and then climb to the maximum value in the starting direction. This cycle will occur in one-sixtieth of a second.

Such a field is described as linearly polarized, indicating that, even though the field vector changes in magnitude and polarity, it is always parallel to a certain direction. Power line fields

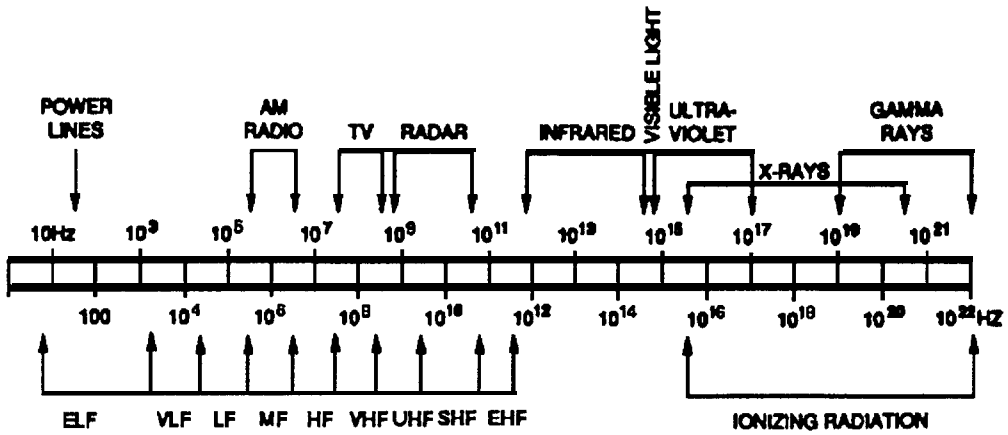


Figure 2-1. The electromagnetic spectrum.

may have a more complex polarization. High voltage lines, for example, often consist of three lines with differing time phases. This term means that the voltages and currents in the different lines reach their peak values at different times. The fields produced by the three lines add together at each point in space and result in a field vector that moves in an ellipse rather than back and forth along a single line. Under certain conditions, the field vector may trace a circle in space during each cycle. This case is referred to as circular polarization.

2.1.2. Radiofrequency Fields

An interesting property of electromagnetic fields is that a changing electric field creates a magnetic field and vice versa. Such effects along with the other properties of electromagnetic fields are described by Maxwell's equations. One solution of Maxwell's equations shows that this field creation will result in the transport of energy through space in the form of electromagnetic radiation. The magnitude of the field produced by a change in the other field is proportional to the time-rate-of-change. ELF fields that change slowly produce very little of the other field. The parallel plate system described above can create a 60-Hz electric field, but this field is changing so slowly that very little magnetic field component is created. If the same system were driven by a 1 MHz (one million hertz) signal generator, the rapid change in the electric field would create a substantial magnetic field and result in some of the energy propagating away as electromagnetic radiation. Electromagnetic radiation travels in a vacuum at the speed of light, c, which is 3×10^8 meters/second. This radiation may also be described by the wavelength, λ which is related to the frequency, f, by $\lambda f = c$. The unit for wavelength is the meter (m).

The electric and magnetic field strengths in a plane electromagnetic wave are related by

$$E/H = 377 \text{ ohms.}$$

The value 377 ohms is called the characteristic impedance of free space. For this case, and to a close approximation for some experimental cases, knowledge of either E or H implies both the magnitude and direction of the other. Also for this case it is possible to define the power density, S, of the wave. The power density is a vector quantity describing the rate at which energy is transmitted through a unit area, and the magnitude is calculated for a free-space, plane wave according to

$$S = E \times H = E^2/377.$$

Power density in SI units is given in watts per square meter (W/m^2), but RF bioeffects exposures are often given in milliwatts per square centimeter (mW/cm^2) as a more convenient unit (1 Mw/cm^2 = 10 W/m^2). A power density of 1 Mw/cm^2 for a free-space, plane wave, translates to an electric field strength of 61.4 volts per meter (V/m) and a magnetic field strength of 0.163 A/m or a flux density of 0.2 microtesla μT). Power density can be a useful measure because some bioeffects studies consider the amount of energy input to the biological system from the electromagnetic field.

A common error is to assume that power density can always be related to field strength in the simple way shown above. In most real world cases, the relationship between field strength and power density is complex and power density units are inappropriate. One example is the reactive near-field of an antenna, which generally extends from the antenna to a distance of one wavelength. In this region, a significant fraction of the energy stored in the field collapses back into the antenna during each cycle rather than radiating away. Because little of this field energy is transmitted as electromagnetic radiation, the power density is significantly lower than would be predicted by the above formula. Reactive fields are common in the environment, especially at low frequencies. For example, the wavelength of power frequency fields (60 Hz) is 5 million meters, indicating that all significant exposures occur in the reactive near-field of the source (power lines, domestic wiring, appliances, etc.).

In reactive fields, no fixed relationship exists between the electric and magnetic field components for all cases. The parallel plate system described earlier, for example, will produce a ratio of electric to magnetic field strength much greater than 377 ohms at low frequencies. A calculation of power density in this exposure field would show very low values, This result is misleading because a dielectric or conductive object placed in the field will absorb more power (energy/time) than is predicted to be incident on the object by the power density calculation. In such cases, the object is absorbing stored energy from the electric field as the movement of charged particles or polarization of the dielectric produces thermal motion in the object. Similarly, a conductor or magnetic material will absorb energy from a pure (time-varying) magnetic field. Eddy currents (discussed later) in conductor and polarization effects in magnetic materials result in heating.

Nonplane wave conditions are common in environmental exposures and most laboratory exposure systems. Exceptions include transverse electromagnetic (TEM) cells, which are specifically designed to maintain plane wave conditions, and anechoic chambers in which microwave frequencies are radiated from antennas and absorbed at the walls to eliminate reflections. (Waves in which all of the electric and magnetic field components are transverse

to the direction of propagation are called transverse electromagnetic waves). Many environmental RF waves, which initially approximate plane waves, reflect off the ground and other conductors resulting in standing waves. EM radiation from a broadcast antenna, for example, may reflect from the ground to create a standing wave which consists of alternating regions of purely electric and purely magnetic fields in a stationary pattern. If the wavelength is short enough (<6 meters or >50 MHz), an individual standing in the field may be exposed to both regions at different body locations. Power density calculations are not appropriate in such conditions.

A more meaningful quantity in many cases is the specific absorption rate (SAR). This quantity is a measure of the power absorbed per unit mass of the biological specimen under study. The common unit is watt per kg (W/kg). SAR is difficult to predict analytically except in geometrically simple objects with homogeneous electrical properties. Numerical techniques, however, such as finite element analysis, have been used to calculate SAR's effectively in the human body (Gandhi, 1982). SAR is particularly useful in bioeffects studies investigating thermal effects. Until recent years, many researchers believed that all EM bioeffects could be explained in terms of the total energy deposited or excess heating in the body resulting from EM-field exposure. Measurement and specification of SAR in a given experiment eliminate ambiguities that may result from specification of external field strength or power density alone. As described earlier, biological specimens can absorb energy from reactive fields for which power density calculations are meaningless. Clearly, power density cannot serve as a surrogate for SAR.

Energy absorbed from electromagnetic field exposures can be compared to the rate at which energy is produced by the body during normal metabolism. The metabolic energy generated by a 70-kg "standard" man, for example, ranges from a basal rate of about 1 W/kg to a maximum of 21 W/kg during strenuous exercise (Polk and Postow, 1986). The 1982 American National Standards Institute (ANSI) standard for electromagnetic fields limits human exposures to a maximum of 0.4 W/kg averaged over the entire body (ANSI, 1982).

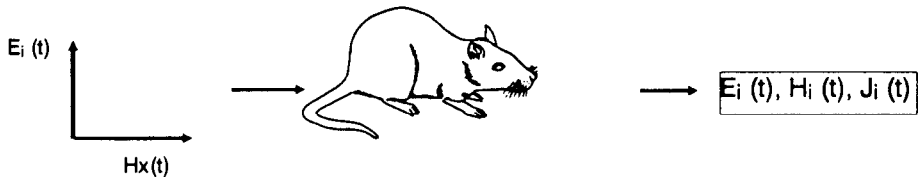
2.2. COUPLING OF ELECTRIC AND MAGNETIC FIELDS WITH THE BODY

The interaction of electric and magnetic fields with the body can be divided into macroscopic and microscopic aspects. Macroscopic interactions are those occurring as a result of introducing a large dielectric object into the field. Viewed in this way, the body may be thought of as an antenna that absorbs energy from the field. Microscopic interactions are those occurring on the cellular or sub-cellular level, such as induced membrane potentials,

changes in ion transport, etc. Although the organism as a whole is exposed to the external fields, the tissues and cells experience a substantially different set of exposure parameters. Many details of macroscopic interactions are presently understood, including total energy absorption, induced surface charges, total currents, and others. Interaction mechanism theories generally address microscopic problems, assuming that local exposure conditions (at the tissue or cell level) have already been defined by evaluation of the macroscopic coupling effects. Table 2-1 illustrates that the transformation of external field into internal field strengths and currents is affected by several factors. These factors are discussed briefly in the following sections, with ELF and RF effects separated into separate sections for simplicity. Detailed discussions of these relationships can be found in publications by the National Council on Radiation Protection (1981), Polk and Postow (1986), Tenforde and Kaune (1987), and Guy (1987).

Internal exposure conditions can, in principle, be derived from the interaction of these fields with the organism. In practice, the precise internal field strengths and current densities are extremely difficult to predict because of the complex structural variations in the body and the highly heterogeneous electrical properties of living tissues. Further research is required to determine the current distributions and internal field strengths at specific points in the body. Such microdosimetry will be required to define the exposure parameters occurring at sites of interest in the body in order to fully evaluate interaction mechanism theories.

TABLE 2-1. FACTORS AFFECTING INTERNAL EXPOSURE CONDITIONS

Ambient Electric and Magnetic Field	Biological System	Internal Electric and Magnetic Fields and Current Density
		
External Exposure	Biological System	Internal Exposure
Frequency Modulation Intensity Polarization	Geometry (size, shape) Orientation Heterogeneous tissue Electrical properties Coupling with other nearby conductors Grounding condition	Internal fields Current densities Local variations due to structure Microscopic variations due to membrane impedances, etc.

2.2.1. Extremely Low Frequency Fields

ELF electric and magnetic fields vary so slowly that they can be considered quasi-static when considering interactions with the body. This approach is possible because the dimensions of the body are very small with respect to the wavelength of the field. When a perfect conductor is placed in a static electric field, currents are induced that rearrange electric charges. The new arrangement of charge produces another electric field that totally cancels out the first field on the inside of the conductor. A similar situation occurs when a human or animal is exposed to a static electric field, except that the finite conductivity and dielectric properties of the body prevent total cancellation of the field internally. The electric field is, however, weaker inside the body than out by many orders of magnitude.

At ELF frequencies, currents flow continuously as the direction of the electric field reverses polarity. Internal electric fields are produced because current flowing through a finite conductivity causes a potential drop. These internal electric field strengths are still orders of magnitude smaller than external fields, but the ratio depends on the frequency of the field. If the exposure (external field before the subject is introduced into the field) electric field strength is held constant, the ratio of internal to external field strength, as well as the total induced body current, increase with increasing frequency of the field. At 60 Hz, a 1 kilovolt per meter (kV/m) exposure electric field will produce internal electric fields of only about 0.1 millivolt per meter (mV/m) to less than 100 mV/m (Kaune and Gillis, 1981). Total short-circuit current (the current passing between the subject and ground) for the same exposure is predicted to be about 15.3 microamperes μA) (Kaune et al., 1987).

The charge redistribution caused by electric field exposure also results in variations in the charge density on the surface of the body. These charges produce changes in the electric field strength on body surfaces. For example, a grounded, erect human exposed to a vertical 60-Hz electric field strength of 1 kV/m will experience surface electric field strengths of up to 18 kV/m at the top of the head (Kaune and Miller, 1984). A human or animal in an electric field thus significantly disturbs both the magnitude and direction of the field in its vicinity.

ELF currents can also be caused or enhanced by contact with conductive objects in the field. A motor vehicle under a power line, for example, will be exposed to a 60-Hz electric field, but current may not be able to flow to ground because of the insulating properties of the tires. A grounded or partially grounded human touching the vehicle will experience body currents with a magnitude depending of the field strength, vehicle size, and other considerations, In high field strength areas, such currents can represent a shock hazard.

Biological substances, with a few rare exceptions, are nonmagnetic, meaning that the magnetic properties are similar to those of air or a vacuum. Consequently, ELF magnetic fields are practically the same inside the body as out, and the presence of the body does not significantly affect the magnitude or direction of the magnetic field. This fact simplifies the development of interaction mechanism theories based on magnetic field exposures because the magnetic field strengths at the tissue or cell level are known,

Changing magnetic fields creates electric fields, as pointed out earlier. These electric fields occur in a circular pattern in planes perpendicular to the direction of the changing magnetic field. If these induced electric fields are inside a conductive object, circular currents known as eddy currents will flow. The intensity of the induced electric fields (and consequently of the eddy currents) depends on the magnetic field strength, the time rate of change of the magnetic field, and the radius of the circular path. A result of the path radius dependence is that higher currents will be induced in larger cross-section areas of the body, such as the torso, during human exposures.

Eddy currents can also be created by the movement of a conductive object in a static magnetic field, such as the earth's field, if the movement causes the total magnetic flux through the closed conductivity path to change. In either case (i.e., either the magnetic field is time-varying and the conductive path is fixed, or the magnetic field is static and the conductor is moving), the phenomenon is referred to as "Faraday induction" of currents. A typical domestic 60-Hz exposure of 0.1 microtesla μT) (Kaune et al., 1990) will produce in a human with a "radius" of 0.1 meter, a current density of about 0.19 microamperes per square meter μA/m^2) [1.9 x 10^{-5} microamperes per square centimeter (μA/cm^2)]. For comparison purposes, the external electric and magnetic field strengths required to produce an internal electric field of 10 mV/m are shown in Figure 2-2. This figure is based on a simple spherical model of a human. Geometrical enhancements of electric field strength occurring in humans will reduce the external electric field needed to produce the 10 mV/m internal E field. It has been estimated that power line magnetic fields produce internal electric field strengths in humans which are only about 15% as high as those produced by power line electric fields (Tenforde and Kaune, 1987).

Magnetic fields also produce a force on electric charges in motion as discussed earlier. This force, known as the Lorentz force, acts only on charged particles moving with a component of motion perpendicular to the magnetic field. It acts in a direction perpendicular to the direction of motion and can result in resonance effects which will be discussed later. The Lorentz force can change the direction of motion of moving charged particles, but it does

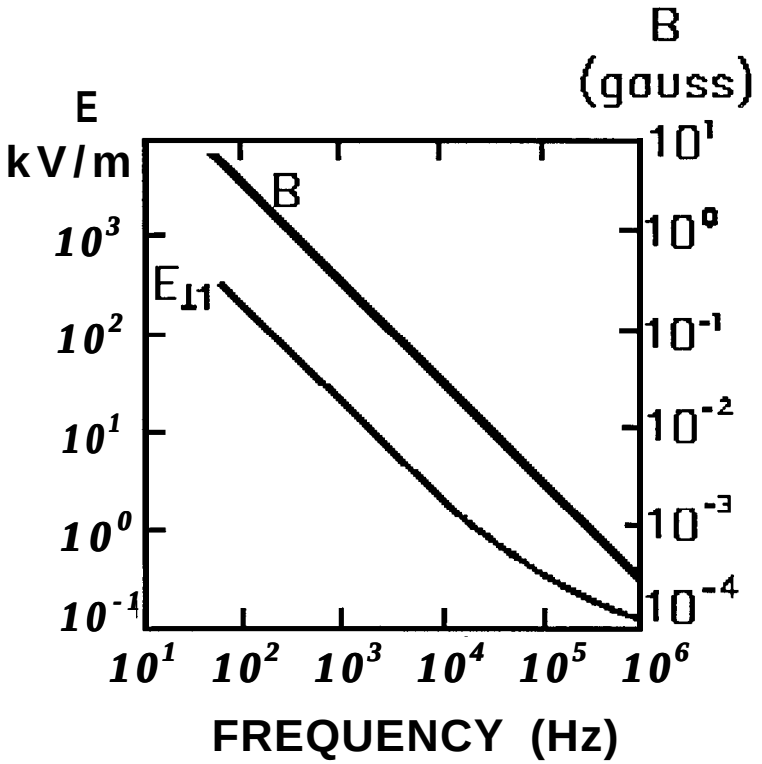


Figure 2-2. External electric and magnetic field required to obtain an internal E field of 10 mV/m.

SOURCE: Polk, 1986a.

not add energy to the system. In the case of moving body fluids, a magnetic field Lorentz force can cause a separation of charged electrolytes of opposite polarities across the diameter of the blood vessel (Persson and Stahlberg, 1989). This charge separation also occurs in a variety of nonbiological substances and is known as the Hall effect. Such effects are very weak with static fields having a flux density similar to the earth's field (less than 50μT), but are more important in nuclear magnetic resonance (NMR) imaging devices, where static magnetic fields of up to 2 tesla (T) are used. The Lorentz force also leads to the magnetohydrodynamic effect which reduces flow in moving electrolyte solutions like blood. A 2-T static magnetic field is predicted to reduce axial flow in the human aorta by 1% to 2% (Easterly, 1982). Perspective on the intensity of such exposures can be gained by comparison with common exposures. A 2-T magnetic field is over 20,000 times greater than the earth's magnetic field and more than two million times greater than a typical domestic 60-Hz magnetic field exposure.

Magnetomechanical effects are another class of direct magnetic interaction. One such effect is the tendency to orient molecules with certain magnetic properties. It has been observed experimentally in biological macromolecular assemblies such as retinal rod outer segments exposed to a static magnetic field of 1T [World Health Organization (WHO), 1987].

Magnetic fields can also affect the electronic spin states of certain reaction intermediates and alter the yield of reaction products. An example is the change induced in the charge transfer reaction occurring during bacterial photosynthesis (Blankenship et al., 1977). This effect is produced at static magnetic field exposures of 10 millitesla (mT).

An interesting direct magnetic effect is the induction of magnetophosphenes. This term describes the sensation of flickering light in the eye when it is exposed to ELF magnetic fields greater than about 10 mT and with frequencies over 10 Hz. Several types of evidence suggest that the magnetic field interaction leading to magnetophosphenes occurs in the retina (Tenforde, 1990). The exact mechanism for this effect is not known at present, but it does illustrate the principle that magnetic fields can interact with the body without substantial heating or energy deposition. The other direct magnetic interactions described above have been studied mostly in regard to intense static magnetic fields and are mentioned here only to introduce some of the known methods by which magnetic fields can affect living organisms. Their importance in ELF bioeffects is not known.

The International Radiation Protection Association (IRPA) recently published interim guidelines on limits of exposure to 50-Hz and 60-Hz electric and magnetic fields (IRPA, 1990). These guidelines are based strictly on induced body currents and known biological effects associated with these currents. The IRPA committee which developed the guidelines reviewed the interaction principles discussed here (WHO, 1987; WHO, 1984) and concluded that insufficient evidence existed to base the guidelines on other types of interactions. While it is agreed that other mechanisms may be important, it is also generally accepted that they are not well enough established to use predictively.

Coupling of ELF fields with the body is complicated by a number of factors. Changing the orientation of the body, for example, can significantly alter coupling and the resulting internal field strengths and current densities. Internal exposures are also affected by polarization of the field, grounding condition, contact with other conductors, and body geometry. The latter point is particularly important when evaluating laboratory bioeffects experiments. Internal electric fields and current densities in a human and a rat exposed to the same external ELF electric field are substantially different. Exposure fields in laboratory experiments are sometimes scaled to compensate for differences in body geometry, but without a detailed understanding of interaction mechanisms, it is not clear which parameter to scale for.

There are fundamental differences between ELF interactions and either ionizing or RF radiation interactions. ELF electric and magnetic fields couple poorly with the body. In contrast to some RF and microwave exposures, the body absorbs very little energy from ELF

fields at environmental exposure levels. ELF bioeffects must therefore result from mechanisms other than heating of body tissues. Another important point is that ELF fields cannot break chemical bonds or cause ionization, as can x-rays, which result in known damage to body tissues and genetic material.

Much attention has been focused on the cell membrane as a likely site of ELF bioeffects. The dielectric constants of cell membranes are so high at ELF frequencies that induced ELF body currents flow mainly around the outside of the cells. Consequently, the interior of the cell (cytoplasm) is shielded from applied fields and currents. Cell membranes have a natural potential that is important in regulating ion concentrations. ELF field exposures impose artificial membrane potentials, but the magnitude of these induced potentials is at least 100 times less than the natural potential. It is not obvious how the diminutive induced potentials might cause an effect, and many of the ELF interaction 'mechanism theories attempt to address this problem (see Section 2.4).

A 60-Hz magnetic field exposure of 0.1 μT will produce a current density in a human of about 0.19 $\mu A/m^2$, as discussed above. An electric field exposure of 10 kV/m is predicted to produce a maximum current density in a human of about 2.0 $\mu A/m^2$ (Kaune and Phillips, 1980). These values are below physiological current densities and at or below predicted noise for nerve impulses shown in Figure 2-3. Under normal circumstances, it is considered that induced signals must exceed the noise floor in order to be detected. In engineering terminology, the signal-to-noise ratio must be greater than one.

Other typical body currents range from 5×10^{-2} to 4 A/m^2 (5 to 400 $\mu A/cm^2$), typically around 10 Hz for the electroencephalogram (EEG) and up to 1 A/m^2 (100 $\mu A/cm^2$) near the firing heart cell (EKG)(Barnes, 1986). Note that the predicted induced current densities from ambient electric and magnetic field sources are orders of magnitude lower than endogenous currents associated with normal physiological processes. Many investigators have found it difficult to understand how such small currents could cause adverse biological effects. It should be noted, however, that the induced current predictions do not consider the extreme complexity of body structure and the interfaces of materials with differing electrical properties. Such heterogeneity may result in intensified currents or other effects at certain locations. Further research will be required to address these questions.

A recent analysis (Weaver and Astumian, 1990) has directly addressed the problem of the signal-to-noise ratio of field-induced potentials to thermal noise in biological systems. For example, the cell membrane is often considered a likely site for interactions of EM fields with

living organisms. Fundamental physical theory can be used to predict fluctuations in cell membrane potentials resulting from thermal noise. The fact that certain bioeffects have been reported to occur at field strengths that induce changes in membrane potential smaller than predicted on the basis of thermally generated fluctuations is perplexing. Some investigators have even rejected the validity of the experimental findings because of this apparent inconsistency.

Weaver and Astumian (1990) as well as Bawin and Adey (1976), have noted that previous analyses have considered noise contributions over a large frequency band. Thermal noise in electrical resistance is proportional to the square root of the bandwidth, so a larger frequency range implies more noise. If certain biological systems respond to signals only within a limited

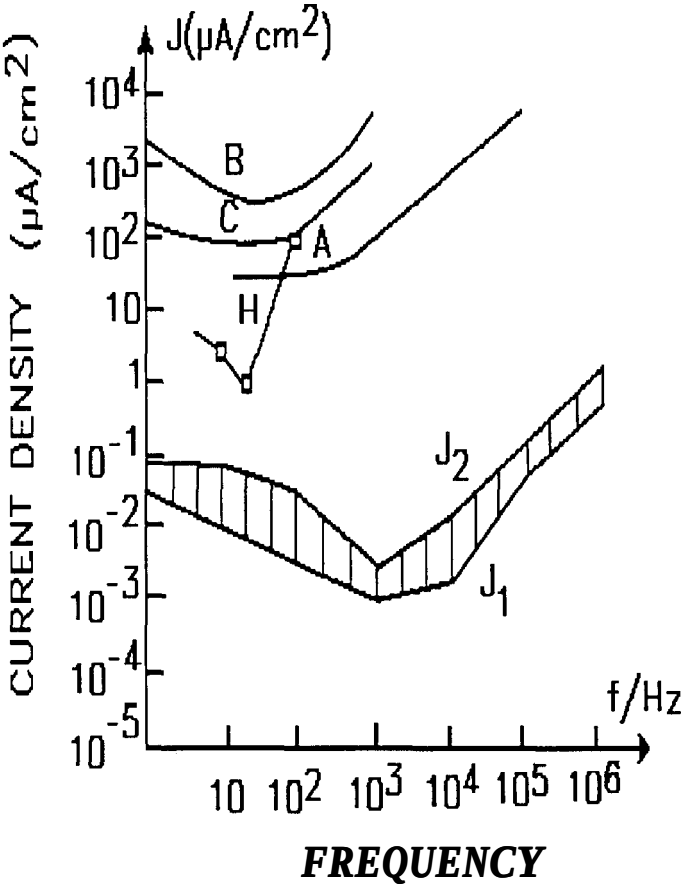


Figure 2-3. The minimum current densities observed to cause various biological changes: (A) threshold for stimulation for muscle or nerve cells; (B) threshold for fibrillation in a dog; (C) threshold for diastolic stimulation in dog hearts; (H) threshold for phosphene release; (J_1,J_2) noise current or current density fluctuations in nerve impulses.

SOURCE: Barnes and Seyed-Modani, 1987.

bandwidth, then the thermally generated noise within that effective frequency band is reduced. Thus, much weaker signals from external sources may be detected. Another argument presented for possible biological sensitivity to weak electric fields is that periodic signals may be signal-averaged over some time period to improve the signal-to-noise ratio.

2.2.2. Radiofrequency Fields

Radiofrequency fields oscillate thousands to billions of times more rapidly than ELF fields, and their interactions with the body are more complex. The body can absorb significant amounts of energy from environmental RF exposures, and safety standards have been established to limit the amount of heating from such exposures (by limiting field strengths). For purposes of illustration, the body can be thought of as a lossy antenna; that is, it absorbs energy from the electromagnetic field, re-radiates or reflects a portion of the energy, and dissipates the rest through resistive and dielectric losses. The efficiency with which an antenna absorbs energy from an electromagnetic field depends on its shape, orientation, coupling with other conductors, and size relative to the wavelength of the field. Figure 2-4 illustrates this principle for spheroidal models of a human and a rat in free space. The energy absorption curves are labelled E, H, and K, depending on whether the long axis of the spheroid is aligned with the electric field, magnetic field, or direction of propagation, respectively. Note that when the electric field is aligned with the long axis of the human model, energy absorption peaks around 70 MHz (in the TV portion of the EM spectrum, see Figure 2-1). The peak is known as the frequency of whole-body resonance and is simply the frequency at which the body dimensions appear as a tuned or resonant antenna to the field. Energy absorption is greatest for the electric-field polarization as shown in Figure 2-4. Resonant frequency is also affected by grounding conditions. A grounded subject will resonate at about one-half the frequency of an ungrounded subject.

It can be shown using electromagnetic theory that an external electric field does not penetrate a perfect conductor (material with infinite conductivity). Exposed to an external electric field, currents will flow only on the surface of the conductor. These currents will create electric fields that cancel the external field so that no internal electric field or internal current densities exist. Real objects, like the human body, do not have infinite conductivity and as a result, small internal electric fields exist. In real objects, both the dielectric constant and conductivity vary with frequency. Schwan and Foster (1980) have characterized the complex behavior of these electrical properties across the RF portion of the spectrum. When the body is exposed to an external RF electric field, an internal electric field is produced which in turn

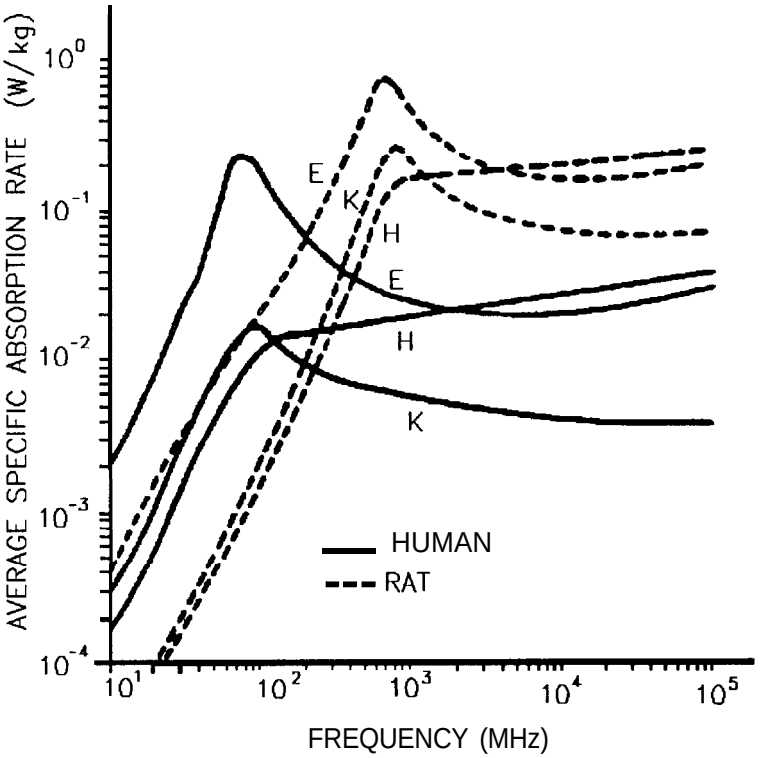


Figure 2-4. Predicted frequency dependence of absorbed energy in spheroidal models of biological bodies. The energy absorption curves are labelled E, H, and K, depending on whether the long axis of the spheroid is aligned with the electric field, magnetic field, or direction of propaganda, respectively.

drives internal currents. The distribution of current density inside the body may be even more complex than for the case of ELF exposures.

Simplified models can be used to study variations in internal field strengths and currents as a function of frequency of the external electric field. Internal electric field strength varies in a fashion similar to the SAR curve of Figure 2-4. At whole-body resonance, the internal electric field strength is comparable in magnitude to the external electric field strength (Barber, 1977). This result is in sharp contrast to the case of ELF exposures where internal electric field strengths are orders of magnitude lower than the external fields.

In general, internal electric field strengths and induced currents increase as the frequency of the external electric field strength is increased up to whole-body resonant frequency. Above the resonant frequency, these quantities, as well as SAR, are reduced and level off, as seen in Figure 2-4. Figure 2-5 illustrates the variation in body current versus exposure frequency as predicted numerically by a lumped impedance model of man. Induced current also peaks at whole-body resonance. Recent studies have indicated that RF currents of 600 to 800

milliamperes (mA) can be induced in humans exposed to 1 mW/cm^2 (61 V/m) fields near whole-body resonance frequencies (Chen and Gandhi, 1989).

Actual induced current densities vary substantially as a function of position within the body due to contrasting tissue electrical properties and body geometry. The distribution of current will also change as the subject moves around in the field, altering body geometry, orientation with respect to the field, and coupling with other objects and ground. Current density, at any frequency, is directly proportional in magnitude to external field strength if other exposure parameters are held constant.

The frequency of whole-body resonance, as well as the general shape of the induced current vs. frequency curve varies with body shape, size, and grounding conditions. The resonant frequency of a small child is significantly higher than that of an adult and much lower than that of most animals used in laboratory studies. The resonant frequency for a rat is about 700 MHz in contrast with about 70 MHz for an adult human (see Figure 2-4). These principles provide some insight into the question of frequency scaling in animal exposure systems. In general, a given electric field exposure will produce a different SAR in a human than in a rat, as

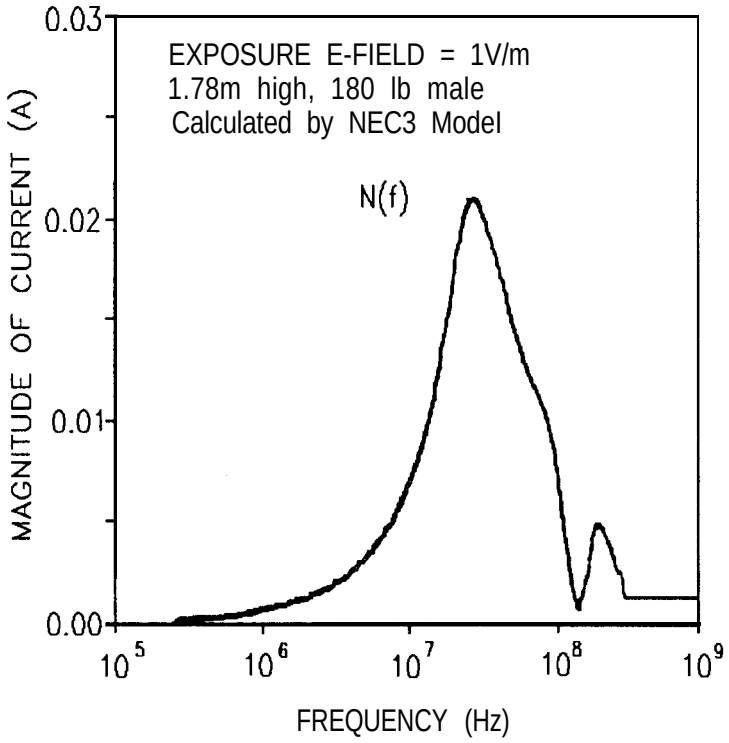


Figure 2-5. Plane wave induced current in humans vs. frequency.

SOURCE: Adapted from Guy, 1987.

illustrated in Figure 2-4. One way to equalize absorbed power in humans and animals is to conduct the animal experiments at a higher frequency so that the SARs are the same. While this approach addresses the problem of total absorbed power, issues of body geometry and local current densities are not as easily resolved.

Differences in geometry between a rat and a human also dictate that different current densities will be produced in a given tissue type (e.g., the liver) in the two species. Further, tissue electrical properties will differ at the two frequencies. For thermal effects experiments, it may be sufficient to equalize SARs, but nonthermal experimental results in animals or tissue cultures cannot be accurately applied to humans until the quantities necessary for the interaction are identified. Otherwise, one does not know whether to adjust for frequency, SAR, current density, or internal field strength. This point emphasizes the need for interaction mechanism theories that will afford some criteria for sorting through the practically infinite range of possible EM-field exposure conditions.

Internal magnetic field strengths are not necessarily the same as those outside the body for radiofrequency exposures. As exposure frequency is increased, the magnitude of induced eddy currents increases. These eddy currents produce a secondary magnetic field that tends to cancel the incident magnetic field inside the body. This shielding capability of an object with finite conductivity (such as the body) is quantified in terms of the skin depth. Skin depth is the distance into the material at which both the electric and magnetic fields from an incident electromagnetic wave are reduced to about 37%. Values of skin depth (or depth of penetration) vary according to the electrical properties of the material. At 915 MHz, for example, the skin depth in muscle tissue is about 3 cm while the skin depth for fat is about 18 cm (NCRP, 1981). Skin depth decreases with increasing frequency, indicating that energy is deposited closer to the surface of the body as exposure frequency increases through the microwave range.

The dielectric constant of cell membranes decreases with increasing frequency. As a result, electrical currents begin to pass through the cell membrane at frequencies of about 0.1 MHz and above, and the cytoplasm is no longer shielded as it is from ELF currents, This fact, along with the slow response times of cellular processes (compared to radiofrequencies), implies that mechanisms of RF and ELF biointeraction may be very different. A possibly important effect demonstrated in the RF range is the rectification of induced currents by the cell membrane (Barnes and Hu, 1977; Montaigne and Pickard, 1984). This process of greater passage of current in one direction than the other results in lower frequency modulation components being extracted from the RF signal. This effect is similar to the way the audio

information modulated on an AM radio signal is retrieved by rectification in a radio. Membrane rectification may be important in that it could result in low frequency signals at the cell level (which may be more biologically active) during an RF exposure. Certain experiments have demonstrated biological responses from both ELF exposures and RF exposures which are modulated at ELF frequencies (Bawin et al., 1973; Blackman et al., 1979).

2.3. AMBIENT EXPOSURE

This section briefly reviews the magnitude of the ELF and RF fields which the general population experiences. The section points out that an adequate analysis of exposure needs to include several other factors in addition to the magnitude of the ambient fields.

For 60-Hz electrical power, several good reviews are available [WHO, 1984; New York Power Lines Project, 1987; Office of Science and Technology Policy (OTA), 1989; Florig et al., 1987]. A description of electric and magnetic field measurements associated with the electric power distribution system in Seattle residences has been published by Kaune et al. (1987). The analysis of Florig et al. (1987) and the OTA (1989) has been summarized in graphs of electric field intensity and magnetic flux density as a function of distance from the source, reproduced here as Figure 2-6. In the graphs, the term “distribution” refers to 5-35 kV primary lines leading from the substation to the neighborhood step-down transformers and the 115/230 V secondaries leading to individual buildings. The term “appliances” refers to such items as electric shavers and blankets. The diagrams do not explicitly include 60-Hz ground currents carried by plumbing pipes, a factor that has recently received more attention. Other sources of exposure, such as television receivers, video display terminals, lighting dimmer switches, and wireless telephones, have significant components of power at higher frequencies, and are also excluded from the graphs. In addition, the earth’s static magnetic field and its perturbations, strong direct currents, and proximity to ferromagnetic materials such as telephones, are other sources of magnetic field exposures. No information is available about personal exposures to these sources.

Ambient RF exposures have been evaluated by scientists at the U.S. Environmental Protection Agency (1986). They described population-weighted average power levels in urban areas calculated from measurements in 15 large cities. The estimated residential median exposure for people in these areas was 0.005 microwatts per square centimeter $\mu W/cm^2$) at FM, radio, and television broadcast frequencies and 0.019 $\mu W/cm^2$ at AM broadcast frequencies. This radiation has frequency components ranging from 30 Hz (audio components of AM signals) to 806 MHz. The report concluded that there is negligible

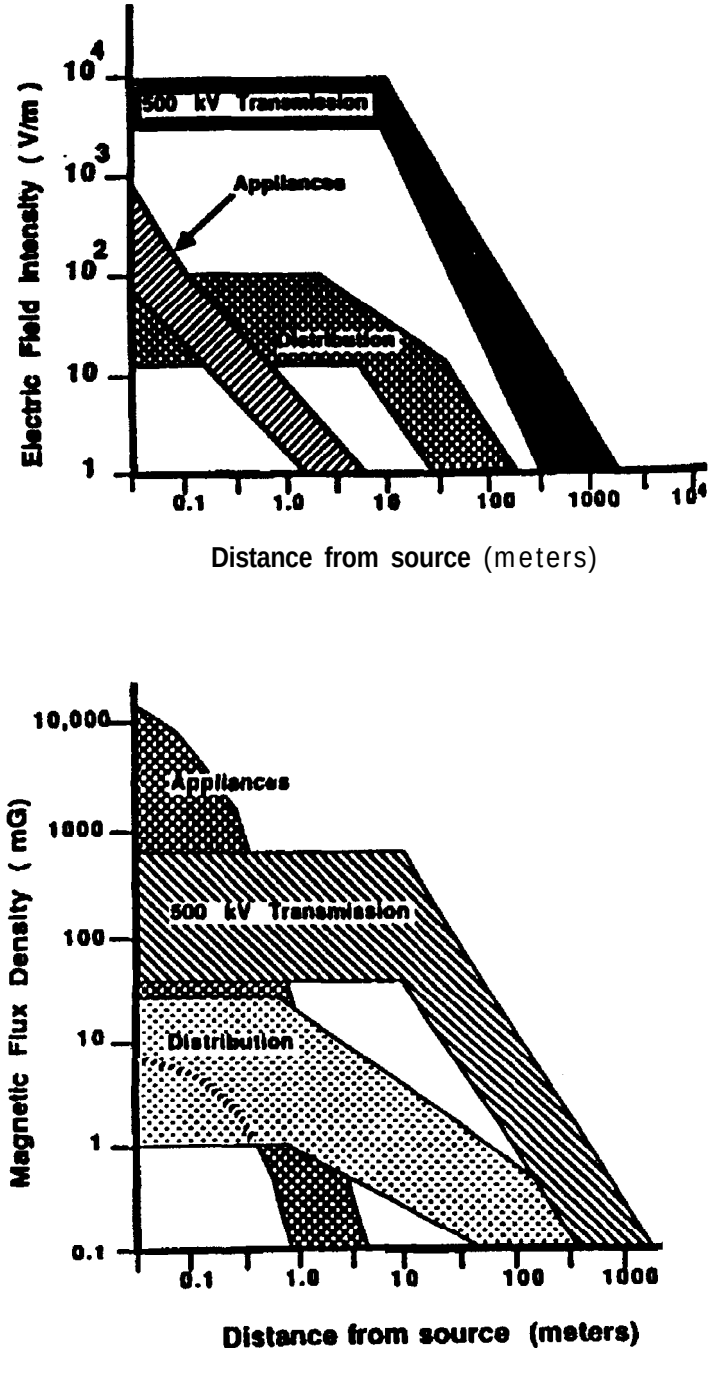


Figure 2-6. Variation in electric and magnetic field intensities at ground level as a function of distance from the source [1 milligauss (mG) = 0.1 μT].

background exposure above 806 MHz. The audio components of the AM broadcast signals contribute negligible absorbed power.

As Florig et al. (1987) point out, an adequate exposure assessment must consider many other factors in addition to the ambient fields described above. For electric fields, the body size, distance, and orientation relative to the source, the presence of shields such as trees, buildings, and vehicles, and the body's resistance to ground are other factors that determine the internal electric fields and currents from a given external field. For magnetic fields, body size is a major determinant of induced internal electric fields and currents. Also, since the induced body currents are proportional to the rate of change of electric and magnetic fields, the product of frequency times field strength is an important factor for field effects,

Since the basic mechanism of the adverse biological effects is not known, the relevant internal measure of exposure cannot be specified. Possible candidates are: (a) internally induced current, spatially averaged over the body; (b) internal electric fields, spatially averaged; (c) current or electric fields existing at some critical organ or target site; (d) a certain critical frequency or set of critical frequencies for the currents or electric fields, averaged over either the entire body, critical organs (such as the brain), or critical cells; (e) a critical time of day when the induced currents or fields are capable of producing the effect; and (f) a critical orientation of the external fields with respect to the earth's static magnetic field. Currently none of these possibilities can be ruled out, and the relevant external exposure parameters are dependent on which biological process is involved.

2.4. PROPOSED MECHANISMS OF INTERACTION

Efforts are now ongoing to develop theoretical models that can explain electric and magnetic field bioeffects. An interesting byproduct of research into the possible harmful effects of EM-field exposures is the recognition that present biological models must have fundamental deficiencies because of their inability to explain observed effects. Research into the mechanisms by which EM fields interact with living systems is therefore accomplishing a dual purpose. It is helping to evaluate the potential for adverse effects and at the same time providing new tools for investigating the basic processes of living systems. While a much deeper understanding of EM-field bioeffects has been developed, it is important to note that no single theory has provided a broad predictive ability or gained widespread acceptance in the scientific community. It is not yet possible, for example, to design epidemiologic studies based on a set of exposure conditions predicted to cause certain bioeffects. More fundamental research will be required to reach this important level of understanding.

The mechanism theories described below are attempts to model biological functions at the cellular and subcellular level in a way that identifies processes that could be affected by EM fields. The primary obstacle for any such theory is to explain how weak fields, which deposit tiny amounts of energy into living systems that are awash with much greater levels of random thermal energy, can be detected by these systems. Only a few of the many attempts to achieve this goal are described here. More detailed information can be found in several reviews (Wilson et al., 1990; Chiabrera et al., 1985; Adey and Lawrence, 1984; Polk and Postow, 1986; Blank and Findl, 1987).

2.4.1. Surface Compartment Model

A number of investigators have developed interaction mechanism theories based on electric field driven alterations in ion transport across cell membranes. These theories attempt to explain experimental findings such as calcium efflux and other effects which might be linked to changes in ion concentrations or gradients. The difficulty encountered by such an approach is that details of cell microstructure such as channel characteristics and operation are only now being elucidated. Theoretical models must therefore either make assumptions about these cell features, or use experimental results to infer their operation.

One theory which has been developed extensively is the Surface Compartment Model (SCM) reported by Blank and Findl (1987). The SCM provides an approximate solution to the complex equations of electrical double layer theory permitting study of transient effects which occur during electrically driven ion transport. In the SCM, the cell interior, inside surface, membrane, outside surface, and exterior are each defined as compartments with specific properties. A set of nonlinear, independent differential equations are then derived to describe the system using principles of conservation of charge and mass along with chemical kinetics. Channel function is modeled as a voltage-dependent permeability, and other properties such as ion mobility in the surface compartment and the rate constants for ion binding and release are assumed.

Cation channels are described physically as being cylindrical in shape with a constriction at the cytoplasmic end in the resting state. The repulsive forces of bound surface charge keep the outer portion of the channel open on the surface of the cell membrane. Gating, or opening of the channel can result from any event that leads to changes in surface charge. For example, mobile gating charges may result from electric field exposure, binding of ligands, or certain enzymatic (e.g., ATPase) reactions. This depolarization shifts negative charges to the inside of the cell membrane, which binds to the inside surface of the channel and opens the

cytoplasmic end by electric repulsion. Another effect of the charge shift is that concentrations of bound counter ions in the channel can be changed (especially if one species is preferentially adsorbed) such that a reversed local concentration gradient is produced. Ion transport would then proceed in a direction opposite the overall gradient (i.e., ion pumping).

The SCM offers a means for studying transient fluxes and concentration changes caused by time-varying currents and fields. This capability is important because of the differences in time frame between electrical and chemical processes. While a membrane can be depolarized in less than 10 microseconds, chemical potentials change by diffusion which proceeds more slowly (e.g., about 1 millisecond over distances of a cell diameter). Rapid electrical changes thus result in temporary electrochemical imbalances and transient fluxes. Evaluation of these transients requires knowledge of the surface properties (such as rate constants for binding and release) because of the influence of absolute concentrations on ion flux.

Channel selectivity, for example, is explained by the SCM through the kinetics of channel opening rather than filtration (channel size vs. ion size). The SCM considers the high concentration of sodium ions on the outside surface of the membrane and the enhanced potassium ion concentration on the inside surface of the membrane due to the membrane charge. If the membrane is depolarized and the gate opened simultaneously, as described above, the ions will diffuse away from the membrane to establish electrochemical balance, and some of the diffusion will be through the channel. Selectivity is predicted by the SCM to arise from the differences in speeds of channel opening and diffusion rates. The more mobile sodium ions will pass through the channel in significant numbers only if the channel opens before the diffusion process is complete. A slowly opening gate will miss the sodium diffusion but pass the more slowly diffusing potassium ions. The channels are assumed to pass both potassium and sodium ions, but appear selective due to gating time. Among the implications of this model is the inference that agents which appear to inhibit certain ion channels may actually be modifying the gating time.

The ratios of ion species which carry charge are also important in the SCM. As described earlier, ratios of sodium and potassium ions in the layers on either side of the cell membrane differ because of the potential difference and concentration differences. An externally applied current passing through the membrane will carry more sodium if directed into the cell (positive charge inward), and more potassium if directed out of the cell. The SCM shows that these effects are not completely reversed when the direction of current is quickly reversed because of transient surface concentration changes that exist until the diffusion processes catch up with the electrical changes. Applied alternating currents thus tend to reduce both of these

cation gradients as sodium ions are transported into the cell and potassium ions out. The effects are additive up to some new equilibrium point and tend towards the same gradient reduction on both sides of the cell. Certain frequency dependent enhancements have been predicted by the SCM (Blank and Blank, 1986).

The effects described above also apply to other ions in the cell environment. Of particular interest are predictions for calcium ions, especially since the influences of applied external electric fields on calcium ion fluxes have been observed experimentally. Calcium is predicted to carry about 1% of the charge through the membrane, but because cytoplasmic concentrations of this ion are so low, relatively small numbers of transported ions lead to large changes in gradient. The binding constant for calcium is high inside the cell and is associated with a number of biological processes

Field-induced ion fluxes have also been described by other models. One theory describes the external bilipid layer of the cell membrane as weakly cationic (containing bound cations), while the inner layer is strongly anionic (Findl, 1987). The combined effect of these layers is to act as the equivalent of a semiconductor P/N junction, passing current in one direction only. Applied currents will transport ions out of the cell if the polarity is in one direction, and have no effect in the opposite direction. This model predicts an overall decrease in intracellular ion concentration when the cell is exposed to an externally applied alternating current. Cellular concentrations of calcium ion are normally low. During various signal transduction processes, these levels may increase by an order of magnitude due primarily to calcium release from mitochondria and other intracellular organelles. Any factor that prevents these signal transients may inhibit normal cell processes and result in bioeffects.

2.4.2. Ion Cyclotron Resonance

Another prominent interaction theory is centered around a phenomenon known as cyclotron resonance. This well-known physical principle describes the motion of a charged particle in a static magnetic field absorbing energy from a time-varying electric or magnetic field. The Lorentz force described earlier bends the path of charged particles moving with a component of motion perpendicular to the direction of the magnetic field. As the particle's direction is continuously altered, it will ultimately move in a circular or helical path around the magnetic lines of force. Outside the earth's atmosphere, where charged particles experience few collisions with other particles, this circular motion can continue for long periods of time. The charged particles in this case are electrons and protons emitted by the sun which are

trapped in the earth's magnetic field. The frequency with which charged particles orbit in a uniform, static magnetic field is determined by

$$\omega = \frac{qB}{m}$$ Equation 2-1

where ω = angular frequency
q = charge of the particle
B = magnitude of the component of the magnetic field perpendicular to the particle's direction of motion, and
m = the mass of the particle.

Note that the frequency is independent of the particle's velocity. The Lorentz force which bends the particle's path is proportional to velocity. A slowly moving particle will thus inscribe a smaller circle than a faster moving particle, but both will complete a revolution in the same amount of time.

In situations where the charged particles lose energy by collisions with other particles such as in condensed media, this circular motion will eventually halt unless energy is added to the system. Energy can be added directly by the action of a time-varying electric field which is parallel to the plane of the orbit. If the frequency of the electric field meets the requirement of Equation 2-1, (i.e., 3) it will continuously add energy to the particle's motion as it orbits. This condition is known as cyclotron resonance and has been used in many physics applications.

Liboff (1985), Blackman et al. (1985), and Polk (1986b) have suggested that cyclotron resonance may play a role in the ELF bioeffects that have been established experimentally. The motivation for this approach was the pattern of frequency dependence in calcium efflux experiments reported by Blackman et al. (1985). The presence of discrete frequency windows argues against Faraday induction which would suggest increasing effectiveness of magnetic field exposure as frequency is increased. Further, Blackman's results demonstrated the importance of the geomagnetic or other static magnetic field in producing the effects. Cyclotron resonance is attractive because it requires a static magnetic field and predicts that responses will occur at discrete frequencies. These frequencies are predicted from Equation 2-1 using the charge and mass of various biologically active ions along with the value of the static magnetic field present during the experiment. The electric field used to drive the ions is directed at a right angle to the static magnetic field, and may be induced directly from an external electric field exposure or by Faraday induction from an oscillating magnetic field. In order to impart energy to the ion, the frequency of the driving field must be equal to the cyclotron resonance frequency, 3, for the given ion.

Although cyclotron resonance of charged particles is a well-known physical principle, it is not clear what role this phenomenon may play in biological systems. At this point, it is possible only to search for bioeffects which occur at the predicted combinations of static and alternating fields corresponding to the cyclotron resonance frequencies for biologically important ionic species. This approach has been applied with limited success to the calcium efflux results (Liboff, 1985; Blackman et al., 1988) but is not compatible for all the frequency and field combinations shown to produce effects.

The most intriguing results occurred in experiments designed specifically to investigate the cyclotron resonance hypothesis. In one experiment (Thomas et al., 1986; Liboff et al., 1989) rats that had undergone prior operant conditioning were exposed to fields "tuned" to the cyclotron resonance conditions for singly ionized lithium (60 Hz, 27.1 μT) in which the 60-Hz magnetic fields were horizontal and in the plane of the earth's static magnetic field. Following 30-minute exposures, the rats showed significant alterations in ability to perform a trained activity (pushing a lever after a time delay). The effect persisted at least one hour after exposure, but less than 24 hours, and was reproducible over a several week period. It occurred only for the combination of static and alternating fields, and not for either field alone. Both the static magnetic field (27.1 μT) and the alternating magnetic field, which must be larger than 27 μT for the effect to occur, are within the range of normal domestic exposures (New York Power Lines Project, 1987).

A second experiment designed to test the cyclotron resonance theory examined the motility of benthic diatoms exposed to fields adjusted for cyclotron resonance of doubly ionized calcium (Smith et al., 1987). In this study, the motility of the diatoms across an agar plate with a 0.25 to 0.5 millimolar (mM) calcium concentration was measured as the frequency of the alternating magnetic field was varied. With the static magnetic field set at 21 μT, diatom motility was seen to peak at 16 Hz, which is a combination for cyclotron resonance in doubly ionized calcium. Motility was also enhanced at the third, but not second or fourth harmonics. The effect occurred only at calcium concentrations slightly less than required for normal diatom movement. At higher concentrations (5 mM), the diatoms were fully motile and the exposure fields produced no significant changes. Because diatom movement depends on transport of calcium ions across the cell membrane, this experiment implies enhanced transport similar to that reported in the chick brain calcium efflux experiments (Bawin and Adey, 1976; Blackman et al., 1988). A few other experimental findings have been used to support the cyclotron resonance theory, but will not be described here (Liboff et al., 1987).

The above findings clearly implicate the importance of the charge-to-mass ratio of biological ions such as appears in Equation 2-1. Efforts to develop a more detailed mechanistic theory based on ion cyclotron resonance, however, have been largely unsuccessful. The primary theoretical difficulty is that the thermal collision frequency for ions in solution is far greater than the cyclotron resonance frequency. Using the geomagnetic field, cyclotron resonance frequencies for biological ions fall in the ELF range under 100 Hz. A resonating ion which therefore orbits in 10 to 100 milliseconds will experience some 10^{12} collisions during this time frame (Halle, 1988). Part of the appeal of resonance phenomena is that a single particle can continuously gain energy over several cycles, thus helping to explain how such low intensity fields can cause bioeffects. Clearly, the high collision frequency precludes completion of even a single orbit in a normal aqueous environment. This high collision frequency and consequential thermalization of resonance-acquired energy argues against any significant buildup of energy by resonating ions. A numerical model of cyclotron movement (Durney et al., 1988) predicts complex trajectories for free ions due to the additional forces exerted by the alternating magnetic field often used to induce an internal electric field. The model indicates that no resonance occurs if the collision frequency is significantly higher than the resonance frequency. Another issue of theoretical interest is that ions are normally hydrated in aqueous solutions. The additional mass of these attached water molecules alters the cyclotron resonance frequency predicted in Equation 2-1.

Liboff and McLeod (1988) has attempted to respond to these questions by suggesting that cyclotron resonance affects ions while they are confined to helical membrane channels. The channel protects the ion from collisions and provides a helical passageway corresponding to the predicted ion trajectory. Halle (1988) however, has argued that the introduction of a helically constrained path eliminates the magnetic effect (Lorentz force orbit). Also, there is as yet no convincing evidence that membrane ion channels are shaped like helical tubes.

Recently, Lednev (1990) has proposed an alternate interaction mechanism theory related to cyclotron resonance which may overcome some of the problems. This theory considers calcium ions bound to oxygen ligands in calcium binding proteins as charged spatial oscillators. Such an oscillator will have a set of characteristic vibrational frequencies. A static magnetic field applied to this system will split excited energy levels into two sublevels separated in frequency by the cyclotron resonance frequency. Application of an exposure field at the cyclotron resonance frequency may result in a transition between these states. Such transitions could then affect calcium binding rates. This model has the interesting characteristic of positioning the ion inside a protein matrix, thus reducing the random thermal

motion that is the primary difficulty of the cyclotron resonance theory for free ions. However, it will be necessary to verify that the vibrational states are not affected by thermal energy.

It is clear that the multiple-collision objection must be answered in some way if the ion cyclotron resonance hypothesis is to be plausible. The answer to these objections will probably come in the study of ion-protein dynamics of the plasma membrane. Nevertheless, the attractive features of this class of hypotheses are: (a) it naturally explains frequency-specific interactions and might ultimately be capable of explaining "intensity windows." The frequency selectivity may be the "antenna" that is needed to "pull" weak EM-field signals out of endogenous "noise" of background electrical activity; (b) it comes close to explaining one of the few effects that have been experimentally induced at the low field strengths comparable to environmental exposure (0.3μT = 3.0 mG); namely, calcium release from chick brain tissue; (c) since it deals with events at the plasma membrane, it has the capability of linking ionic phenomena with hormone-specific chemical signaling mechanisms; (d) it is generic enough to include several different ions as candidates.

2.4.3. Cooperative Mechanisms

An entirely different approach to explaining the mechanisms behind non-thermal effects has been advanced by Fröhlich (1988). It is motivated in part by assertions based on classical linear physics, that the energy deposited in a biological system by nonthermal EM-field exposure is insufficient to produce significant direct interactions with biological molecules, Instead, Fröhlich and others have attempted to identify higher states of order or coherence in biological systems which may be sensitive to weak interactions.

The ideas described by Fröhlich are difficult to comprehend in the present context because they are based on concepts of theoretical physics rather than molecular or cell biology. Within the framework of molecular biology, it is generally assumed that biological functions can be derived by studying the chemical and structural properties at the microscopic and molecular levels. The investigator considers average properties such as diffusion and reaction rates of various substances. From a physics viewpoint, however, another level of complexity exists. Groups of particles may interact with the number of possible interactions depending exponentially on the number of particles. Such systems are referred to as "many body systems" and are not solved for exact motions, but described by state functions. These state functions relate to the energy of the system and other properties. Using this formalism, it is found that various states of order or correlation of properties are possible at specific energy levels.

Examples are given of lasers and superfluid helium. In an optically pumped laser, a substance is exposed to incoherent light (there is no phase correlation between waves). This energy is absorbed by the system producing coherent light in which the phases of the light at different locations are synchronized. Thus, a high coherence is established over long distances beginning with a more random supply of energy. Conservation of energy is not violated by such a system because of the excess pumping energy, but this example does illustrate the development of an ordered state (coherence) among many particles (the excited states of the atoms) which is not apparent from study of a single particle. In superfluid helium cooled near absolute zero, the entropy approaches zero but the atoms exhibit apparent disorder similar to higher temperature liquids. However, the macroscopic wave function describes a correlation of the motion of the atoms. This subtle order reduces the entropy to near zero in spite of the lack of spatial order one would expect. The point here is that in many-body systems, other types or order and coherence are possible besides the obvious spatial type found in crystalline structures.

Ignoring for a moment the microscopic view which represents the basis for modern biology, Fröhlich looks at biological systems as a whole and seeks to describe the important physical aspects. He finds that (a) they are relatively stable but far from equilibrium, (b) they exhibit a nontrivial order, and (c) they have extraordinary dielectric properties, The third point refers in part to cell membranes which support an electric field of 10^7 V/m. Because of the lack of spatial order (at the level of ions), Fröhlich hypothesizes that other types of order or coherence play an important role in the description and properties of biological systems. In reference to the first point, he assumes that living systems consist of various excited states that are stable or metastable. It is these correlations and excited states through which weak electromagnetic fields are able to interact even when sufficient energy is not available to affect individual particles directly in a significant way.

Much of the mathematical detail of this framework depends on nonlinear dynamics and deterministic chaos. This branch of mathematics is relatively new and predicts highly complex, but structured behavior from systems involving nonlinear forces. An introduction to this field can be found in Davies (1988). Chaos is predicted even in simple systems meeting the appropriate conditions, such as a two dimensional pendulum with a nonlinear driving force. It can be shown mathematically that multiple, or even infinite states of motion can exist with equal probability. Although the equations of motion are deterministic in a strict sense, errors in initial conditions are multiplied with each cycle so that exact motion is unpredictable in practice. Such systems display highly erratic and sometimes nonrepetitive behavior, but

exhibit certain predictable and common characteristics. Under certain conditions, partially stable states can be achieved which are highly sensitive to external forces especially if these forces occur at specific frequencies. Fröhlich suggests that the high sensitivity and functionality in living systems may result from ordered states within the apparently chaotic motions and arrangements of biological particles. As in the case of a laser where coherent light is produced from incoherent light, the higher order modes in living systems are driven by, but decoupled from the surrounding random thermal motion. An example is self-excited oscillations or limit cycles which are characteristic of certain nonlinear systems under specific conditions, and may help explain threshold and saturation effects in biological experiments.

A feature of this viewpoint is that ordered or coherent states can exist over large distances, thus offering a mechanism by which cells may communicate in spite of the short range of chemical forces. This long-range biological coherence may provide growth control as exists in healthy tissue but is absent in cancer. A number of investigators have expanded Fröhlich's approach, and sought to test predicted consequences experimentally (Fröhlich, 1988; Adey and Lawrence, 1984). Rowlands (1988) has studied rouleaux formation or stacking of red blood cells during clotting. From a strictly electrostatic viewpoint, one would expect repulsion between the cells due to the negative electric charges on each cell. Instead, an attractive force extending over microns of distance is observed which represents an order of magnitude greater range than is associated with chemical forces.

Conceptually, Fröhlich's approach does not define or restrict the properties or physical quantities which are coherently coupled. However, attempts have been made to identify specific cases. One of the earliest observations in this respect is the unique electrical conditions existing in cell membranes. Given the electric field (10^7 V/m), the membrane thickness, and an estimated elastic constant, Fröhlich calculates that the membrane should oscillate in electric fields in the frequency range of 10 GHz to 100 GHz. Fields produced by each cell might be coherently coupled. Other aspects of the theory indicate that interactions with such excited coherent modes will be frequency and amplitude sensitive. Grundler et al. (1988) have observed such effects in the growth of yeast cells near 42 GHz. Enhancement and reduction of growth rates were found at closely spaced frequency intervals for nonthermal exposures. Other experimental results supporting this theory can be found in Fröhlich (1988).

Lawrence and Adey (1982) have proposed a model by which weak signals could be transmitted through cell membranes. This model suggests that solitons or solitary waves may carry weak signals inside cells. Solitons are nonlinear waves that do not dissipate like ordinary waves. In this case, solitons are thought to travel along intramembranous protein

particles (IMPs) that pass through the cell membranes. This process is summarized in three steps: First, weak electrochemical events are sensed by glycoproteins on the cell surface. The surface events are then amplified and transmitted to the cell interior along an IMP. Finally, these signals are coupled to internal enzyme systems in the cell as well as the nucleus and other organelles. It is suggested that this process may be affected by externally applied fields. A detailed explanation of this theory can be found in Adey (1990).

The concepts of biological coherence offer a new approach for studying the properties of highly complex living systems, and may help explain the high sensitivity of certain biological systems. There is a tendency to reject these ideas because they are difficult mathematically, and because they deal with nonlinear properties which have often been avoided in an effort to reduce complex problems to simple terms. Further, the problems of coherence and many-body interactions are seldom discussed in most disciplines and often cannot be solved by direct means. The problems are theoretically solvable, but very complex. Deterministic chaos is also unfamiliar in most disciplines, but has been clearly demonstrated in many physical processes including turbulent flow, nonlinear circuits, cavitation, and even in biological processes such as EEG and stimulated heart beat (Kaiser, 1988). The role that these principles play in other biological processes has yet to be established and will require further investigation. Perturbation of metastable excited states may be the mechanism through which the low energy of nonthermal EM exposures are able to interact with biological systems.

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T h i s p a g e l e f t i n t e n t i o n a l l y b l a n k

3. EPIDEMIOLOGIC STUDIES OF ELECTROMAGNETIC FIELDS AND CANCER

3.1. INTRODUCTION

The epidemiologic literature for radiofrequency (RF) radiation was previously reviewed by the U.S. EPA (1984) and by Elder (1987). But, in the past few years, there has been a marked increase in epidemiologic studies reporting an association between cancer and electric and magnetic fields. Concern extends not just to RF radiation but also to exposure from electrical power transmission and usage. The studies generally fall into one of three categories: occupational, environmental, and residential exposures. Results have been reported for different geographic regions, countries, age groups, industries, and occupational classifications. Many of the studies focus on 50- or 60-hertz (Hz) fields, the frequencies used for power transmission. These studies have been described in various review articles (Ahlbom, 1988; Brown and Chattopadhyay, 1988; Coleman and Beral, 1988; Easterly, 1981; Modan, 1988; Savitz and Calle, 1987; Sheikh, 1986).

There have been studies on cancer in children and cancer in adults. Childhood cancer studies have involved exposure to magnetic fields in the home, either measured or estimated by power line wiring configurations (Table 3-1). The results of these studies bear directly on the risk of cancer in exposed persons. Studies of children and adults are evaluated separately. The presumed frequency of exposure is relevant. Studies that examined populations with exposure to RF radiation are evaluated separately from studies of 50 or 60 Hz, the frequencies of electrical power transmission. Many of the occupational studies use job titles or employment in industries or occupations with potential exposure to electromagnetic (EM) radiation, a surrogate of exposure. These studies may involve exposure to different EM frequencies, either singly or in combination, and so the most relevant frequency of exposure may be unclear. Since it is likely that electric and magnetic fields from 50- or 60-Hz frequencies or extremely low frequency (ELF) electromagnetic radiation predominate, the occupational studies with unknown or mixed frequency exposure are described together with 50- or 60-Hz occupational studies. It should be noted that higher frequency fields, specifically RF radiation, may be modulated at lower frequencies. Demarcation by frequency is somewhat arbitrary but is important to any given study with respect to determining if a specific health effect could explicitly be identified with a particular frequency of exposure or a given job title or class of jobs.

TABLE 3-1. SUMMARY OF STUDIES OF CHILDHOOD CANCER

Author(s) (Yr.)	Study Design	Study Population	Comparison Group	Results	Highlights/Deficiencies
Aldrich et al. (1984)	case series	Girls, Jacksonville, FL	N A	Noted cluster of 5 cases of very rare endodermal sinus tumors in girls, all black, in one zipcode area.	Residence in neighborhoods with high elevated exposures to magnetic fields estimated to range from 40 to 1690 mG.
Wertheimer and Leeper (1979)	case-control	Children who had died before age 19 of cancer in Colorado between 1950-79 and lived in the Greater Denver (CO) area.	Children identified from birth certificate files, sorted by month and county of birth.	Significant excess risks associated with residence in homes coded as have a relatively high magnetic field as denoted by a wiring configuration code (HCC). OR = 3.09, all cancers, one address. ORs by site and by (time) type of address ranged from 2.08-2.98.	Coding not masked. Codes reasonably correlated with measurements.
Fulton et al. (1980)	case-control	Children with onset of leukemia before age 21 between 1964-78, as listed in records of the Rhode Island Hospital.	Two controls (of same birth yr.) per case drawn from State birth certificate records.	No differences found between cases and controls.	Used dwellings as basis for comparison; multiple dwellings permitted for cases but not for controls.
Tomenius et al. (1982); Tomenius (1986)	case-control	Children 0-18 yrs. old diagnosed with cancer and registered in the Swedish Cancer Registry during 1958-73.	Children matched for age, sex, and church district of birth, drawn from parish birth registration records.	Significantly increased risk associated with living near any electrical structure (OR = 1.3) or near a 200 kV power line (OR = 2.1) and with magnetic fields of >0.3μT (>3.0 mG) measured outside dwellings (OR= 2.1)(if no electrical structures were visible, OR = 2.3) and with magnetic fields <0.3μT (<3.0 mG) if dwellings were near 200 kV lines (OR = 2.6).	Used dwellings as basis for comparison. One inconsistent result, i.e., excess risk from 200 kV lines concentrated among lower exposures, e.g., <0.3μT (<3.0 mG).
Myers (1985)	case-control	Children 0-15 yrs. old diagnosed with cancer between 1970-79 and born in Yorkshire Health District.	Children with birth yr. and address similar to case. 2 controls per case dying from 1975-79 and for all live cases.	Risk ratios elevated for most cancer sites and distance or field strata. Not statistically significant increases; a few p-values marginal.	Estimated 15% case underascertainment. Case and control selection differs over time and within and between groups. Small numbers. Low exposures.
Savitz et al. (1988)	case-control	Children diagnosed with cancer between 1976-83 when residents of the Denver SMSA, drawn from Colorado Central Cancer Registry.	Children selected by random digit dialing from same telephone exchange as case and matched for age and sex.	Elevated risks (1.35) for all cancers for living in a home with magnetic fields >2 mG and in high code(s) homes. Trend tests of two 5-level wire code analyses were significant. CI exceeded unity for risk ratios, all causes, for homes lived in 2 yrs. before diagnosis and coded as Very High (OR = 5.22) and for High (vs. Low) coded diagnosis homes (OR = 1.53) and for risk ratios for brain cancer (OR = 2.04) for High (vs. Low) diagnosis homes. Odds ratios were elevated for all but one site in analyses for dichtomous wire codes.	Carefully designed, conducted, and analyzed study. Any potential biases would come from controls that had more stable in residence histories than cases and low response rates for making measurements and for interviews. Higher risks for codes than measures. Higher risks under low power use. Significant trend tests give some suggestion of dose response.

TABLE 3-1. SUMMARY OF STUDIES OF CHILDHOOD CANCER **(continued)**

Author(s) (Yr.)	Study Design	Study Population	Comparison Group	Results	Highlights/Deficiencies
Lin (1989)	case-control	Children diagnosed with cancer in the last 5 yrs. in the Taipai Metropolitan area.	Hospital controls. Children matched on age, sex, and date of admissions to same hospital.	Nonsignificant excess risks for all cancers (1.3) leukemias (1.3) lymphomas (2.0) and brain tumors (1.09).	High exposures as residence within 50 m (> 20 kV) of powerlines, transformers, or substation.
Coleman et al. (1989)	case-control	84 children < 18 yrs of age diagnosed with leukemia, drawn from Thames Cancer Registry, England, for 1965-80, who resided in four boroughs of London.	141 children with solid tumors except lymphomas, drawn from the same registry, matched on age, sex, year of diagnosis, and borough of residence.	Nonsignificant trend of increasing risks with decreasing distance from sources. OR = 1.63, 1.49, and 0.75 for distances of < 25, 25-49, and 50-99 m, respectively.	Subjects residing over 100 m from overhead lines and substations used as reference group in analysis of subsets grouped by distance. Introduces possibility of exposure in this group to other unknown sources, possibly diluting response.
Spitz and Johnson (1985)	case-control	Children who had died from neuroblastomas between 1964-78 in Texas.	Children randomly selected from Texas birth rosters with same distribution of birth yrs. as cases.	Evaluated paternal occupation. Significantly increased risk if father worked in a broad exposure cluster that included electrical and similar occupations. ORs elevated but similar when jobs regrouped as high (2.14) and low (2.13). OR= 11.75 if father an electronic worker.	Couldn't discern different risks under applied exposure groupings. Confounding possible. Paternal occupation from birth certificates.
Wilkins and Koutras (1988)	case-control	Persons < 20 yrs. old who died in Ohio between 1959 78 with primary brain cancer as underlying cause on death certificate.	Randomly selected from Ohio birth listings between 1940-67 and paired to case on sex, race, and yr. of birth.	Excess risks for various industrial and occupational groups. Significant OR (2.7) for electrical assembling, installing, and repairing occupations within the Structural Work occupational class. Significant OR (3.6) for electrical assembling, installing, and repairing occupations within the Machinery Industry. Again, these occupations were part of **a** broader group of structural work occupations.	Paternal occupation from birth certificates and coded using a method to develop low toxic exposure reference group. Coded for occupation and industry.

Cl = 95% confidence interval, OR = odds ratio, NA = not available.

3.2. STUDIES OF CHILDREN

3.2.1. 50- or 60-Hertz Exposures

Wertheimer and Leeper (1979) reported the results of a case-control study that examined the cancer mortality of children in relation to electrical wiring configurations. Cases were children who died of cancer in Colorado before age 19 between 1950 and 1973. The source(s) used to identify cases or the source(s) of cancer mortality data were not stated. Cases were also required to have been in Colorado and have lived at Greater Denver area addresses between 1946 and 1973. Two sets of controls were developed. The first, called "file 1 controls," were next Denver-area birth certificates drawn from files organized by birth month and county. The second set, called "file 2 controls," were next Denver-area birth certificates taken from alphabetical listings grouped by the years 1939-1958, 1959-1969, and 1970-1974. Birth addresses were taken from birth certificates. "Death" addresses were defined as the parents' address 2 years prior to diagnosis of the case and were obtained by searching city directories. For cases that could not be traced in this manner, the address listed on the death certificate was taken as the death address. If a "file 1 control" could not be traced, a "file 2 control" with a birth date most similar to the case was selected. The authors stated that the proportion of controls with an address coded as of "high-current configuration (HCC)" (see below) was similar between used file 1 controls (21%) used file 2 controls (23%), and the pool of controls available but not selected (25%). The author indicates that selection bias is, thus, probably not an issue. The methods for this assessment were not, however, stated.

There were 344 cancer cases who met the study selection criteria. Of these, birth address information was lacking for 72 cases or the birth occurred prior to 1946, and death address information was lacking for 16 cases. As a result, analyses of birth address were made for 272 cases and their controls and of death address were made for 328 cases and their controls.

Maps were made of the electrical wires and transformers in the vicinity of birth and death addresses for cases and controls. Primary [13-kilovolt (kV)] wires were classified as "large-gauge" or "thin." Large-gauge wires are designed to carry high currents. Homes were classified as having either a "high-current configuration (HCC)" or "low-current configuration (LCC)." HCC homes were (1) less than 40 meters from large-gauge primaries or an array of six or more thin primaries, (2) less than 20 meters from arrays of 3-5 thin primaries or high tension

(50-230 kV) wires, (3) and less than 15 meters from first-span secondary wires (240 volts) defined as secondaries issuing directly from the transformer without any loss in current through a service drop beyond the pole. LCC homes were all other configurations. If first-span wires carried current to only one or two single family homes, the homes so served were also considered LCC. The lowest potential exposure was considered to be homes beyond the pole at the end of a secondary line (called “endpoles”). They had no distribution lines running past them.

A significantly greater proportion of cancer cases had lived in homes classed as HCC. This was more pronounced for cases and controls who had lived in one residence from birth to death. The distribution of cases and controls in the dichotomous wire code classification of HCC versus LCC was examined for three types of residences of the cases and controls, i.e., persons who had a single residence that was the same at birth and death, persons who had moved and the code for their birth residence was evaluated, and persons who had moved and the code for their “death” residence was evaluated. For subjects with the same death address as birth address, i.e., “stable residence,” 44% of the cases had lived in a home classified as HCC vs. 20.3% of corresponding controls. For subjects who had moved, 32.5% of the cases had lived in a home at the time of their birth which could be classified as HCC vs. 20.1% of controls, and 37% of the cases had lived in a home just prior to their death that could be classified as HCC vs. 24.0% of controls. These differences were statistically significant (Table 3-2), with the highest significance in the “stable residence” group.

Odds ratios were not given but were calculated from the available data (Table 3-2). For subjects with a “stable” address, the odds ratio was 3.09, indicating an excess risk of cancer in children living in HCC homes throughout their lifetimes. The relationship persists, albeit less strongly, when the children had moved during their lifetimes.

The distribution of cases and controls by HCC and LCC residence at birth and at death was presented for leukemias, lymphomas, nervous system tumors, and all other cancer combined (Table 3-3). For all cancer sites combined and for both types of addresses, the proportion of cases who resided in HCC homes was greater than the proportion of controls. There was no difference in the risk of all other cancer between cases and controls when consideration was given to death address alone. No statistical tests were performed nor odds ratios developed by the authors. Again, these have been calculated from the reported data (Table 3-3) by the reviewers. The excess proportion of leukemia cases who resided in

TABLE 3-2. DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO VARIOUS RESIDENCES CODED AS HIGH CURRENT CONFIGURATION (HCC) OR LOW CURRENT CONFIGURATION (LCC) FOR TOTAL CANCERS[a]

A. Stable/one residence

	Case	Controls	Total
HCC	48	26	74
LCC	61	102	163
Total	109	128	237
%HCC	44	20.3	
x^2	14.4		
p	<0.001		
OR	3.09		
95% CI	1.68-5.71		

B1. Moved/birth residence only

	Case	Controls	Total
HCC	53	29	82
LCC	110	115	225
Total	163	144	307
%HCC	32.5	20.1	
x^2	5.4		
p	< 0.02		
OR	1.91		
95% CI	1.09-3.34		

B2.[a] All birth addresses

	Case	Controls	Total
HCC	101	55	156
LCC	171	217	388
Total	272	272	544
%HCC	37.1		
x^2	18.2		
p	<0.0001		
OR	2.33		
95% CI	1.56-3.49		

C1. Moved/death residence only

	Case	Controls	Total
HCC	81	48	129
LCC	138	152	290
Total	219	200	419
%HCC	37.0	24.0	
x^2	7.6		
p	< 0.01		
OR	1.86		
95% CI	1.19-2.91		

C2.[a] All death addresses

	Case	Controls	Total
HCC	129	74	203
LCC	199	254	453
Total	328	328	653
%HCC	39.3	22.6	
x^2	18.2		
p	<0.0001		
OR	2.23		
95% CI	1.56-3.18		

[a]B2 and C2 calculated for this report. Odds ratios (OR) calculated for this report. CI = confidence interval.

SOURCE: Wertheimer and Leeper, 1979.

TABLE 3-3. DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO VARIOUS RESIDENCES CODED AS HCC OR LCC FOR SPECIFIC CANCER SITES[a]

Leukemias

A. All Birth Addresses				B. All Death Addresses			
	Cases	**Controls**	**Total**		**Cases**	**Controls**	**Total**
HCC	52	29	81	HCC	63	29	92
LCC	84	107	191	LCC	92	126	218
Total	136	136	272	Total	155	155	310
%HCC	38.2	21.3		%HCC	40.6	18.7	
x^2	8.5	p=0.004		x^2	16.8	p<0.0001	
OR	2.28			OR	2.98		
95% CI	1.29-4.05			95% CI	1.72-5.15		

Lymphomas

	Cases	**Controls**	**Total**		**Cases**	**Controls**	**Total**
HCC	10	5	15	HCC	18	11	29
LCC	21	26	47	LCC	26	33	59
Total	31	31	62	Total	44	44	88
%HCC	32.3	16.1		%HCC	40.9	25.0	
x^2	1.4	p= 0.24		x^2	1.9	p=0.17	
OR	2.48			OR	2.08		
95% CI	0.64-10.00			95% CI	0.76-5.71		

Nervous System Tumors

	Cases	**Controls**	**Total**		**Cases**	**Controls**	**Total**
HCC	22	12	34	HC	30	17	47
LCC	35	45	80	LCC	36	49	85
Total	57	57	114	Total	66	66	132
%HCC	38.6	21.1		%HCC	45.5	25.8	
x^2	3.4	p = 0.24		x^2	4.8	p=0.03	
OR	2.36			OR	2.40		
95% CI	0.95-5.89			95% CI	1.08-5.36		

All other cancers

	Cases	**Controls**	**Total**		**Cases**	**Controls**	**Total**
HCC	17	9	26	HCC	18	17	35
LCC	31	39	70	LCC	45	46	91
Total	48	48	96	Total	63	63	126
%HCC	35.4	18.7		%HCC	28.6	27.0	
x^2	2.6	p=0.11		x^2	~~0	p=1.0	
OR	2.38			OR	1.08		
95% CI	0.85-6.74			95% CI	0.46-2.54		

[a]Chi-squared, two tail p-value, and odds ratios (OR) calculated for this report. CI = confidence interval.

SOURCE: Wertheimer and Leeper, 1979.

HCC-coded homes was statistically significant at both “birth” residences as well as “death” residences. The odds ratios were 2.28 and 2.98, respectively. The risk of cancer of the nervous system was significantly elevated in children who had lived in HCC-coded homes whether “birth” address or “death” address is used. Bearing in mind that the “death” address represents the parents’ address 2 years prior to case diagnosis, the authors argue that the stronger positive association for death address may represent a late or promotional effect. This is speculative, at best, since the strongest association for overall cancer is in children who had lived at only one (“stable”) address. The authors suggested that the observed broad associations with different cancer types may indicate that an HCC-relationship may be indirect or reflect some exposure effect on the physiologic processes of the child. The lack of cancer site specificity is, however, not unusual. Many agents have been shown to produce cancers at multiple sites.

Certain demographic factors that could relate to the development of cancer were examined to consider whether they could explain the observed association of excess cancer mortality in children who had resided in HCC homes. These factors were urban-suburban differences, socioeconomic class, family patterns of cancer, traffic congestion, and sex. There was a slight but nonsignificant excess of suburban addresses among controls. A trend, albeit not significant, toward higher socioeconomic class was seen in the cases. The authors stated that their tracing methods might have biased the selection of controls of lower socioeconomic status. But an analysis of three class groupings (based on occupation) revealed no significant difference in the percent of discarded and retained controls with HCC-coded homes among the three socioeconomic classes. There was also a trend toward firstborns and older mothers among cases, but, again, the results for this factor were not statistically significant. The authors stated that the association also held under analysis within maternal age and sibling order categories, but the data were not provided. Cases were found to generally live closer to high traffic routes, but the HCC association held in an analysis of proximity to high traffic and other routes. The excess of HCC residences was significant for both males and females, but the relationship was observed to be stronger for males.

The authors noted what they considered to be a striking finding, that is, six cases lived near (less than 150 meters from) a substation, and all six cases were within 40 meters of large primary wires. However, none of the controls lived near a substation. This latter finding is

consistent with expectation since it was estimated that less than one home in 1000 in Denver is near a substation.

One drawback discussed by the authors involved mapping and coding. It was not done blindly, that is, without knowledge of whether a case or control lived at the residence. Blinding is necessary to ensure that ascertainment of exposure (or outcome) for both cases and controls is comparable and without bias, but it is often not possible for various practical reasons. For this study, it would seem that identification and classification of physical structures outdoors would be less subject to misclassification or manipulation by the coder than would information from sources such as records or interviews that could be more amenable to interpretation or influence. As a check on the possible introduction of bias into the procedures, a random sample of 140 addresses (70 cases and 70 controls) was recoded by an assistant unaware of the case or control status of the addresses. Agreement as to wire configuration coding was found to be 91%. For the addresses (N=12) where coding differed, the split between supporting or not supporting an HCC association with excess cancer was about even A small blinded study was conducted for birth addresses in Colorado Springs and Boulder. The same relationship with wire code was observed, but the results were not statistically significant which, according to the authors, was likely due to small numbers.

A second problem with this study is a lack of an adequate discussion of latent effects with respect to the various cancers. It is possible that certain site-specific cancers such as lymphoma and/or central nervous system cancer may present an onset period longer than that of leukemia and the net effect of lumping them all together as one group would be to mask individual differences in length of latency. The fact that children who have always lived at the same location have a higher risk of total cancer than those who have moved would seem to support this thesis. Differences in risk seen in “birth” residency cases separately from “death” residency cases may only be a reflection of the expression of different cancers, that is, lymphoma in “birth” residency cases and leukemia in “death” residency cases. In any event, this topic could have been more adequately discussed by the authors.

This study did not provide measures or estimates of magnetic field exposure, but a seemingly reasonable surrogate was employed, i.e., classification by proximity to current sources with differing potential for presenting high vs. low magnetic field exposure, namely, wiring code configurations. Later studies have demonstrated a relationship between wiring

code and measured field values (Savitz et al., 1988; Kaune, 1987). Classification into two groups (HCC and LCC) does not, however, readily permit examination of dose response.

The authors stated that the observed increased risk is rarely greater than a factor of 2 or 3. The authors noted that the magnitude of the risk, if true, may be less important than the prevalence of the HCC exposure which is widespread; that is, a true but small risk could yield an important increase in childhood cancer. This is a reasonably well-done study that supports the possibility that exposure to EM fields (as estimated by wire code) is associated with cancer.

Fulton et al. (1980) conducted a case-control study of childhood leukemia in Rhode Island which attempted to replicate the study on electrical wire configurations done by Wertheimer and Leeper (1979). Cases were identified from records of the Rhode Island Hospital and consisted of 155 patients whose onset of leukemia occurred between 0 and 20 years of age and between 1964 and 1978. The actual geographic area covered (patient base) for this hospital is not given. It was also not explicitly stated whether all cases were Rhode Island births or not. Thirty-six cases were excluded because they had lived out-of state for some time during 8 years prior to disease onset; 119 cases remained for study. Two controls of the same birth year were randomly selected from Rhode Island birth certificate records to match with cases on the basis of having the same year of birth.

The basis for comparison was exposure to electric power lines at addresses. The 119 cases produced 209 case addresses; all addresses prior to onset were included. Of the 119 cases, 66 had lived at only one address, 34 had lived at two addresses, and 19 had lived at three or more addresses. There were 240 control addresses identified from birth certificates. The residences and nearby power lines were sketched and the shortest distance between the home and lines was measured with a calibrated, split-image, optical range finder. Maps were made for 198 case addresses and 225 control addresses. Addresses that could not be mapped were not included in the analyses. Residence at both birth and diagnosis were included for the cases; only birth residence was included for controls. Approximating the method used by Wertheimer and Leeper, four types of wires were identified, e.g., high tension, large gauge primary, small gauge primary, and secondary bundle (including two hot lead and one cold ground wire).

Since power lines can have several wires, the wire information was grouped per address into a summary exposure value weighted by each type of wire present. The weights used were the relative median field strengths obtained by Wertheimer and Leeper (1979). The

maximum and median measurements were taken at a point described as 75 centimeters (cm) above ground, under the wires. The source of this information from the Wertheimer and Leeper study is not given. The summary exposures of controls were divided into quartiles to assign four exposure categories for both cases and controls of very low, low, high, and very high relative exposures.

Across the four exposure groups, the control addresses were compared to the case addresses in toto and to the case address by cell type (lymphoblastic or other), by stable address, by age at onset (<7 years or ≥7 years), and by socioeconomic status (high vs. low). In no analysis was the percentage of control addresses different from the percentage of cases distributed across the four exposure groups. The authors saw no trend or tendency; the frequency distributions in all situations were approximately equivalent.

The greatest difference ($p<0.20$) occurred when “stable” addresses (cases who had lived in only one home) were compared to the control addresses. It should be noted that this may be the most appropriate comparison because, overall, of the 119 cases, 55% had only one address (or, alternatively, of the 198 mapped case addresses, about 29% had one address prior to onset), and all the controls had only one mapped (birth) address. Address histories were not developed for controls. The mixing of multiple addresses for cases but not for controls is inappropriate.

Furthermore, the method of comparing “addresses” of cases and controls rather than actual persons is methodologically flawed. The authors noted in their paper that the 119 cases provided a total of 209 *different* “addresses” or a excess of 90 additional addresses. If you assume that exposure to magnetic fields is associated with leukemia, then you would have to assume that no exposure to fields is not associated with leukemia. Multiple addresses on the same case are not likely to be all located in relevant magnetic fields. Hence, the 90 additional addresses included for the cases probably have a distribution of association of exposure to magnetic fields similar to that of the control addresses. The net effect then of adding 90 essentially nonexposed case addresses would be to dilute the effect and reduce perhaps what might have been a positive finding to a nonpositive finding. Furthermore, the authors made no effort to estimate the mean and median magnetic fields in the four categories of exposure utilized. However, residential estimates of intensities by means of mathematical formulation were accomplished. The authors could not substantiate that their wiring code categories reflected “high” or “low” EM fields.

As with Wertheimer and Leeper, odds ratios were not presented. The applied statistical tests were not cited. The authors did note that matched-pair analysis was not used because the controls and cases were not matched except for selection of same birth year.

A communication between the authors (Fulton et al.) and Wertheimer revealed that her field strength readings were for three-phase wires and so were representative of groups rather than single wires. Fulton et al. then reweighted and recalculated the summary exposure values. They reported similar overall results, that is, no association; these data are not given in the paper.

The authors intended to repeat the substance of the Wertheimer and Leeper approach to examining wiring and childhood leukemia in another geographic region. Although some aspects of the study are similar to the Denver study, there are sufficient differences and methodological problems with this study to negate its use as a validity check to the Wertheimer and Leeper study. The methodological flaws of this study limit its usefulness in assessing the risks of EM fields.

Tomenius et al. (1982; Tomenius, 1986) conducted a case-control study on the incidence of childhood cancer in the county of Stockholm, Sweden. The county encompasses all of the City of Stockholm plus 22 surrounding communities. In Sweden, 50-Hz alternating current (AC) is used, and most wires are buried.

Cases were drawn from the Swedish Cancer Registry for 1958-1973 and included 716 individuals aged 0-18 years who were born and diagnosed in the county of Sweden. This represents the exclusion of 175 cases from a total of 891 diagnosed and registered in the system. Exclusions were primarily cases who did not meet the birth and diagnosis residency requirements. Also, only primary tumors were included. The cases consisted of 660 malignant and 56 benign tumors.

Controls were matched to cases for age, sex, and church district of birth and were selected from birth registration records in parishes. Controls (N=716) also were limited to birth and residence in the county of Stockholm. There were 400 cases who still lived in the same church district of birth at the time of their diagnosis; their controls also lived in the same church district at the time of diagnosis. There were 316 cases who had moved from their church district of birth by the time of their diagnosis; their controls could either still live inside or outside the birth district. The matching procedures produced more dwellings for cases (N=1172) than for controls (N=1015).

Exposure to EM fields at the residences of cases and controls was evaluated by determining proximity to electrical sources and by taking single outdoor measurements. Electrical structures indicating possible high-current flow were noted if they were within 150 meters of dwellings. These structures were high voltage wires (6-200 kV), substations, transformers, electric railroads, and subways. Distance was measured by pacing off by foot. There was little information on how long the electrical structures had been present, but inquiries with residents living near 200 kV wires revealed that most wires had been in place at the times for both birth and diagnosis. Measurements were made in a blinded fashion. Magnetic fields were measured at the entrance to single family homes and near both the outside and individual doors for apartment houses. Electric fields were not measured.

There were 1172 dwellings among the cases and 1015 dwellings for the controls, i.e., 2187 total dwellings. Eighty-nine dwellings were demolished or unoccupied; a total of 2098 addresses were visited (cases=1129, controls=969). Odds ratios (called relative risks by the author) were developed using the total 2098 dwellings (rather than the number of persons) and were evaluated by the chi-square test. Unfortunately, this study employs the same methodology as the Fulton et al. (1980) study (inclusion of multiple and different case addresses on the same case).

Very few visible electrical constructions were noted for the sampled dwellings, i.e., 196 out of 2098 dwellings or 9.3%. The structures examined were 200 kV wires, 6 to 200 kV wires, substations, transformers, electric railroads, and subways. The most common structure was electric railroads (N=58), and the least common was substations (N=12). There was a significant excess risk of cancer in cases with dwellings within 150 meters of 200 kV wires [odds ratio (OR)=2.1] and a significant excess of case dwellings near all electrical structures considered together (OR=1.3) (Table 3-4). The distributions were also stratified by distance from electrical constructions, i.e., 0-49, 50-99, and 100-150 meters (not shown here). However, the risk tended to increase with increasing distance, an inverse relationship, from electrical structures. This result is the opposite of what might be anticipated, but numbers were small in some strata so the results are probably unstable. The mean magnetic field measurements made for case and control dwellings grouped by electrical structures were generally similar except for distance from 200 kV wires, where the mean value was 0.183 microtesla (μT) at case dwellings and 0.329μT at control dwellings. This result is contradictory. But this contradiction may be evidence of the difficulty of using “distance” from the source as a

TABLE 3-4. ODDS RATIOS FOR THE DISTRIBUTION OF THE 2098 DWELLINGS OF CANCER CASES AND CONTROLS BY TYPE OF ELECTRICAL STRUCTURE VISIBLE WITHIN 150 METERS

Electrical Structure	Gases	Controls	Odds Ratio
200 kV wires	32	13	2.1[a]
6 to < 200 kV wires	12	6	1.7
Substations	7	5	1.2
Transformers	12	14	0.7
Electric railroads	36	22	1.4
Subway	20	17	1.0
Total	119	77	1.3[a]

[a]Per authors, $p \leq 0.05$, chi-square test, and only given if expected numbers in each category were at least 5 and if odds ratios were different than 1.0.

SOURCE: Tomenius, 1986.

surrogate of dose. This study suffers from the same methodological flaws that pervade the Fulton et al. study (i.e., inclusion of multiple case addresses on the same case.

Birth and diagnosis dwellings were also examined separately. The observation of excess risk for dwellings near 200 kV lines held for both birth and diagnosis dwellings, plus there were significantly more case dwellings than control dwellings with fields $\leq 0.3\mu T$. The anomalous result of a positive association with fields < 0.3 μT, if dwellings were near 200 Kv lines, persisted.

It was previously noted that multiple dwellings per person were included in the analysis, and risk ratios were calculated on this basis. This approach is not appropriate as mentioned earlier; the risk estimates should relate to the exposure status of individuals. Tomenius stated that, of the 45 dwellings with visible 200 kV wires, only three cases had different birth and diagnosis dwellings. Therefore, 42 individuals had lived in one dwelling (29 cases, 13 controls) ail their lives. it is, thus, possible to examine the risk of living in close proximity to 200 kV lines in cases and controls who always lived at the same dwelling, as follows:

		Cases	Controls	Total
Within 150 meters	Yes	29	13	42
of 200 kv	No	223	397	620
wires?	Total	252	410	662

In this situation, the odds ratio becomes 3.97, with a 95% confidence interval of 1.94-8.24. This analysis obviates questions dealing with latency. This suggests that when length of residence *increases* in the vicinity of such magnetic fields, the risk ratio tends to sharpen and increase.

The distribution of case dwellings and control dwellings with respect to one-time-only measurements of magnetic fields at dwelling entryways was presented (Table 3-5). The average value of magnetic field measurements was similar in both case and control dwellings. Yet, significantly more case (all causes) dwellings were found to have been located in magnetic fields ≥ 0.3μT (OR=2.1). For dwellings not near electrical constructions, a significant excess of case dwellings with fields ≥ 0.3μT was observed (OR=2.1), but no excess was seen for dwellings that were located near visible electrical structures. Therefore, this implies that the source of the fields and the estimated risk is from sources other than the structures surveyed by the investigations. It is evident that the identified structures in the study are imperfect as a surrogate for magnetic field levels. And, as noted, these measurements were made outdoors. This result also seems at odds with the differences that were noted in the analysis of individuals who live within 150 meters of 200 kV lines. The average magnetic field measures for dwellings near 200 kV lines were significantly greater than the overall average, and the levels increased with closeness to the lines. A gradient of potential exposure was observed. Yet, when dwellings were grouped as either ≥ 0.3μT or <0.3μT, the odds ratio was significantly increased for case dwellings for which measurements were <0.3 μT. As seen with the inverse relation with distance, this apparent association with levels of exposure <0.3μT does not fit a typical dose-response relationship.

This reverse relationship may be an artifact. Proximity to “visible” 220 kV wires may not be a valid indicator of exposure without knowing how long the case or control lived in the dwelling prior to the diagnosis. Because of the possibility that latency may have played a role in the development of these cancers, it would have been more meaningful to have had a minimum residency period before classifying a case or control according to a single measurement of the magnetic field strength just outside of the doorway of the dwelling of the case or control. Furthermore, it would have been much more relevant if all of the analyses done in this paper dealt with individuals rather than addresses and multiple addresses on the same individual. It

TABLE 3-5. MAGNETIC FIELD MEASUREMENTS FOR CASE AND CONTROL DWELLINGS AND ODDS RATIOS BY MAGNETIC FIELD LEVEL AND TYPE OF ELECTRICAL CONSTRUCTION

	Case Dwellings	Control Dwellings	Both	Odds Ratios
Average Magnetic Field (μT)	0.069	0.068	0.069	----
Range	----	----	0.0004-1.9	___
Average Field, 200 kV lines nearby	----	----	0.22	
Total:				
≥ 0.3 μT	34	14	48	2.1[a]
< 0.3 μT	1095	955	2050	1.0
Total	1129	969	2098	
No construction:				
≥ 0.3 μT	27	10	37	2.3[a]
< 0.3 μT	983	882	1865	1.0
Total	1010	892	902	
Any Electrical Construction:				
≥ 0.3 μT	7	4	11	1.5
< 0.3 μT	112	73	185	1.4
Total	119	77	196	
200 kV wires:				
≥ 0.3 μT	5	4	9	1.1
< 0.3 μT	27	9	36	2.6[a]
Total	32	13	45	2.1[a]

[a]Per authors, $p \leq 0.05$, chi-square test, and only given if expected numbers in each category were at least 5 and if odds ratios were different than 1.0. Ratios calculated from total case control distribution of 2098 dwellings.

SOURCE: Tomenius, 1986.

appears that the significant odds ratios is mainly due to a deficit of control dwellings that are classified in the category of exposure <0.3 T. Perhaps this deficit resulted because some of the 200 kV wires were not “visible” to the observer. Misclassification because of the above stated reasons may be the explanation for this anomaly in the data.

Probably a finding of greater importance is the observation that the risk of cancer is much greater when only the cases and controls who had no change in residency are considered, as follows:

Strength of Magnetic Field	Case	Control	Odds Ratio
≥ 0.3 μT	10	3	5.4*
< 0.3 μT	242	407	

*p<0.05

However, another interesting finding is that when the analysis is properly restricted to just “persons” and only residency at birth is considered, then again the risk of cancer is greater for those persons residing in more intense magnetic fields, as follows:

Strength of Magnetic Field	Case	Control	Odds Ratio
≥ 0.3 μT	21	8	2.7*
< 0.3 μT	661	673	

*p<0.05

Likewise, in the same type of analysis but considering only residency at diagnosis, a similar result is obtained as follows:

Strength of Magnetic Field	Case	Control	Odds Ratio
≥ 0.3 μT	21	9	2.4*
< 0.3 μT	676	689	

*p<0.05

When specific cancer sites, that is, leukemia, lymphomas, nervous system, and/or other sites were analyzed, based upon case dwellings and control dwellings, only cancer of the nervous system is significant (Table 3-6) while that of lymphomas and/or other sites are nonsignificantly elevated. Leukemia is actually below expectation with a risk of 0.3. If persons were used as the units from which to calculate risk, all of these estimates would be elevated. It is likely that the risk of lymphoma and risk of cancer of other sites would be significant. However, although the risk of leukemia would be raised slightly, it would still fall below one. It should be noted that the rate of leukemia seems to be unusually low in this Swedish population, regardless of the EM fields issue. This may reflect some anomaly in the cancer registry. There is some evidence that leukemias may be underreported in the Swedish cancer registry (Mattsson and Wallgren, 1984). Again, two problems emerge from these findings: first, the actual risks using persons rather than dwellings cannot be calculated precisely, and, second, length of residency at the address where the measurement of the magnetic strength was done is not known so that latency cannot be assessed. However, despite the limitations of this study it does add to the evidence that EM fields are possibly associated with certain forms of cancer, i.e., nervous system, lymphomas, and cancer of other sites, nonspecified. A general observation can be drawn from the varied multiple analyses, that is, positive associations were generally seen if residence was near 200 kV lines and if measured magnetic fields were $\geq 0.3\mu T$.

TABLE 3-6. RISK RATIOS FOR SPECIFIC CANCER SITES AND MAGNETIC FIELD LEVEL

All Visible Structures[a]	≥ 0.3 μT	<0.3 μT
Sites:		
All	2.1[b]	1.0
Leukemia	0.3	1.0
Lymphomas	1.8	1.0
Nervous System	3.7[b]	1.0
Other Sites	--	1.0
All Malignant Neoplasms	1.8	1.0
Benign Neoplasms	--	1.0

[a]Data for 200 kV wires and other visible structures, considered separately, were given in the paper but are not given here
[b]Per authors, $p \leq 0.05$, chi-square test, and only given if expected numbers In each category were at least 5 and if odds ratios were different than 1.0.

SOURCE: Tomenius, 1986.

Myers et al. (1985) reported preliminary results of a case-control study that examined childhood cancer in relation to 50-Hz magnetic fields from overhead power transmission and distribution lines. A somewhat different approach for estimating magnetic field strengths was taken in this study. Exposure was estimated from records of load currents rather than from spot measurements or coded wire configurations.

Cases were defined as all children aged 15 years or less when diagnosed with cancer between 1970-1979 and born within the Yorkshire Health Region in England. Cases were identified from a childhood cancer register, formed from Health Service records. Additionally, cases were included if their mother resided in the health district of study at the time of birth of the subject child. A complete listing of incident cases was available for the period 1975-1979. For the period 1970-1974, only children who had died by 1982 could be identified and included plus a few survivors. Therefore, all cases diagnosed in 1970-1974 are not included in the study. The authors estimated that the underascertainment of incident cases was 15% of the total.

Controls for deceased cases diagnosed between 1970-1974 were drawn from the local birth registry and were chosen to have a similar birth date and nearby birth address to the case. Control selection had been previously developed and made in the course of conducting the National Oxford Childhood Cancer Survey. Two controls per case were similarly selected for cases diagnosed between 1975-1979 and for live cases diagnosed before 1975. It was noted that control of local birth registers had been assumed by the Health Service after 1974; thereby, the quality and completeness of the information collection differ in the two study periods.

A total of 376 cases and 590 controls were included in the study. Of these, 37 (9.8%) cancer cases and 44 (7.5%) controls lived within 100 meters of an overhead power line.

A master roster of birth addresses was assembled to mask the case vs. control status of the subjects when coding exposure estimates. Magnetic field exposures from overhead power lines for case and control addresses were estimated by calculations that accounted for maximum current load and by distance from the line. Load information was taken from records of Electricity Boards. Maxiumum recorded loads over 1974-1984 were used. Lines not in use at the time of birth of a subject were excluded. Because some relevant information could not be derived from the electricity records, certain assumptions had to be made which

the authors believed tended to increase the calculated values. Distance was obtained from measurements on Ordnance Survey maps.

Statistical analyses were based on a stratified case-control design, and risk ratios were calculated by the maximum likelihood method after Mantel-Haenszel with confidence limits after Miettinen.

Distance of residence from an overhead power line was grouped into intervals of 0-24, 25-49, 50-74, 74-99, and greater than 100 meters (Table 3-7). The latter grouping was taken as the reference group. For all cancers considered together, the odds ratios were greater than unity at all distances less than 100 meters, but there was no trend of increased risk with decreased distance. The largest ratio was 1.6 at 24-49 meters. No value was statistically significant. For analysis of lymphomas and leukemias, considered together, and of solid tumors, there was no clear pattern of increased risk with decreased distance. The risk ratios were generally elevated, but no increase was statistically significant. The highest risk ratio estimated for lymphomas and leukemias was 2.6 at 50-74 meters; statistical significance may be viewed as marginal with a p-value of 0.05.

TABLE 3-7. DISTRIBUTION OF CASES AND CONTROLS BY DISTANCE FROM OVERHEAD POWER LINES AND BY CANCER TYPE

	Distance[a]	Cases	Controls	RR[a]	95% CI[a]	p-value[b]
Lymphomas/ Leukemias	0-24	1	3	0.5	0.06-5.0	0.29
	25-49	8	8	1.6	0.6-4.3	0.18
	50-74	9	6	2.4	09-6.6	0.05
	75-99	3	5	1.0	0.2-4.1	0.48
	> l00	169	269	1.0	---	--
Solid Tumors	0-24	3	3	1.6	03-8.1	0.27
	25-49	4	4	1.6	0.4-6.5	0.25
	50-74	5	10	0.8	0.3-2.4	0.26
	75-99	4	5	1.3	0.35-4.9	0.35
	> 100	170	277	1.0	---	--
All Cancers	0-24	4	6	1.1	0.3-3.8	0.46
	25-49	12	12	1.6	0.7-3.6	0.12
	50-74	14	16	1.4	0.7-2.9	0.13
	75-99	7	10	1.1	0.4-3.0	0.41
	> l00	339	546	1.0	---	--

[a]Distance is in meters. RR = risk ratio, Cl = confidence interval.
[b]Level of significance at 5%.

SOURCE: Myers et al., 1985.

In this analysis, the risk of lymphomas/leukemia or "solid" tumors was not associated with increasing distance (in four strata) from 50-Hz overhead power lines. However, when the distances are collapsed to only two categories, i.e., <100 meters versus ≥ 100 meters, then the risk ratios are 1.5, 1.2, and 1.4 for lymphomas/leukemias, solid tumors, and all cancer, respectively. These slightly elevated risk estimates suggest that there may be an association with "closeness" to power lines, but this association may be sharpened by utilization of actual measurements of the magnetic field intensity rather than a poor surrogate such as distance.

The next analysis by the authors was to take only those cases and controls who resided within 100 meters from the overhead power lines and assign an estimated magnetic field strength in milligauss to each person and then estimate risks based upon intensity of the fields (Table 3-8). Although most of the risks were elevated, none were significant, and no dose-response relationship surfaced. Field values were grouped as less than 0.010, 0.010-0.099, 0.10-0.99, 1.00-9.99, and greater than 10.00 milligauss (mG). In units of

TABLE 3-8. DISTRIBUTION OF CASES AND CONTROLS BY ESTIMATED MAGNETIC FIELD LEVEL IN MILLIGAUSS (mG) AND BY CANCER TYPE

	Field (mG)	Cases	Controls	RR[a]	95% CI[a]	p-value[b]
Lymphomas/ Leukemias	<0.010	6	4	2.4	0.7-8.3	0.08
	0.010-0.099	7	5	2.2	0.7-7.0	0.08
	0.10-0.99	4	8	0.8	0.2-2.7	0.36
	1.0-9.99	2	4	0.8	0.1-4.4	0.40
	>10.0	2	1	3.2	0.3-31.2	0.16
Solid Tumors	<0.010	3	4	1.2	0.3-5.5	0.38
	0.010-0.099	6	8	1.2	0.4-3.6	0.36
	0.10-0.99	5	7	1.2	0.4-2.2	0.40
	1.0-9.99	2	1	3.3	0.3-31.8	0.15
	>10.0	0	2	NA	NA	NA
All Cancers	<0.010	9	8	1.8	0.7-4.7	0.11
	0.010-0.099	13	13	1.6	0.7-3.5	0.11
	0.10-0.99	9	15	1.0	0.4-2.2	0.47
	1.0-9.99	4	5	1.3	0.3-4.8	0.35
	>10.0	2	3	1.1	0.2-6.5	0.47

[a]RR = risk ratio CI = confidence interval, NA= not applicable.
[b]Level of significance at 5%.

SOURCE: Myers et al., 1985.

microtesla, these grouped ranges are less than 0.001, 0.001-0.0099, 0.01-0.099, 0.1-0.999, and greater than 1.0 μT. Again, subjects residing over 100 meters from a line were taken as the reference group.

However, this analysis suffers from several limitations. Unfortunately, to calculate odds ratios they used as a reference those cases and controls located beyond 100 meters from the power lines on the implicit assumption that none of those cases and controls were exposed to magnetic fields. Obviously, it would have been more appropriate to classify everyone according to their respective magnetic field strengths and then analyse for dose-response relationships. It is likely that persons living beyond the 100-meter point were subject to magnetic field exposures from other sources. The character of these fields are probably not different from those produced by overhead power lines. Furthermore, the vast majority of the few cases and controls that did fall within 100 meters were subject to magnetic fields intensities that were very low, i.e., less than 1.0 mG (0.1 μT). With the few cases and controls that could be classified into five-field level strata (Table 3-8), the authors did note an elevated risk ratio for lymphomas/leukemias (OR= 3.2) in the category with the highest magnetic field intensity, i.e., >10.0 mG (1.0 μT), based upon three persons. The residual category of solid tumors as well as all cancers also produced elevated risks for most of the field strength subcategories. But, again, the small numbers indicated little power to detect any moderately elevated odds ratios as significant if there is a true risk.

There are other potential problems that are not addressed by the authors. The accuracy of the estimated magnetic field strengths, calculated from data on load, is an issue. Measurements per dwelling were not made. Similarly, the calculations may not reflect exposure received in the past. Length of residency is not addressed. A recent residence should not necessarily be counted as the residence of exposure. The estimated underascertainment of cases (about 15%) in the face of elevated but nonsignificant excesses in risk raises the concern that the risk ratios and their precision may be underestimated assuming a similar distribution pattern would be seen for additional cases. Consequently, there are limits to the extent that this paper can help determine the potential carcinogenicity of electric and magnetic fields.

Savitz et al. (1988) reported on the results of a case-control study of childhood cancer and exposure to 60-Hz magnetic fields in residences in Denver, Colorado. These results were also reported in Ahlbom et al. (1987) and Savitz (1987). All cases of cancer among children aged

14 years or younger, residing in the Denver Standard Metropolitan Statistical Area, and diagnosed January 1, 1976, through December 31, 1983, were to be included in the study. Cases were primarily identified from the Colorado Central Cancer Registry. Additional ascertainment was completed using records of area hospitals. Over 98% of the cases were confirmed either by microscopy, direct visualization, or radiography. Additionally, pediatric oncologists reviewed diagnostic accuracy.

Controls were identified using random digit dialing methods and were matched to cases on age (±3 years), sex, and telephone exchange area. Controls were restricted to those children who had lived at their residence at the time of diagnosis of their matched case. This approach excluded children who had recently moved into the area. The authors pointed out that because the “control pool” did not include children who had left the area between the time cases were diagnosed and controls were selected, bias could be introduced if migration was due to magnetic field exposures and control versus case status.

If located and if consent was given, case and control parents were interviewed using a detailed questionnaire. The preferred interviewee was the biologic mother. Inquiries were made about potential risk factors for childhood cancer, e.g., family demography, residential history, family cancer history, in utero and postnatal exposure to x-rays and medications, parental occupational history, and medical history of the child and of the mother during pregnancy. Telephone interviews (11% for cases, 2% for controls) were conducted if parents had moved from the study region or if parents refused an in-home interview.

Electric and magnetic field measurements were made at residences that were occupied prior to diagnosis and were taken near the front door, the child’s bedroom, the parents’ bedroom, and any room reported to have been occupied by the child on an average of one or more hours per day. Measurements were taken near the center of the room to avoid proximity to appliances or large metal objects. To attempt to isolate the outdoor contribution to magnetic fields in the home, measurements were made under both “low power” (home power off) and “high power” (all lights and selected appliances on) conditions. Because these were short-term or spot measurements, potential confounders were noted, e.g., time of day, day of week, outdoor temperature, and domestic electric load on the distribution system. For the latter, data were made available from the Public Service Company of Colorado.

Consideration was made of how to summarize the measurement data to derive a summary home value. Correlation between three approaches, e.g., a simple arithmetic mean of all

values, a mean of three locations measured in all homes, and a time-weighted average, was very high (0.95). As a result, simple arithmetic means were used. Magnetic field values were then categorized by cutoff scores of 0.65, 1.0, and 2.5 mG (0.065, 0.1, and 0.25 μT). Electric field values were similarly categorized, i.e., 6.0, 9.0, and 14.0 volts per meter (V/m). The rationale for these cutoff values was not stated. Dichotomous categories were also developed, using 2.0 mG (0.2 μT) and 12.0 V/m as the cutoffs for magnetic and electric fields, respectively, in order to isolate the high end of the distributions.

In addition, wiring configuration codes were also developed. Procedures were used to mask the case or control status of the occupants of coded residences. Coding methods were based on those used by Wertheimer and Leeper (1979).

The distribution of cases by selected cancer site is given in Table 3-9 which also indicates the number and percentage response by cancer site. Overall, the interview response rate for cases (70.8%) was poorer than that for the controls (79.9%). Table 3-10 shows the number and percentage of cases and controls, for whom magnetic field measurements were derived and wire codes were never proscribed. Only 36% of the case residences were measured for electric and magnetic fields, while 74.5% of the residences of the corresponding controls were measured. This response rate is poor. Because the nonrespondents were mostly persons who had moved after diagnosis, the “measured” homes were occupied by the most residentially stable. Wire codes, on the other hand, were obtained for a noticeably higher proportion of both cases (89.6%) and controls (93.2%), and these response rates are similar. Wire codes could be developed for a similar proportion of case and control homes. However, very few case homes could be measured.

When consideration is given to magnetic field measurements (stratified into four levels: <0.65, 0.65-<1.0, 1.0-<2.5, and 2.5+ mG), the risk of cancer under low-power conditions is elevated, albeit nonsignificantly, with increased exposure. However, in contrast, the risk of cancer under high-power conditions is weak, and when intensity of electric fields is elevated under high-power conditions, the risk is equal to that expected (Table 3-11). These results must be considered somewhat unreliable due to the rather large “nonresponse” (almost 70% in the cases) on measured readings.

These same data were used to evaluate site-specific cancer under low-power, high-power, and high-voltage conditions with measured values dichotomized, i.e., ≥ 2.0 mG and <2.0 mG, (Table 3-12). Again, the results are equivocal. Nonsignificantly elevated risks were observed

TABLE 3-9. ELIGIBILITY, RESPONSE, AND LOSSES FOR CANCER CASES, CASE SUBGROUPS, AND CONTROLS: DENVER STANDARD METROPOLITAN STATISTICAL AREA

Group	No. of Eligibles	Interviewed		Untraced		Refusals[a]	
		No.	%	No.	%	No.	%
Cancer Cases	356	252	70.8	61	17.1	35	9.8
Leukemia	103	73	70.9				
Acute lymphocytic leukemia	83	59	71.1				
Brain	67	48	71.6				
Lymphoma	35	26	74.3				
Soft tissue	32	26	81.3				
Other cancers	119	79	66.4				
Controls	278	222	79.9				

[a]Includes individual refusals and physician refusals.

SOURCE: Savitz et al., 1988.

TABLE 3-10. DISTRIBUTION OF ELECTRIC AND MAGNETIC FIELD MEASUREMENTS AND WIRE CODES FOR CANCER CASES, CASE SUBGROUPS, AND CONTROLS: DENVER STANDARD METROPOLITAN STATISTICAL AREA

Group	No. of Eligibles	Field Measurement		Wire Code	
		No.	%	No.	%
Cancer Cases	356	128	36.0	320	89.9
Leukemia	103	36	35.0	97	94.2
Acute lymphocytic leukemia	83	26	31.3	78	94.0
Brain	67	25	37.3	59	88.1
Lymphoma	35	13	37.1	30	85.7
Soft tissue	32	14	43.8	32	100.0
Other cancers	119	40	33.6	102	85.7
Controls	278	207	74.5	259	93.2

SOURCE: Savitz et al., 1988.

TABLE 3-11. CANCER RISK IN RELATION TO MEASURED MAGNETIC FIELDS AND ELECTRIC FIELDS, UNDER LOW- OR HIGH-POWER USE CONDITIONS, IN RESIDENCES OCCUPIED AT DIAGNOSIS: DENVER STANDARD METROPOLITAN STATISTICAL AREA

Exposure Level	Odds Ratio	95% Confidence Interval
Magnetic Fields (mG)[a]: low-power use		
0 - <0.65	1.00	
0.65 - <1.0	1.28	0.67-2.42
1.0 - <2.5	1.25	0.68-2.28
2.5+	1.49	0.62-3.60
Magnetic Fields (mG)[a]: high-power use		
0 - <0.65	1.00	
0.65 - <1.0	1.13	0.61-2.11
1.0 - <2.5	0.96	0.56-1.65
2.5 +	1.17	0.54-2.57
Electric Fields (V/m)[b]: high-power use		
0 - <6.0	1.00	
6.0 - <9.0	0.88	0.49-1.58
9.0 - < 14.0	1.23	0.68-2.22
14.0+	0.90	0.43-1.88

[a]mG = milligauss.
[b]V/m = volts per meter.
1.0 mG = 0.1μT

SOURCE: Savitz et al., 1988.

TABLE 3-12. CANCER RISK (ODDS RATIOS WITH 95% CONFIDENCE INTERVALS IN PARENTHESES) IN RELATION TO MAGNETIC FIELDS AND ELECTRIC FIELDS, CATEGORIZED INTO TWO EXPOSURE GROUPS[a] AND MEASURED UNDER LOW- OR HIGH-POWER USE CONDITIONS, IN RESIDENCES OCCUPIED AT DIAGNOSIS: DENVER STANDARD METROPOLITAN STATISTICAL AREA

Site	Magnetic fields: low power ($\geq$ 0.2 μT)	Magnetic fields: high power ($\geq$ 0.2 μT)	Electric fields: high power
All Cancers	1.35 (0.63-2.90)	1.04 (0.56-1.95)	0.93 (0.53-1.61)
Leukemia	1.93 (0.67-5.56)	1.41 (0.57-3.50)	0.75 (0.29-1.91)
Acute lymphocytic leukemia	1.56 (0.42-5.72)	1.05 (0.34-3.26)	0.67 (0.22-2.04)
Lymphoma	2.17 (0.46-10.31)	1.81 (0.48-6.88)	0.70 (0.15-3.27)
Brain	1.04 (0.22-4.82)	0.82 (0.23-2.93)	0.53 (0.15-1.81)
Soft tissue sarcomas	3.26 (0.88-12.07)	1.65 (0.44-6.20)	0.64 (0.14-2.96)
Other Cancers	0.31 (0.44-2.14)	0.49 (0.14-1.66)	1.65 (0.78-3.51)

[a]For magnetic fields, < 2.0 mG and 2.0+ mG. For electric fields, < 12.0 V/m and 12.0+ V/m.

SOURCE: Savitz et al., 1988.

for leukemia, lymphoma, brain, and soft tissue under low-power conditions. But high-power conditions produced somewhat reduced risks at these same sites. It is problematic that the risk estimates for magnetic fields are greater under low-power usage conditions than under high power. One might have expected that the greater the exposure, the greater the magnitude of the response. However, a possible explanation may be that while all measures reflected present day single exposures, measures for high-power use reflect the most transient and variable exposures, as is the nature of exposure from appliances. Also, this seeming reverse dose-response relationship must be viewed in light of the poor nonresponse of cases on measured electromagnetic exposure. In addition, the author points out that electrical consumption at the time of measurement could have influenced the results. Electrical demand on the system at the time of diagnosis and before diagnosis was not known. It must also be remembered that these measurements were taken many years after the diagnosis, perhaps as much as 9 years. Savitz et al. (1988) concluded that, because long-term field exposures could not be captured through measurement procedures, no further analysis would be done using these values. The pitfall is that it is not known whether the missing data, if it were available, would have produced a different, perhaps unbiased result.

The main point to be gained from this analysis is that, there appears to be a modest increase in risk, up to 3.26, in several types of cancer in children who resided in homes where magnetic fields were $\geq$ 2 mG. If 3.0 mG was used, similar to Tomenius, the authors noted an increase in site-specific odds ratios. No numbers are given, but they were stated to be imprecise.

Stratified analyses for low-power use magnetic field data were made to examine potential confounding with maternal age, father's education, per capita income, maternal smoking during pregnancy, and traffic density. The authors stated that the adjusted odds ratios did not differ appreciably from the odds ratios developed with magnetic field cutoffs of 2.0 mG. The adjusted risk ratios for total cancer ranged from 1.2 to 1.5 versus an unadjusted risk ratio of 1.4, and the risk ratios for all adjusted leukemias ranged from 1.8 to 2.4 versus an unadjusted risk ratio of 1.9. The adjusted estimates were less precise with fewer subjects. Only lymphomas, when adjusted, seemed to be confounded for per capita income since the risk ratios changed from 2.2 to 3.2.

Wire code configurations were also developed and categorized as buried, very low, low, high, and very high (Table 3-13). Considering the limitations of the measurement data, the

TABLE 3-13. CANCER RISK (ODDS RATIOS FOR ALL SITES COMBINED) IN RELATION TO A FIVE-LEVEL WIRING CONFIGURATION CODE FOR RESIDENCES OCCUPIED AT THE TIME OF DIAGNOSIS OR 2 YEARS BEFORE DIAGNOSIS: DENVER STANDARD METROPOLITAN STATISTICAL AREA

A. At Diagnosis:

Code	Number[a] Cases	Controls	Odds Ratio	95% Confidence Interval
Buried[b]	95	88	1.00	- - -
Very low	29	17	1.58	0.81-3.07
Low	107	102	0.97	0.65-1.45
High	70	44	1.47	0.92-2.37
Very high	19	8	2.20	0.93-5.21
Missing	36	19	- - -	---

Mantel Chi-Square test for trend = 2.03, p = 0.02

B. Two Years Before Diagnosis:

Code	Number[a] Cases	Controls	Odds Ratio	95% Confidence Interval
Buried[b]	36	47	1.00	- - -
Very Low	11	15	0.96	0.39-2.34
Low	50	56	1.17	0.65-2.08
High	30	28	1.40	0.71-2.75
Very High	8	2	5.22	1.18-23.09
Missing	221	130	- - -	- - -

Mantel Chi-Square test for trend = 2.31, p =0.01

[a]The differences in the number of cases and controls per group reflect the availability of data.
[b]Taken as the reference group.

SOURCE: Savitz et al., 1988.

wire code surrogate of exposure is probably a more useful estimate of relevant magnetic and electric fields. Unlike measurements, which were made many years after diagnosis, wiring configurations are historically more stable or permanent and so probably give a better estimate of actual exposures at the time of and before diagnosis. In addition, about 90% of both cases and control homes could be coded. That wiring code is probably a good indicator of exposure is supported by the limited actual measurement data taken under low- and high-power magnetic use conditions, as follows:

		Magnetic Fields (mG) by Wire Code				
		Buried	Very Low	Low	High	Very High
High Power	Mean	0.60	0.77	1.09	1.61	2.92
	Median	0.39	0.45	0.73	1.12	2.01
Low Power	Mean	0.49	0.53	0.71	1.22	2.12
	Median	0.30	0.30	0.51	0.90	2.16

A clear gradient of increasing intensity of exposure with increasing wire code is readily apparent.

Subjects who lived in homes with buried wires were assumed to be the no exposure group (Table 3-13). The highest risk, which was not significant, for cancer at all sites was obtained for very high wire code homes (OR=2.2). Although the confidence intervals spanned unity in all code categories, the Mantel chi-square test for trend was significant (2.03, p=0.02). The investigators also coded the wiring configurations, where possible, of homes occupied 2 years prior to diagnosis to allow for possible latency. The gradient was sharper here. A significant risk (OR=5.22) was seen for very high code homes. Again, the Mantel chi-square test for trend was statistically significant (2.31, p=0.01), providing evidence of a dose-response relationship for cancer of all sites combined.

When consideration was given to the site-specific cancers (leukemia, lymphoma, brain, soft tissues, and other cancers) by a dichotomized two-level wire code, i.e., low (buried, low, very low) and high (high versus very high), it was found that the risk was elevated at all sites, except lymphoma (Table 3-14). For brain cancer and total cancer (all sites combined), the risk was significantly elevated at 2.04 and 1.53, respectively. Furthermore, when only the most extreme codes were used, i.e., buried versus very high, the risks were even higher, but the numbers were too small to detect an elevated risk as significant. For leukemia, the risk was 2.75, for brain it was 1.94, and for lymphoma it was 3.3. Again, the authors stated that stratified analyses to evaluate confounders did not demonstrate any changes in these risk estimates.

In summary, this paper provides evidence that exposure to EM fields, as represented by wiring codes, is positively associated with certain site-specific cancers, most notably leukemia, lymphoma, and brain cancer. In addition, a significant dose-response relationship is evident for total cancer based upon wire code configurations at the time of diagnosis as well as 2 years before (Table 3-13). Average and median measurements of the intensity of the magnetic

TABLE 3-14. CANCER RISK (ODDS RATIOS) IN RELATION TO DICHOTOMIZED WIRE CODES (LOW VS. HIGH AND BURIED VS. VERY HIGH) FOR RESIDENCES OCCUPIED AT THE TIME OF DIAGNOSIS FOR ALL CANCERS AND FOR SPECIFIC SITES: DENVER STANDARD METROPOLITAN STATISTICAL AREA

A. Two Level Wire Code

	Low[a]	High[a]	Odds Ratio	95% Confidence Interval
Controls	207	52	---	---
Total cases	231	89	1.53	1.04-2.26
Leukemia	70	27	1.28	0.90-2.63
Acute lympho-cytic leukemia	59	19	1.28	0.70-2.34
Lymphoma	25	5	0.80	0.29-2.18
Brain	39	20	2.04	1.11-3.76
Soft tissue	23	9	1.56	0.68-3.55
Other cancers	74	28	1.51	0.89-2.56

B. Very High Versus Buried Wire Code

	Buried[a]	Very High[a]	Odds Ratio	95% Confidence Interval
Controls	88	8	---	---
Total cases	95	19	2.20	0.98-5.21
Leukemia	28	7	2.75	0.94-8.04
Acute lympho-cytic leukemia	24	6	2.75	0.90-8.44
Lymphoma	10	3	3.30	0.80-13.65
Brain	17	3	1.94	0.47-7.95
Soft tissue	13	2	1.69	0.33-8.78
Other cancers	27	4	1.63	0.46-5.81

[a]Low = buried, very low, low; High = high, very high.

SOURCE: Savitz et al.. 1988.

fields calculated for each of the five wiring codes support the use of wiring configuration codes as surrogates for exposure to magnetic fields. In the wire code category denoting highest exposure, called “very high,” the magnetic field intensities fall mostly in the range of 2 mG to 3 mG. Average and median measurements taken in the remaining four wire code categories fall below 2 mG.

There are two problems with the data that could influence detection of a significant association of actual measured magnetic fields with cancer. First, there was a poor response for making magnetic field measurements (36% of the case residences were measured while

74.5% of the control residences were measured). The authors suggested that the low and differential response may introduce bias, and if there had been an "improved response for magnetic fields," the observed odds ratios would have been elevated. Lack of such exposure information would tend to bias the results toward the null. Second, the measurements were taken many years after diagnosis, up to as much as 9 years later. Such measurements probably do not adequately reflect long-term past magnetic field intensities prior to and during the time of diagnosis. The authors also pointed out that although wiring codes are not perfect predictors of magnetic field intensities, they do tend to remain stable over long periods of time and "better approximate historical field levels."

In a very brief discussion appearing as a "project resume," Lin and Lu (1989) have reported preliminary results of a case-control study of childhood cancer and residential exposure to EM fields. Cases were diagnosed in the last 5 years (actual period of time is not stated) in the Taipei Metropolitan Area in Taiwan. The 216 identified cases were matched to 422 hospital controls on the basis of age, sex, and date of admission to the same hospital of case diagnosis. EM-field exposure was classified as either low or high, with high exposure defined as residing within 50 meters of either a high tension power line (20 kV or greater), a transformer, or a substation. Elevated nonsignificant risks of lymphomas, leukemias, and cancers (all sites combined) were found. However, these are based on small numbers and the power to detect these risks as significant is low. The results were:

	Odds Ratio	Confidence Interval
All cancers	1.30	0.92 - 1.84
Leukemias	1.31	0.78 - 2.21
Lymphomas	2.0	0.62 - 6.50
Brain Tumors	1.09	0.50 - 2.37

Additional information not available in the report is needed to evaluate this study more thoroughly. These brief results were presented at an annual Department of Energy (DOE) review of research on biological effects of 50- and 60-Hz electric and magnetic fields.

For completeness, one case series reported in the 'literature should be described. Aldrich et al. (1984) identified an unusual cluster of five cases of endodermal sinus tumors in black children (all girls) from a hospital-based tumor registry in Jacksonville, Florida. These tumors are very rare; the authors noted that little is known about their etiology, but they have been associated with twinning and are more frequently seen in black females.

The authors discussed possible factors that might be related to the development of endodermal sinus tumors in these five cases, including possible interaction between EM fields and various other environmental factors and interaction between genetic or familial factors and environmental agents. The area was primarily residential, but there were many large warehouses, an electromotive plant, and a lead smelter. The plants were stated to be in compliance with emission standards. Random blood leads were taken from residents in the area, including case family members, and were found to be similar to blood lead levels in persons residing in other parts of Jacksonville. The area was also crossed by US. Highway 1, railroad lines, and electrical power lines. The latter included primary distribution lines (26 kV) providing residential service via transformers and six primary transmission electrical lines each with 69 kV phase to phase. These lines had been in place since the 1950s, i.e., throughout the lifetime of the cases. The distance that cases resided from the 69 kV lines ranged from 14 to 592 feet. Estimated magnetic fields at these distances were calculated and ranged from 0.04 to 1.69 gauss (40 to 1690 mG).

As a case series, this report provides little evidence that could bear on determining whether there is a causal relationship between EM fields and cancer. The authors discussed several factors, including possible exposure to EM fields, that might be related to this rare cancer. No factor was named as being causally related to endodermal sinus tumors. The authors suggested that further consideration be given to potential environmental exposures, including EM fields.

3.2.2. Electromagnetic-Field Exposure at Unspecified Frequencies

The following studies are of cancer in children associated with exposures of fathers to potential carcinogens encountered occupationally.

In a case-control study, Spitz and Johnson (1985) examined neuroblastoma deaths in children under age 15 in Texas between 1964 and 1978 in relation to paternal occupation. Birth certificates corresponding to each case of neuroblastoma were obtained from the Texas

State Department of Health. If a birth certificate was not found, the case was excluded. These birth certificates were then matched to one randomly selected control birth certificate within the same birth year and to the 100th certificate within the same birth year from State birth rosters grouped according to year of birth. There were 157 cases and 314 controls. Fathers' occupation and industry at time of birth of the subject child were taken from the birth certificates of both cases and controls and coded according to the Standard Industrial Classification Manual (1972). These broad industrial code groups (agriculture, construction, retail, etc.) were also regrouped into "clusters" based on shared exposures to different agents and then further subdivided. This method was described in Hsieh et al. (1983).

The risk of neuroblastoma for the broad industrial groups ranged from 0.55 to 1.35, and none was significantly elevated. A significant increase in risk (OR=3.17, CI=1.13-8.89) was seen in the exposure cluster corresponding to aromatic and aliphatic hydrocarbons. This cluster included workers in electric, electronic, and printing occupations; electricians; insulation workers; and utility workers. In an attempt to define this "cluster," occupations in the cluster were reclassified into two groups corresponding to differing levels of exposure to electromagnetic radiation. The first group, whose exposure was presumed to be higher, included electricians, electric and electronic workers, linemen, utility employees, and welders. The second group had lower presumed exposures and included (but was not limited to) electric equipment salesmen and repairmen. The risks were elevated in both groups, 2.14 (Cl=0.95-4.82) and 2.13 (CI=1.05-4.35), respectively. The latter was significant. Of interest is the fact that for children whose fathers were electronic workers, the risk was 11.75 and was statistically significant (CI=1.40-98.55). The authors noted that this job had potential EM-field exposure.

The major problems with these data involve use of birth certificate records for the derivation of fathers' employment as well as lack of detailed exposure information on EM fields. Occupational designations from vital documents are not fully reliable. The occupation of interest is not necessarily the occupation listed on the birth certificate at the time of birth but should be that occupation the father was in before conception. There is little detail regarding paternal employment before conception. Furthermore, no data are presented regarding maternal exposure before conception. This study suggests the need for further in-depth research.

Wilkins and Koutras (1988) reported on the results of a case-control study that examined mortality from brain cancer among Ohio-born children in relation to paternal occupation. Cases were identified as white children less than 20 years old who had died in Ohio from 1959 through 1978 and whose death certificate listed primary brain cancer as the underlying cause of death. Specific types of brain cancer could not be determined from death certificate data. Deaths occurring from 1959 through 1968 were coded according to the Seventh Revision of the International Classification of Diseases (ICD7: 193.0), and deaths occurring from 1969 through 1978 were coded according to the eighth revision (ICD8: 191). Birth certificates were traced by linkage to name, parent's name, and date of birth as listed on the death certificate. Father's industry and occupation were recorded on Ohio birth certificates only for births before 1968; therefore, decedents born after 1967 were excluded from the study. Subjects were excluded if the usual residence of the mother, as noted on the birth certificate, was not Ohio. After exclusions and matching, there were 491 cases available for study (282 males and 209 females).

Controls were randomly selected from State listings of birth certificates for the period 1940 to 1967. Each case was paired to a control of the same sex, race, and year of birth. The same exclusion criteria were applied to the controls plus twins, siblings, or cases of stillbirths were excluded as controls.

Fathers were classified with respect to both industry of employment and occupation. Industry coding followed the method described by Hoar et al. (1980) who used the Standard Industrial Classification Manual (1972) to establish a group of low exposure industries, i.e., low exposure to toxic substances. For this study, the fathers classified as working in these low exposure industries were taken as the referent (or control) group in odds ratio analyses for industry. Fathers' occupation was coded according to the U.S. Department of Labor's Dictionary of Occupational Titles (1977). For analyses of occupation, the low exposure or referent group was considered by the authors to be a collection of occupations with presumably little or no exposure to toxic substances, i.e., professional, technical, or managerial occupations; clerical and sales occupations; and packaging and materials handling occupations. For other analyses, further refinements to the referent group were achieved by the combination of low occupational exposure and low industrial exposure into industry-specific occupational categories.

Odds ratios were computed using a multiple linear-logistic regression model. Odds ratios were adjusted by adding various potential risk factors to the model, i.e., mother's and father's age, birth weight, birth order, and proportion of farmland in mother's county of residence at the time of the subject's birth (a surrogate for urban/rural residence). The authors noted that matching could not be maintained when applying paternal low exposure reference categorizations, and so sex and year of birth, the matching factors, were added to the model. The cases and controls were not found to differ on the various birth characteristics examined.

The risk of brain cancer was significantly elevated in 5 of the 12 industry classes examined, i.e., agriculture, forestry, fishing (OR=2.4, CI=1.2-4.9); construction (OR=2.3,CI=1.3-4.1); metal (OR=1.8, Cl=1.1-2.9); machinery (OR=1.7, Cl=1.1-2.7); and transportation (ship building, motor vehicles, aircraft, and other transport methods) (OR=1.6, Cl=1.0-2.40). The latter result is similar to the result of Preston-Martin et al. (1982), discussed later.

Examination of seven major occupational groupings only yielded significantly increased risk for structural work (OR=2.1, CI=1.4-3.1). The odds ratios for six subgroups within the structural work class were all greater than 1.0, but only construction (OR=2.0, Cl=1.0-3.8) and electrical assembling, installing, and repairing occupations (OR=2.7, CI=1.2-6.1) were significantly elevated. Risks were significantly elevated for paternal employment in agriculture (OR=2.0, CI=1.0-4.1). The odds ratio for welders, cutters, and related occupations was greater than 1.0 (OR=2.7, CI=0.9-8.1). Odds ratios were increased, but not significantly, for other major occupational groups and subgroups. Subgroups across several major groupings seemed to involve work with or around metal and so were evaluated as a combined group. A significantly increased risk for paternal work with metals resulted (OR=1.6, Cl=1.1-2.3).

As previously mentioned, analyses were also made of industry- and occupation-specific combinations, using subjects with fathers employed in low exposure industries with low exposure occupations as the referent group. Unknown occupations (15 cases, 10 controls) were included in the reference group [as were occupations that were known but could not be classified (6 cases, 3 controls)]. This inclusion could represent a possible source of misclassification bias which, if present, could underestimate the risk for an affected subgroup.

It is not clear why the authors designed the study the way they did. With the individually matched cases and referents it seems they could have performed a conditional logistic regression analysis instead of breaking the matching to do a multiple logistic progression analysis. It is also not clear who was included in the industry- and occupation-specific

analyses. Was it that particular industry and the “low exposure” group or did they include a lot of dummy variables?

Significantly increased risks were seen for agriculture (OR=2.4, Cl=1.1-5.4); construction (OR=2.0, Cl=1.0-4.0); processing occupations in the metal industry (OR=5.3, Cl=1.0-27.2); structural work in the metal industry (OR=3.9, CI=1.2-12.8), which includes welders; and electrical assembling, installing, and repairing as part of structural work occupations within the machinery industry (OR=3.6, CI=1.3-10.0).

The authors of this study (as well as the authors of the Spitz and Johnson [1985] study) concluded that paternal occupation might be a risk factor for childhood brain tumors, particularly in agriculture, construction, metal-related jobs, and electrical assembling, installing, and repairing occupations in the machinery industry. Although exposure to electricity, and presumably EM fields, is likely, the potential for exposure to chemicals, metals, and other agents is also likely. The authors specifically point out that exposure to a number of aromatic and aliphatic hydrocarbons (solvents), beryllium, nickel, lead, and zinc occurs to persons in these occupations. Limitations of this study include use of death certificates to identify cases and the use of birth certificates to identify father’s occupation. Occupation, as given on a birth certificate, may be imprecise, subject to error, or not reflect the relevant causal occupational exposure before conception. These difficulties may lead to random misclassification and will lead to a reduction of the estimates of risk. The authors made no attempt to identify categories having high potential for exposure to EM fields. They were more interested in identifying low exposure categories for toxic substances, in general. The authors stated that this paper was exploratory. Hence, little can be gained from this paper that will help in determining whether EM fields are associated with cancer.

3.2.3. Summary

There have been eight case-control studies on childhood cancer, and one case study of cancers in young girls concerning exposure to EM fields. Six of the studies have examined childhood cancer and residential exposure to EM fields from power transmission and distribution sources (Wertheimer and Leeper, 1979; Fulton et al., 1980; Myers et al., 1985; Tomenius, 1986; Savitz et al., 1988; Lin and Lu, 1989). All six were of a case-control design, Two other case-control studies examined cancer in children in relationship to fathers’ occupation (Spitz and Johnson, 1985; Wilkins and Koutras, 1988).

The case series (Aldrich et al., 1984) reported on a cluster of endodermal sinus tumors in girls in Jacksonville, Florida, living near power lines. By the nature of their design, case series usually do not provide the type of information needed to determine causality.

Wertheimer and Leeper (1979) studied cancer mortality among children in the Denver area from 1950 through 1973. Control children were drawn from birth certificate files and were selected for similarity in birth month and county where born. For children who had only one address throughout their lifetime, a significantly greater proportion of cases (all cancer sites combined) had lived in homes that were classified as HCC. A significant risk (OR=3.09) of cancer was found for those children who had lived at only one residence classified as HCC. Unfortunately, analysis by cancer site for “stable” residences was not provided. Additionally, both birth residence and death residence, considered separately, were also significantly elevated for total cancers although the magnitude of the risk was somewhat lower. Excess risks were also observed for leukemia, lymphoma, and nervous system tumors. Estimated risks ranged from 2.08 to 2.98. Although some potentially biasing factors and confounders may be present, the study reports significant risks of certain site-specific cancers as well as total cancer.

One potentially limiting factor in this study is that wiring configuration codes may not be an accurate estimator for magnetic fields. A second issue is that coding was not conducted in a blinded fashion. Coding physical structures such as wires may be less subject to misinterpretation and bias than other sources of exposure information. But, the potential for misclassification bias cannot be fully resolved without actual field measurements prior to diagnosis.

In the study by Fulton et al. (1980), Rhode Island residences of children with leukemia were compared to residences of controls. This study provided no significant findings. However, methodological flaws limit its usefulness. A major difficulty is the comparison of multiple case dwellings to control dwellings. The multiple case dwellings probably included homes with little or no exposure to electric and magnetic fields. This, in effect, represents exposure misclassification and could, thereby, introduce a dilution of response. Furthermore, the four subjective categories representing levels of exposure are not defined well. This paper cannot be used to support or refute a carcinogenic effect.

The study by Myers et al. (1985) compared children with cancer diagnosed between 1970-1979 and born in Yorkshire, England, to controls with a similar birth date and nearby

address. Elevated nonsignificant risks were obtained in many of the analyses. The highest of these was 2.4 (p=0.05) for leukemia evaluated for residences at 50-74 meters in comparison to residences at or beyond 100 meters. Thus, this study showed slightly increased risks for lymphomas, leukemias (combined), solid tumors, and cancer (all sites) in children residing within 100 meters of overhead power lines. This suggests an association is present with closeness to overhead power lines. This study is flawed in that the comparison children were those who lived beyond 100 meters from such lines on the assumption (erroneously) that they would not be exposed to magnetic fields. These reference children may have magnetic field exposures from other sources. This dichotomy also produced a second flaw, and that is the number of children living within 100 meters of lines is so small as to produce results with little chance to show a significant association. Only residence at birth was used as the marker for actual exposure. There is no information on duration of residency at the birth address. The observation of many elevated risk ratios without statistical significance raises issues that may be important in evaluating this study. For example, the small number of cases and controls and the low estimated magnetic field levels make it difficult to discern effects, if they exist. In addition, the authors stated that cases were underascertained by about 15%. This study is limited in terms of its contributions toward resolving the question of the potential carcinogenicity of EM fields.

Tomenius (1986) examined cancer among children (0-18 years of age) diagnosed in the county of Stockholm, Sweden, during 1958-1973. Again, like Fulton et al. (1980), residences of the cases were compared with the dwellings of control children matched for age, sex, and church district of birth. Proximity to “visible” electrical structures was evaluated, and magnetic fields were measured, primarily at entryways. For all cancer sites considered together, significantly elevated risk ratios were reported if dwellings were within 150 meters of 200 kV lines (OR=2.1) or were near any visible electrical structure (OR=1.3). When dwellings were examined with respect to measured magnetic fields alone, without consideration of whether visible electrical structures were visible, excess risks for all cancers (OR=2.1) were also seen when magnetic field levels were $\geq$ 0.3μT (or $\geq$ 3 mG). Similarly, risks were elevated for lymphomas (OR=1.8), nervous system cancers (OR=3.7, statistically significant), and total malignancies (OR=1.8). However, within groups of dwellings with nearby visible electrical structures, especially 200 kV wires, excess risks were associated with magnetic field levels of <0.3μT (or <3.0 mG). This result is inconsistent with the overall results for residing near 200

kV wires, made without regard to measurement data. But it may be an artifact in that proximity to visible 200 kV lines may not be a valid indicator of exposure without knowledge of how long the case or control lived in the home prior to the diagnosis. A minimum residency requirement may have been needed as well as measurements within the home. Another major problem with this study is the use of (multiple) dwellings, rather than individuals, to form the basis of comparison. But, the available data permit evaluation of the risk of cancer for children with only one address with measured magnetic fields of ≥ 0.3μT and, in this situation, the risk of cancer is significant (OR=5.4). Likewise, in one of the few analyses of "persons" where only residency at birth is considered, the risk of cancer in children who are exposed to ≥ 0.3μT, is significant (OR=2.6). In the same children, if residency at diagnosis is considered, the risk is still significant (OR=2.4). The fact that the risk of leukemia in children subject to measured fields ≥ 0.3μT) is considerably below expected (OR=0.3) should be regarded as a suspect finding (Table 3-6).

In general, this paper support the finds of Wertheimer and Leeper (1979) despite the flaws in its design and analysis. The nonpositive findings on leukemia should be considered suspect without a review of study methods and protocols to determine why a significant deficit should occur. The small number of leukemia cases, in general, may reflect some problem with case ascertainment or the cancer registry. One study that evaluated Sweden's cancer registry found underascertainment for leukemia to be about 18% (Mattsson and Wallgren, 1984).

Savitz et al. (1988) conducted a case-control study to assess the relationship between residential exposure to EM fields and childhood cancer. Measured magnetic field values grouped into two categories (<2.0 mG and ≥ 2.0 mG) yielded moderate nonsignificant increases in odds ratios at most sites. However, the lack of a clear-cut significant association of actual measured magnetic fields with cancer is probably a reflection of two problems with the data. First, there was a poor response for obtaining magnetic field measurements (36% of case residences, versus 74.5% of control residences). The authors suggested the possibility that bias was introduced and that bias may have been reduced by an "improved response for magnetic fields," thereby resulting in higher odds ratios. Second, the measurements were short-term and were taken many years after diagnosis and may not adequately reflect long-term or past magnetic field levels prior to diagnosis.

Significant associations were seen when evaluating the distribution of cases and controls with respect to five wiring code categories. Wiring codes were examined at the time of case diagnosis and, where possible, 2 years prior to diagnosis. The risk of cancer increased significantly with increased exposure, denoted by wiring codes. The test for trend with respect to wiring strata was statistically significant which indicates a dose-response relationship both at and 2 years prior to diagnosis. The risk of cancer in children who had lived in homes with the greatest exposure to magnetic fields coded as “very high” 2 years prior to diagnosis was significantly elevated (OR=5.22, 95% Cl =1.18-23.09). Regrouping wire codes into only two strata yielded more precise estimates and permitted evaluation by cancer site. Excess risks of leukemia, brain cancer, and other sites, were seen when the distribution of cases and controls were compared with respect to low versus high wire code. In these analyses, the 95% confidence intervals for the odds ratios for total cancers (OR=1.53) and brain cancer (OR=2.04) exceeded unity.

One concern with the study’s methods is that controls had to have lived at the same residence at the time of diagnosis of the corresponding case (to ensure comparability in time) as they did at the time of study selection. Controls, thus, were more residentially stable than cases. Families with cases of childhood cancer were not required to still live in the area. The direction of the potential bias introduced by this particular requirement is not known according to the authors. This lack of residential stability in the Savitz et al. study led to the limited response rate for field measurements. This is a more serious problem. Missing data is intuitively disturbing. Analyses in the study that attempted to assess this issue suggest that improved response for measured magnetic fields would tend to increase the odds ratios to make them more representative of actual risks. The risks, as given, are probably underestimated. Several possible confounders were evaluated and found not to affect the estimates. This paper provides evidence that exposure to EM fields, as representated by wire codes, is positively associated with certain site-specific cancers, most notably leukemia, lymphoma, and brain cancer.

Lin and Lu (1989) have presented preliminary and sketchy data in a brief discussion of childhood cancer in Taiwan in relation to residence near power lines, transformers, or substations. Elevated but nonsignificant risks were found for all cancers, leukemias, lymphomas, and brain tumors. Statistical power was low. The authors provide no discussion of the findings.

Spitz and Johnson (1985) examined neuroblastoma deaths in children under age 15 in Texas between 1964 and 1978 in relation to paternal occupation, as recorded on birth certificates. Significantly increased risks were seen in a cluster of broad industrial groups, grouped on the basis of presumed shared exposures to aromatic and aliphatic hydrocarbons, which included electric and electronic workers and utility workers. The occupations in the cluster were reclassified according to whether fathers were electricians, electric and electronic workers, linemen, utility workers, and welders or whether fathers were electric equipment salesmen or repairmen or others with some possible exposure to EM fields. These two groups had presumed higher versus lower EM-fields exposure, respectively. Elevated risks were seen in both groups, the latter being significant. Interestingly, for one specific occupation, the children of electronic workers had an excess risk (OR=11.75) that was statistically significant. Because of major uncertainties in information derived from birth and death certificates, i.e., lack of information on occupation of the father before conception as well as no information regarding material exposure, this paper suggests further in-depth research be done.

Wilkins and Koutras (1988) examined brain cancer in Ohio children in relation to paternal occupation, as recorded on birth certificates, A collection of occupations with presumed minimal exposure to toxic agents was used as the reference group. Risks were significantly elevated in children of fathers employed in several broad industrial classes and occupational groupings, one of which was electrical assembling, installing, and repairing occupations (OR=2.7, CI=1.2-6.1). This paper is more exploratory than supportive since the authors were not specifically interested in any particular exposures, including EM fields, Several areas of pursuit were suggested for future studies, including EM fields. Both of these studies use the somewhat unreliable information (on father's occupation) listed on birth certificates.

In conclusion, nine case-control studies have examined childhood cancer. Two studies involved cancer in children vis-a-vis their fathers' occupation. Seven studies examined residential exposure to 60-Hz electric and magnetic fields, and six of these yielded elevated risk estimates for leukemia, lymphoma, brain cancer, and total cancer. Two studies in particular found significant risks of lymphoma, leukemia, and nervous system cancer in children exposed to magnetic fields estimated by wiring configurations, The estimates of risk are modest, on the order of a 1.5 to threefold increase. These two studies by Wertheimer and Leeper (1979) and Savitz et al. (1988) present the fewest difficulties with respect to issues of bias, confounding, or other methodological problems. In the Savitz et al. study, wiring codes,

the surrogate of exposure used, provided the best evidence of a dose-response relationship with respect to risk of childhood cancer. The greatest risk of childhood cancer occurred among children whose addresses prior to and at the time of diagnosis were determined to be from magnetic fields associated with the highest wire code. Magnetic field measurement data, although of limited availability, were in the range of 2 mG to 3 mG in this highest wiring code category.

The study by Tomenius (1986) also found significantly high risks of lymphoma and nervous system cancer in children exposed to similar magnetic field intensities (i.e., $\geq$ 3.0 mG) or $\geq$ 0.3 μT. However, he found an exceptionally low risk of leukemia (OR=0.3) in children exposed to the same intensities. This rather low estimate for leukemia suggests an anomaly in the data, possibly in the selection of leukemia cases into the Swedish Cancer Registry during the period of study (1958 to 1973), and selection bias may be a possibility. There is some evidence that leukemia cases may be underreported to the Swedish Cancer Registry. In any event, before this finding can be accepted on face value, it should be reevaluated.

The study by Meyer et al. (1985) reported a nonsignificant excess risk of leukemia/ lymphoma, solid tumors, and total cancer in children located within 100 meters of 50-Hz power lines. But this paper has methodological flaws that tend to reduce the estimated relative risk ratios toward the null, thereby obscuring any true differences between groups.

Only the Fulton et al. (1980) study found no unusual distribution of exposure between his case dwellings versus his control dwellings based upon wiring codes that were similar to, but not identical to, those of Wertheimer and Leeper. However, this study has major flaws that preclude its usefulness in assessing the carcinogenicity of EM fields. These problems were discussed in detail in the individual study reviews.

The Lin and Lu (1989) study, although demonstrating excess but nonsignificant elevated risks in Taiwanese children living within 50 meters of high tension power lines (20 kV or greater), is very sketchy and contains few details involving the study methodology.

Finally, the two remaining studies suggest fathers' occupational exposure to EM fields may be a reason for the finding of a significantly high risk of neuroblastoma and brain cancer in children. Although supportive, these two studies suggest future research in this area. Children with these cancers tended to have fathers whose occupations, as reported on the birth certificates, fell into certain broad industrial categories thought to include exposure to EM fields. Actually, occupation before conception would have been more meaningful. These

categories also included potential exposure to aromatic and aliphatic hydrocarbons as well as other toxins. All the residential studies, except that by' Fulton et al. (1980), provide evidence of a consistently positive but modest risk of leukemia, lymphoma, and nervous system cancer in children under age 20 from exposure to power frequency magnetic fields estimated by wiring codes.

Measurement data that were available suggested that exposures were in excess of 2 mG. Little is known about the factors important in the development of cancer in children. Bias and confounding cannot be completely ruled out in these studies. Most biases in these studies would tend to result in random exposure misclassification which tends to bias results toward the null, resulting in underestimation. However, confounding or exposure to other carcinogenic agents as an explanation is probably less valid in studies of children than in studies of adults, because children experience a less diverse exposure environment over a shorter period of time. Savitz et al. (1988) evaluated possible confounding factors and found none to explain the positive results.

3.3. STUDIES OF ADULTS

3.3.1. Radiofrequency Exposure

The following two reports have been previously reviewed (U.S. EPA, 1984) but are repeated here for completeness.

Lilienfeld et al. (1978) completed a broad survey of the mortality and morbidity experience of Foreign Service employees and their dependents to assess the potential health consequences of microwave irradiation of the U.S. Embassy in Moscow. The health status of Foreign Service employees and those from other agencies who had served in the U.S. Embassy in Moscow from 1943 to 1976 was compared with that of employees at eight other embassies or consulates in Eastern Europe over the same time period.

The microwave irradiation of the U.S. Embassy in Moscow was first detected in 1953 and subsequently varied in intensity, direction, and frequency over time. The frequencies ranged from 0.6 to 9.5 gigahertz (GHz) (Pollack, 1979; U.S. Senate, 1979). The measured average power densities over time are given in Table 3-15.

Extensive efforts were launched to identify and trace the populations. Information on illnesses, conditions, or symptoms were sought from two major sources: (1) employment

TABLE 3-15. MICROWAVE EXPOSURE LEVELS AT THE U.S. EMBASSY IN MOSCOW

Time Period	Exposed Area of Chancery	Power Density and Exposure Duration
1953 to May 1977	West Facade	Maximum of 5 $\mu W/cm^2$ 9 hrs/day
June 1975 to Feb. 1976	South and East Facade	18 $\mu W/cm^2$ 18 hrs/day
Since Feb. 7, 1976	South and East Facade	Fractions of a $\mu W/cm^2$ 18 hrs/day

SOURCE: Lilienfeld et al., 1978.

medical records, which were fairly extensive because of examination requirements for foreign duty, and (2) a self-administered health history questionnaire. Questionnaire responses were validated for a stratified sample by review of hospital, physician, and clinic records. Death certificates were also sought, although other sources also were used to ascertain mortality status.

Standardized mortality ratios for various subgroups were calculated for each cause of death, were standardized for age and calendar period, and were specific for sex. Similar procedures were used to develop summary indices of morbidity.

A total of 4388 employees and 8283 dependents were studied. More than 1800 persons with 3000 dependents were employed at the U.S. Embassy in Moscow, and 2500 persons with more than 5000 dependents were employed at the comparison posts. Ninety-five percent of the employees were traced. Receipt of completed questionnaires was less successful, with an overall response rate of 52% for State Department personnel.

Based on information in medical records, various health problems were generally similar, with two exceptions. Moscow employees had a threefold greater risk of acquiring protozoal infections than comparison post employees. In general, both sexes in the Moscow group had somewhat higher frequencies of most of the common kinds of health conditions reported. Lilienfeld et al. (1978) stated, “However, these most common conditions represented a very heterogeneous collection, and it is difficult to conclude that they could have been related to

exposure to microwave radiation since no consistent pattern of increased frequency in the exposed group could be found."

Some excesses were reported by Moscow employees in the health history questionnaire. Both sexes reported more eye problems due to correctable refractive errors. More psoriasis was reported by men and anemia by women, The Moscow employees, especially males, reported more symptoms such as irritability, depression, difficulties in concentration, and loss of memory. It is possible, however, that a bias due to awareness of potential adverse effects is operating, since the strongest differences were present in the subgroup with the least exposure.

The observed mortality was less in both male and female employees than expected, based on U.S. mortality rates (Table 3-16). The male employees had lower mortality than did female employees. Cancer was the predominant cause of death in both sexes. The risk of leukemia

TABLE 3-16. OBSERVED AND EXPECTED NUMBER OF DEATHS, STANDARDIZED MORTALITY RATIOS (SMR), AND 95% CONFIDENCE INTERVALS (CI) BY ALL CAUSES OF DEATH, SPECIFIED CAUSES OF DEATH FROM CANCER, AND POST FOR MALE AND FEMALE STATE AND NONSTATE DEPARTMENT EMPLOYEES COMBINED

Cause of Death	Moscow			Other Posts		
	Number of Deaths		SMR	Number of Deaths		SMR
	Observed	Expected	(95% CI)	Observed	Expected	(95% CI)
All causes (0.5, 0.7)	49	105.3	0.47 (0.4-0.6)	132	223.7	0.59
Malignant neoplasms	17	19.0	0.89 (0.5-1.4)	47	41.1	1.1 (0.8-1.5)
Digestive organs	3	4.6	0.65 (0.4-1.9)	11	10.8	1.0 (0.5-1.8)
Brain tumors/CNS neoplasms	0	0.9	0.0	5	1.5	3.3 (1.1-7.7)
Pancreas	1	1.0	1.0 (0.0-5.6)	1	2.2	0.5 (0.0-2.5)
Lung	5	5.8	0.86 (0.3-2.0)	11	12.2	0.9 (0.4-1.6)
Leukemia	2	0.8	2.5 (0.3-9.0)	3	1.7	1.8 (0.4-5.3)
Hodgkin's disease	0	0.5	0.0	0	0.7	0.0
Breast	2	0.5	4.0 (0.5-14.4)	3	1.2	2.4 (0.5-7.0)
Uterus	1	0.2	5.0 (0.1-27.9)	0	0.0	0.0
Cervix	1	0.1	10.0 (0.3-55.7)	0	0.0	0.0

SOURCE: Lilienfeld et al., 1978.

was elevated both at Moscow [standardized mortality ratio (SMR=2.5)] and at comparison posts (SMR=1.8). Neither SMR was statistically significant. Comparison post employees had a statistically significant excess risk (SMR=3.3) of nervous system tumors. In general, the Moscow and comparison groups did not differ appreciably in overall and specific mortality. However, the population was relatively young; it may have been too early to detect long-term mortality effects.

The authors concluded that no convincing evidence was discovered to implicate microwaves in the development of adverse health effects at the time of the analysis. But they also carefully discussed the limitations inherent in the study: uncertainties associated with the reconstruction of the employee populations and dependents, difficulties in obtaining death certificates, the low response rate for the questionnaire, and the statistical power of the study. An important limitation relates to ascertainment of exposure. Problems relative to individual mobility within the embassy and variation of field intensities within the building are present in this study as in any other. No records were available on where employees lived or worked, so one had to rely on questionnaire responses to estimate an individual's potential for exposure. The highest exposure level [18 microwatts per square centimeter ($\mu W/cm^2$)] was recorded for only 6 months in 1975-1976; thus, the group exposed to the most intense fields had the shortest cumulative time of exposure and of observation in the study. These intensities are considered to be very low. It is also not clear what exposures may have been experienced by employees at the comparison posts.

Robinette and Silverman (1977) and Robinette et al. (1980) examined mortality and morbidity among US. naval personnel occupationally exposed to radar. Records of service technical schools were used to select subjects for the study; the men graduated from technical schools during the period from 1950 through 1954. Exposure categorizations were made on the basis of occupational specialty. The exposure group (probably highly exposed) consisted of technicians involved in repair and maintenance of radar equipment. The "controls" (probably minimally exposed) were involved in the operation of radar or radio equipment. It was estimated from shipboard monitoring that radiomen and radar operators (in the low-exposure group) were generally exposed at less than 1 milliwatt per square centimeter (mW/cm^2), and gunfire control and electronics technicians (in the high-exposure group) were exposed to higher levels during their duties. Over 40,000 veterans were included in the study, with about equal numbers in these two major exposure classifications. The mean age in 1952

of the low-exposure group was 20.7 years and of the high-exposure group, 22.1 years. In conjunction with naval personnel, an effort was also made to develop an index of potential exposure, termed Hazard Number, for a limited portion of the population. This number was based on the duty months multiplied by the sum of the power ratings (equipment output power of gunfire-control radars (ship) or search radars (aircraft)) where technicians were assigned.

Medical information was obtained through Navy and Veterans Administration records. Records were searched for information on four major end points: (1) mortality, (2) morbidity via in-service hospitalizations, (3) morbidity via Veterans Administration (VA) hospitalizations, and (4) disability compensation. Mortality was ascertained through the VA beneficiary system. Mortality ratios were calculated for both the low and the high group, standardized for year of birth and using the combined experience of both groups as the standard population.

For the low-exposure groups, mortality ratios were only slightly elevated for diseases of the circulatory system (1.07); the cancer residual, other malignant neoplasms (1.19); and the total residual, other diseases (1.08). Cancers of the digestive tract (1.14), respiratory system (1.14), and lymphatic and hematopoietic systems (1.19) were elevated for the high-exposure group, but none of the increases was statistically significant. The differences in mortality from malignant neoplasms of the lymphatic and hematopoietic system, although elevated, were not statistically significant.

As seen in Table 3-17, comparisons were also made within the high-exposure group across Hazard Number categories. In this case, only two comparisons were statistically significant: (1) the difference in respiratory tract cancer between those with a Hazard Number smaller than 5000 versus larger than 5000, and (2) the test for trend for all diseases combined. These results may be fortuitous since one or two positive findings might be expected when many statistical comparisons are made. Furthermore, additional information relative to the development of lung cancer, e.g., smoking histories, could not be obtained; the mortality data were obtained from death certificates, and obtaining background information from next-of-kin was not feasible. Among men whose work received the high hazard rating, elevated but nonsignificant risks were also seen for all cancers combined (SMR=1.44), cancer of the lymphatic and hematopoietic system (SMR=1.64), and the residual category of miscellaneous cancers (SMR=1.17) as well as circulatory diseases (SMR=1.17).

TABLE 3-17. NUMBER OF DEATHS FROM DISEASE AND MORTALITY RATIOS[a] BY HAZARD NUMBER: U.S. ENLISTED NAVAL PERSONNEL EXPOSED TO MICROWAVE RADIATION DURING THE KOREAN WAR PERIOD

Cause of Death	International Classification of Diseases (8th Rev.)	Number of Deaths: Low Exposure	Number of Deaths: High Exposure: Total	High Exposure: Hazard Number 0	High Exposure: Hazard Number 1-5000	High Exposure: Hazard Number 5000
All diseases	000-796	325 (1.04)	309 (0.96)	63 (0.82)	160 (0.91)	86 (1.23)
Malignant neoplasms	140-209	87 (0.96)	96 (1.04)	22 (0.99)	45 (0.90)	29 (1.44)
Digestive organs	150-159	14 (0.85)	20 (1.14)	6 (1.49)	11 (1.14)	3 (0.78)
Respiratory tract	160-163	16 (0.85)	24 (1.14)	4 (0.82)	10 (0.86)	10 (2.20)
Lymphatic and hematopoietic system	200-209	29 (0.83)	26 (1.18)	6 (1.09)	12 (1.04)	8 (1.64)
Other malignant neoplasms	Residue	37 (1.19)	26 (0.82)	6 (0.78)	12 (0.70)	8 (1.17)
Diseases of circulatory system	390-458	167 (1.07)	150 (0.93)	36 (0.94)	73 (0.83)	41 (1.17)
Other diseases	Residue	71 (1.08)	63 (0.92)	5 (0.30)	42 (1.13)	16 (1.08)

[a]Mortality ratio (in parentheses) standardized for year of birth; the combined experience of the low and high exposure groups is taken as the standard.

SOURCE: Robinette et al., 1980.

Differential health risks with respect to hospitalized illness around the period of exposure were not apparent. Subsequent VA hospitalizations and disability awards provided incomplete information. Because the study focused largely on the use of automated VA record systems, it was not possible to determine non-Navy or non-VA hospitalizations, nonhospitalized conditions, reproductive histories, or subsequent employment histories. Since actual individual exposure could not be reconstructed retrospectively, only an estimate of the potential exposure of the individuals was possible. Longer follow-up of the population would be useful.

Milham (1985b) investigated mortality among amateur radio operators who were members of the American Radio Relay League and whose deaths were reported in the League's magazine between 1971 and 1983. Proportional Mortality Ratio (PMR) analyses were performed. Death certificates were obtained for 280 deaths in Washington State and for 1411 deaths in California. Expected values were generated using 1976 U.S. age-specific white male death frequencies. It was reported that PMRs were significantly elevated for all leukemias, and acute and chronic myeloid leukemia considered separately and together. The author also noted a strong association between League membership and an occupation with potential exposure to EM fields. For cases from the state of Washington, the PMR for amateur radio operators who were also in electrical-exposure occupations was 2.64. The PMR for operators whose obituary did not mention such a job was 2.10. There may be biases in this study due to ascertainment of the deaths from the League's magazine. It is not clear if all deaths of members would be so reported. Deaths of ex-members may not be reportable, and the experience of ex-members may be different than that of continuing members. On the other hand, this study illustrates use of an innovative and accessible source of survival information useful for an exploratory study.

Milham (1988) next investigated the mortality of 67,829 men licensed as amateur radio operators between January 1, 1979, and December 31, 1984, with the Federal Communications Commission and who resided in California and Washington State. Deaths were sought in California and Washington State. SMRs were calculated using U.S. death rates to estimate expected deaths.

Observed deaths (Table 3-18) were significantly lower than expected for all-cause mortality and for mortality from all malignant neoplasms combined, pancreatic cancer, cancer of the respiratory system, all circulatory diseases combined, all respiratory diseases combined, and all accidents, SMRs were elevated for several cancer sites, and statistically significant excesses were found for specific sites in lymphatic and hematopoietic tissues, namely, acute myeloid leukemias (SMR=1.76) and multiple myelomas and other neoplasms of the lymphoid tissues, considered together (SMR=1.62). The latter rubric is the category for lymphomas other than lymphosarcomas and reticulum-cell sarcomas and Hodgkin's disease. It was not stated why this heterogeneous group of lymphomas was considered with multiple myelomas; separate analyses were not presented. It would seem to be more appropriate to evaluate deaths from multiple myeloma separately. However, Milham noted that the observed deficit for

TABLE 3-18. MORTALITY IN WASHINGTON STATE AND CALIFORNIA: U.S. FEDERAL COMMUNICATIONS COMMISSION (FCC) AMATEUR RADIO OPERATOR LICENSEES, JANUARY 1, 1979, TO DECEMBER 31, 1984

	Observed	Expected	SMR[a]
All causes	2485	3478.9	71*
All malignant neoplasms	741	836.9	89*
Esophagus	22	19.4	113
Stomach	30	29.6	102
Large intestine	88	79.0	111
Rectum	14	18.2	77
Liver	11	16.8	65
Pancreas	27	41.9	64*
Respiratory system	209	315.6	66
Prostate	78	67.6	114
Urinary bladder	16	24.1	66
Kidney	19	20.1	94
Brain	29	20.8	139
Lymphatic and hematopoietic tissue	89	72.1	123
Lymphosarcoma/reticulosarcoma	5	10.6	47
Hodgkin's disease	5	4.1	123
Leukemia	36	29.0	124
Lymphatic	9	8.7	103
Acute	3	2.5	120
Chronic	6	5.5	109
Unspecified	0	0.8	0
Myeloid	18	12.9	140
Acute	15	8.5	176*
Chronic	3	3.5	86
Unspecified	0	0.9	0
Monocytic	0	0.6	0
Unspecified	9	6.7	134
Acute	6	3.4	176
Unspecified	3	2.5	120
Other lymphatic tissues	43	26.6	162*
All circulatory diseases	1208	1731.7	70*
All respiratory diseases	127	252.5	50*
All accidents	105	164.5	64*

[a]SMR = standardized mortality ratio.

*p < 0.05

SOURCE: Milham, 1988.

lymphosarcomas and reticulosarcomas (ICD8: 200) (SMR=0.47) nearly cancelled out the excess observed for deaths from other neoplasms of the lymphoid tissue (ICD8: 202.0). The risk of Hodgkin's disease (SMR=1.23) was also elevated but not significantly. For the leukemias, the SMRs were elevated at all sites for which deaths were observed, but, as mentioned, only deaths from acute myeloid leukemias were found to be significantly in excess.

This is a study with a large population (67,829 licensees; 232,499 accumulated person-years; 2485 deaths). Excess risks are seen at several cancer sites but are especially concentrated at tissues of the lymphatic and hematopoietic system, where certain excess risks were found. The risk of acute myeloid leukemia was significantly elevated. Leukemias generally predominate in younger ages. Chronic leukemias were low.

Since licensing is required for amateur radio operators, enumeration of the population should be reasonably complete although licensing per se does not provide information on usage and exposure. Milham cites survey data that found that amateurs practice their hobby about 6 hours per week. It would seem that licensees would have exposure but the extent and degree is not clear and is probably variable. However, the potential for exposure misclassification would tend to bias estimates towards the null.

These results may or may not bear on risks from other frequencies, either of RF or ELF radiation, or even on the operating frequency. Amateur radios operate at the low end of the RF band of the electromagnetic spectrum. Modulations to lower frequencies are known to occur (Personal conversation with E. Mantiply, Office of Radiation Programs, U.S. EPA, February, 1990). Among Washington State licensees, Milham found that about 31% had jobs that involved potential EM-field exposure. Exposure to many different frequencies among part of the population is, thus, a possibility. Confounding exposures to chemicals are possible but could not be evaluated in this study.

This study points to excess risks for various cancers of the lymphatic and hematopoietic system, especially acute myeloid leukemia, among amateur radio operators in Washington State and California, some of whom also may have experienced occupational exposure to EM fields. Further studies of this source are warranted.

Milham (1988) extended the above analysis by examining the mortality in the amateur radio operators according to their Federal Communications Commission (FCC) license class. Depending on one's level of expertise and experience, an individual will be granted one of five specific licenses, i.e., novice, technician, general, advanced, or extra. These license classes

can, thus, serve to some extent as surrogates for duration of exposure. There were, as might be expected, some differences in age by license class. The average age of persons per class was: novice, 38.4 years; technician, 44.3 years; general, 49.5 years; advanced, 51.4 years; and extra, 49.2 years. It would have been interesting to know also the median ages and age ranges by class.

As in the previous analysis, SMRs were derived, and expected deaths were calculated by applying age, sex, race, year of death, and cause-specific U.S. mortality rates to age-stratified years at risk. Results were presented for each license class for a limited number of causes of death, i.e., all causes combined, all malignant neoplasms, brain cancer, all lymphatic and hematopoietic neoplasms, all leukemias, myeloid leukemia, and multiple myeloma and other lymphomas, considered together. The SMR for Hodgkin's disease was elevated in the earlier analysis, but mortality from Hodgkin's disease by license class was not reported in this paper.

All-cause mortality in all license classes was significantly lower than would be expected based on general U.S. mortality. SMRs for the most advanced license class, extra, were the lowest for all-cause mortality and for deaths from all malignant neoplasms. These results may indicate that some survival, socioeconomic, or other sort of bias may be operative. Generally, SMRs were lowest among the deaths of licensees in the novice class, the youngest group. Milham states that, in a sense, the novice class provides an internal control group. It would be interesting to see results in any further analysis of amateur radio operators, if novice operators are treated as a control subset of the population.

Other than the lower SMRs in the novice class, there is no other gradient in the SMRs by license class. In fact, SMRs are generally highest in the second level license class, technicians. This group had a statistically significant excess of deaths from all lymphatic and hematopoietic neoplasms, considered together. Deaths in the general license class resulted in a significantly elevated SMR for multiple myeloma and other lymphomas (202-203). With the exception of the novice class, SMRs were generally elevated, although not significantly, for all classes for the lymphatic and hematopoietic cancers reported. This excess risk was also true for deaths from brain cancer, but none of the observed increased SMRs was significantly different than expectation.

Since this study reanalyzes results given in an earlier report by specified strata, it, thus, is an attempt to identify where risks are operative in a scheme that is a surrogate of duration of exposure. The greatest risk seems to be centered in the technician license class which is the

class between novice and the more advanced license classes. This group was also intermediate in average age. The similarity in age for the three upper classes may mask any differences between those groups. No clear or distinct gradient by class was observed. It appears, therefore, that either license class may not be a good exposure surrogate (special unknown conditions may be operative for technician class licensees or their operational activity may differ), or class exposure has nothing to do with cancer.

The Environmental Epidemiology Program in the State of Hawaii Department of Health (1986) investigated cancer incidence in census tracts with and without broadcast towers in Honolulu, Hawaii. This study was prepared for and reported to the City Council of the City and County of Honolulu in 1986.

Cancer incidence data was collected from the Hawaii Tumor Registry which registers all newly diagnosed cases of cancer in the State, except cases of squamous and basal cell carcinoma of the skin. Cases are identified from all hospitals, and private pathology laboratories as well as from searches of death certificates. Less than 2% of cases are identified solely from death certificates, and 94% of cases are microscopically confirmed.

Nine census tracts with broadcast towers and two without towers were examined. Expected number of cases for the census tracts were calculated using age- and race-specific rates for the State for the period 1979-1983. Standardized incidence ratios (SIRs), representing the ratio of observed to expected values, were computed, and tested at a significance level of p=0.01. Confidence intervals were not presented.

Age-adjusted rates and SIRs by sex were presented for each census tract and for tracts categorized as having towers (N=9) and not having towers (N=2). For all tracts with towers combined, the summary SIR for all cancers was 1.45 for males and 1.27 for females, and both values were significant at p=0.01. The SIRs for all cancers for both sexes in the two tracts without towers, taken together, did not differ from unity (male SIR=1.05, female SIR=0.85). The SIR, for leukemias were also elevated, but statistical significance at the p=0.01 level was not achieved. The SIRs for individual census tracts were significantly elevated for all cancers among males for eight of the nine tracts with towers, and not elevated for the two tracts without towers. Among females, the SIRs for all cancers was significantly elevated in only two census tracts, and these contained towers. Four other tracts with towers had elevated SIRs, but the excess was not statistically significant. Age-adjusted rates and SIRs were also examined in individual tracts for leukemias in both sexes, but the number of cases was very

small, making the results unstable. Bearing this in mind, it was noted that there was a tendency for elevated SIRs for both sexes in census tracts with towers.

Because of its diverse ethnic populations, ethnicity and race are critical factors to consider in health studies in Hawaii. To this end, race was another factor controlled in the study. The authors stated that small numbers precluded simultaneous adjustment for age, race, and sex.

After adjusting for race, the SIR for all cancers for tracts with towers was 1.88 ($p <= 0.01$). The SIR for all cancers for the tracts without towers was 1.07 and was not significantly elevated. For individual tracts, the SIRs were again significantly elevated for eight of the nine tracts with towers. The one tract with towers that did not demonstrate an excess in all cancers after adjustment for race was the same tract that did not show excess cancer after controlling for age and sex. For the two tracts without towers, the SIR for all cancers was significantly elevated in one (SIR=1.31) but not in the other, after adjusting for race; this did not occur in the analysis that controlled for age and sex although the one tract had consistently higher rates and SIRs than the other. Again, analyses for leukemias yielded very small numbers of cases in individual census tracts. No result was statistically significant, but tracts with towers, individually and overall, presented elevated SIRs for leukemias.

In summary, using State rates as the standard schedule of rates, the observed deaths in tracts with towers for all cancers were significantly greater than expected values. Tracts without towers did not appreciably differ. Differences for leukemias could not be discerned.

This study is of a type that can be called an ecological study or that is of an ecological design, meaning that relatively broad populations (here, from census tracts) are examined rather than individuals. It is difficult to determine causal relationships from such studies. And this difficulty is aggravated by typically weak measures of exposures. In this case, broadcast towers are sited in certain census tracts, but it is not known if the cases of cancers were exposed to RF radiation or, if so, at what levels. The dichotomous estimate of exposure is only a crude proxy-some tracts have towers, others do not. Studies of this design also cannot usually address confounding factors except those that are broad demographic characteristics such as age, sex, or race, readily available from vital and census records.

The authors pointed out the limitations inherent in the study, including issues such as personal exposure, latency, duration of exposure, confounders, and so forth. They do not comment, however, on “urban/rural” differences that could be a factor in Oahu. The tracts with towers largely constitute downtown Honolulu and Waikiki; the tracts without towers are more

centrally located on the island, have less dense population centers, and have some agricultural lands and mountainous/valley areas. The study does indicate that further investigation are warranted.

It should be noted that this study followed an EPA (Office of Radiation Programs) measurement study of potential public exposures near broadcast towers in populated areas in Honolulu (U.S. EPA, 1984), where there was a concern over the health risks and ancillary problems posed by broadcast transmitters. Conservation and preservation concerns have led to restrictions on the siting of commercial broadcast towers. As a result, most tower sites impinge on populated areas. The EPA study measured emissions close to towers and generally found that levels of RF radiation tended to approach or exceed various voluntary exposure guides. The RF exposures in Honolulu may be unique given environmental restrictions, topography, and population density patterns in relation to radiating sources. Several military and navigational sources also exist on Oahu. The EPA data, plus the data from this study, point out the potential need for analytical studies of Hawaiian populations that, if feasible, examine more analytically health indices with more detailed exposure assessment.

Hill (1988) investigated the mortality of 1492 men in a radar research and development project at the Massachusetts lnstitute of Technology (MIT) during World War II conducted in what was known as the Radiation Laboratory (Rad Lab). The term radar is an acronym that refers to the use of electromagnetic energy for detecting and locating reflecting objects, Radars generally operate within the microwave portion (0.3 to 3.5 GHz) of the electromagnetic spectrum.

The cohort was scientific, technical, and senior management staff members ever employed at the Rad Lab between October 1940 and January 1946. Support personnel, such as technicians, clerks, or guards, were not included. The population was ascertained from records retained by MIT and was traced from World War II through 1986. Multiple sources of follow-up information were used, especially alumni organizations and Social Security Administration (SSA) files. Only 4.6% of the subjects were not traced beyond the 1940s. Over 67% were traced into the 1980s, and about 80% were traced into the 1970s. There were 52,805 person-years accumulated.

Vital status of the cohort was determined from various sources, including state death certificates or city/town clerk reports and SSA records of earnings reports or beneficiary claims. Cause of death data were based on death certificates or city/town clerk reports.

Cause(s) were coded according to criteria developed by the National Center for Health Statistics for coding with the International Classification of Diseases, Adapted for Use in the United States (ICDA), 8th Revision. A trained nosologist supervised and reviewed coding.

Comparisons were to U.S. white males and a population of white male physician specialists. The latter were assumed to be similar in socioeconomic status. Because of certain characteristics of the populations, physicians were only compared to Rad Lab staff members who were at least were 25 years old at first employment, and follow-up was censored to end in 1974. Internal comparisons were also made.

Two approaches were used to estimate the exposure environment at the Rad Lab. First, summary estimates based on the parameters of two typical radar systems of 1943 vintage were calculated. It was estimated that the maximum power density in the near field of the systems' antennas could be about 2 to 5 mW/cm^2, corresponding to a specific absorption rate (SAR) of 0.1 to 0.4 watts per kilogram (W/kg). Second, a surrogate estimate of exposure was derived from the job patterns in Lab Divisions which were organized around the basic equipment and systems being tested and developed. A three tier ranking system was used (1 = little or none, 2 = low or moderate, and 3 = highest) to represent a gradient of potential exposure of the various jobs and projects in relation to each other, e.g., administrative (low) < work with receivers (medium) < work with transmitters (high). The radiation levels that would define such groupings could not be determined. The longest divisional assignment of an individual was used to rank his exposure. Over half the population was ranked as most highly exposed by mostly working with transmitters or operating systems. The rest of the cohort was about equally divided between low or moderate exposure. About 25% of the men in ranking group 2 (moderate) had worked on Beacons and LORAN (navigational systems). These systems fall in the Low Frequency rather than the microwave portion of the electromagnetic spectrum.

All mortality results were for white males. There was no information available on confounding exposures. SMRs were calculated to compare the Rad Lab cohort to U.S. white males and to physician specialists. The SMRs were evaluated by deriving 95% confidence limits based on tabled values of the exact Poisson distribution. In addition, the direct method of standardization, to adjust for age, was also used in comparisons to physician specialists and in internal comparisons. The Rad Lab cohort was also compared to physicians using Cox's proportional hazards model to handle differences in time-dependent variables (age or

length of follow-up) and to estimate risk ratios. This is another approach to age adjustment. The only independent variable evaluated was cohort (Rad Lab staff or physician); the cohorts were already uniform with respect to race and sex. No other potentially relevant variables were available on physicians to permit comparisons to Rad Lab cohort members.

With respect to expected mortality based on U.S. rates, the overall mortality in the population was lower than expected. This probably reflects a “healthy worker” effect and the socioeconomic status of the population, and may be evidence that the protective benefit (or, rather, the selection bias) of actively working is enhanced in professional occupations (here physical scientists largely believed to be employed at universities, in government, or in high technology industries). Several specific causes of death were elevated, but no excess was statistically significant. These increases occurred for certain cancers (skin, prostate, testis, and cancers whose nature was unspecified) and mental disorders. With censoring to include only men at least 25 years of age at entry to the study and to end follow-up in 1974, elevated SMRs were again seen for selected cancers (pharynx, gallbladder and bile ducts, pancreas, skin, prostate, Hodgkin’s disease, and cancers whose nature was unspecified) and cirrhosis of the liver. The SMR was greatest for Hodgkin’s disease. No excess was statistically significant. These two SMR analyses also provided limited evidence of no differential risk by two different periods of latency. The strong healthy worker effect observed limits the value of these SMR results, but they point to causes requiring further study.

Mortality was also lower for Rad Lab staff members than for physicians (Table 3-19). Rather than implicating nonionizing radiation (NIR) exposure, the study may have demonstrated a difference in survival and all-cause mortality between two professions, that is, physicians versus scientists, chiefly physicists and engineers. The physicians were internists, ophthalmologists, and otolaryngologists. For all causes combined, the staff members had a lower rate of mortality than physicians. The risks for deaths from diseases of the circulatory system and from external causes, e.g., accidents, were significantly lower for staff members than for physicians. The deficit of deaths from these two causes was probably responsible for better survival in the Rad Lab cohort. The rates for all malignant neoplasms were the same. The rates were also approximately the same for deaths from all other causes, considered together. But increased risks were seen for lymphomas, particularly Hodgkin’s disease; cancers of the nervous system; and cirrhosis of the liver. Given these excesses, the Rad Lab deaths may have an infectious, immunological, and/or behavioral component.

TABLE 3-19. MORTALITY OF RAD LAB STAFF AND PHYSICIANS, THROUGH DECEMBER 31,1974, FOR ALL CAUSES OF DEATH AND CANCERS. PART A. STANDARDIZED MORTALITY RATIOS (SMRs) FOR STAFF AGED 25 YEARS OR MORE AT ENTRY, EXPECTED VALUES BASED ON RATES IN PHYSICIANS. PART B. MORTALITY RISK RATIOS FOR STAFF MEMBERS VS. PHYSICIANS USING COX'S PROPORTIONAL HAZARDS MODEL

	Part A: Standardized Mortality Ratios				Part B: Proportional Hazards Model		
Cause	Observed	Expected	SMR	95% Cl	Risk Ratio (Rad Lab: Physicians)	Maximum Likelihood Chi-Square	(p-value)
All Causes	213	246.01	0.87	0.78-1.02	0.6392	41.06	(<0.OOOO)[b]
All Malignant Neoplasms	47	42.96	1.09	0.80-1.45	0.8385	1.43	(0.8655)
Neoplasms, Lymphatic & Hematopoietic Tissues	-	-	-	-	1.0646	0.03	(0.8655)
Neoplasms/Lymphoid Tissue	-	-	-	-	1.0646	0.86	(0.3538)
Lymphomas	4	1.89	2.12	0.59-5.42	1.3804	0.21	(0.6463)
Lymphomas/Other Lymphoid	-	-	-	-	1.0880	0.02	(0.8989)
Leukemias	2	3.14	0.64	0.08-2.30	0.7200	0.29	(0.5920)
Hodgkin's disease	3	0.21	10.34	2.13-30.23[b]	4.0186	2.17	(0.1406)
Gall Bladder/Bile Ducts	2	0.14	14.29	1.69-50.29[b]	11.2728	4.08	(0.0435)[b]
Pancreas	5	3.12	1.68	0.52-3.74	1.169	0.11	(0.7383)
Brain and Nervous System	3	2.80	1.07	0.22-3.13	0.8449	0.09	(0.7587)
Nervous System Neoplasms[a]	3	0.89	4.26	0.70-9.85	-	-	-
Malignant Melanoma/Skin	-	-	-	-	3.7957	1.63	(0.2013)
Prostate	-	-	-	-	0.8583	0.12	(0.7273)

[a] Excluding brain tumors.
[b] Confidence intervals (Cl) don't overlap 1.0; or ≤ 0.05.

SOURCE: Hill, 1988.

Internal comparisons were made with three broad exposure groups (Table 3-20). No gradient in mortality on the basis of presumed exposure was seen. Age-adjusted death rates were greatest among the group with the lowest presumed exposure for all causes combined and in all major disease groupings; therefore, there was no evidence of dose response. But, the procedure used to identify and stratify exposure may have introduced confounding negative factors that would appear to be stronger than the influence of exposure differences, if such differences exist and affect outcome. Men in the low-exposure group mostly had management, administrative, or support jobs rather than scientific and technical jobs; the differences in mortality may thus reflect professional or socioeconomic differences among exposure groups. Despite this, the results do not necessarily mean that an exposure gradient does not exist.

The two other exposure groups (medium and high) were more similar in profession and age. The risk of death from all causes combined and in major disease groupings was greater in the high-exposure group, but was not statistically significant. Numbers were small. The rates for all cancers combined were approximately the same. Excesses for Hodgkin's disease, nervous system cancers, and cirrhosis of the liver were greatest for the medium-exposure group. The reasons underlying the observations are not clear. The medium-exposure group contains subjects exposed to several frequencies of NIR; about 25% worked with low frequencies rather than microwaves.

In summary, the overall survivorship of Rad Lab staff members was better than U.S. white males and a group of physician specialists. The study did not demonstrate significantly increased risk for total mortality or mortality from specific causes to be associated with NIR exposure, primarily from microwave frequencies. However, deaths from certain diseases were elevated, e.g., Hodgkin's disease and digestive diseases, especially cirrhosis of the liver. Results for the cohort grouped by an exposure ranking scheme were equivocal. Paradoxically, the mortality rates were highest in the group with the lowest presumed exposure which may reflect some sort of socioeconomic bias. There is a slight gradient in the rates for major causes of death between the groups with intermediate and highest exposure potential; this may reflect frequency specificity.

This study had a good tracing rate and a sufficient follow-up period to evaluate cancer, but the necessary censoring of the data set to permit comparisons to physicians reduced an already small study population. Statistical power was low for some cancers. Exposures for

TABLE 3-20. AGE-ADJUSTED MORTALITY RATES PER 1000 PERSON-YEARS FOR ALL CAUSES OF DEATH AND SELECTED CANCERS FOR RAD LAB WHITE MALE STAFF MEMBERS BY EXPOSURE RANKING GROUP BASED ON PREDOMINANT DIVISION OF WORK, FOLLOWED THROUGH DECEMBER 31,1986

Cause of Death	Rank 1 Low		Rank 2 Medium		Rank 3 High		Mortality Risk Ratios[a]		
	#	Rate	#	Rate	#	Rate	Rank 2:1	Rank 3:1	Rank 3:2
All causes									
Crude	150	11.97	66	5.26	90	6.87	0.44	0.57	1.31
Adjusted		9.07		6.76		7.44	0.75	0.82	1.1
All malignant neoplasms	34	2.02	20	1.70	42	1.65	0.84	0.82	0.97
All lymphocytic cancer	4	0.25	4	0.31	5	0.19	1.24	0.76	0.61
Lymphomas	2		2		2				
Hodgkin's disease	1		1		1				
Leukemias	2		1		2				
Multiple myeloma	0		1		1				
Brain/CNS neoplasms	1	0.06	3	0.26	1	0.04	4.33	0.67	0.15

[a]All the confidence intervals (not shown) overlap.

SOURCE: Hill, 1988.

individuals could not be determined but were estimated by surrogates. There were no data on other risk factors. Lack of smoking information is probably not a problem, because low mortality for circulatory disease and lung cancer suggests smoking may not have been prevalent in the cohort.

Szmigielski et al. (1988) examined cancer incidence among Polish career military personnel. The authors stated that radar exposures predominated, but ELF exposures were also noted. Large and consistent differences in cancer rates in exposed versus unexposed personnel were found for all sites reported (Table 3-21). Most of the data is on cancer of the lymphatic and hematopoietic system, and not all cancer sites were discussed. Generally, rates in the exposed group were six times larger than rates in the unexposed group.

The study was described as retrospective, but the exact design employed is difficult to discern. In fact, the presentation of the procedures, results, and analyses is atypical. For example, only rates per 100,000 are given; the numbers forming the basis of computed rates are not given (Table 3-21). Furthermore, most rates are only graphically displayed in figures rather than listed in tables. The author noted that, due to limits, the number of cancer cases and the size of the population, overall and within age groups, could not be presented. Although not stated, it is possible these limits were governmentally imposed restrictions.

In summary, mixed results are seen with studies that focused primarily on exposures to RF radiation. Two early studies (Lilienfeld et al., 1978; Robinette et al., 1980) showed only a slight tendency for increased cancer risk in general and for several specific cancer sites. This tendency was slightly stronger for cancers of the hematopoietic system. These studies suffer from either very low-exposure levels, crude exposure estimators, and/or limited follow-up periods. The study of RF exposure and cancer, evaluated for census tracts in Hawaii (Environmental Epidemiology Program, State of Hawaii, 1986), found significant excess risk for leukemia if census tracts contained RF towers, but small numbers and the crude exposure proxy, given the ecological design, limit this study's usefulness. The study by Hill (1988) found some excess risks for some cancer sites, specifically lymphomas, Hodgkin's disease, cancers of the nervous system (excluding brain cancer), and cancers of the digestive system, but overall, the results are generally nonpositive or, if positive, usually not statistically significant. Leukemias were not elevated. Misclassification with respect to exposure was possible. In contrast, Milham conducted several increasingly more analytical studies of ham radio

TABLE 3-21. INCIDENCE RATES PER 100,000 PER YEAR (1971-1980), FOR POLISH MILITARY PERSONNEL GROUPED BY WORK EXPOSURE TO RADIOFREQUENCY AND MICROWAVE RADIATION AND BY AGE

Type of Cancer		E Group[a]	NE Group	Total Population
All Neoplasms	All ages	192.2	64.2	
	40-49	350.0	<50	
Lung Cancer	All Ages	33.2	23.6	
Hematolymphatic	All Ages	50.8	7.4	8.9
	20-29	26.3	2.7	3.6
	30-39	29.7	3.0	3.8
	40-49	81.3	9.9	11.8
	50-59	117.6	29.6	32.7
LGR[a]	All Ages	6.0	1.8	
	20-29	18.8	2.1	
	30-39	-	0.9	
	40-49	11.6	2.5	
	50-59	-	3.0	
Ly Sa, Lymp[a]	All Ages	18.3	2.2	
	20-29	-	0.3	
	30-39	-	0.3	
	40-49	46.5	4.2	
	50-59	58.8	8.9	
CLL[a]	All Ages	6.1	1.3	
	20-29	-		
	30-39	9.9	0.3	
	40-49	11.6	1.4	
	50-59	-	8.9	
ALL[a]	All Ages	3.0	0.1	
	20-29	8.9	0.3	
	30-39	-		
	40-49	-		
	50-59	-		
CML[a]	All Ages	12.2	0.5	
	20-29	8.8		
	30-39	19.8	1.2	
	40-49	-	0.3	
	50-59	29.4	1.1	
AML[a]	All Ages	6.1	1.1	
	20-29	-		
	30-39	-	0.3	
	40-49	11.6	1.8	
	50-59	29.4	2.2	
PL[a]	All Ages	-	2.2	

[a]E=exposed, NE= not exposed, LGR= malignant lymphogranulomatosis, Ly Sa, Lymp= lymphosarcomas and other lymphomas, CLL=chronic lymphocytocytiic leukemia, ALL=acute lymphoblastic leukemia, CML=chronic myelocytic leukemia, AML=acute myeloblastic leukemia,

SOURCE: Szmigielski et al., 1987.

operators are found positive and statistically increased mortality risks for acute myeloid leukemias (SMR=1.76) and, considered together, multiple myelomas and other neoplasms of the lymphoid system (SMR=1.62) among FCC-licensed amateur radio operators in California and Washington State. For leukemias, all SMRs were elevated, but only the SMR for acute myeloid leukemias was statistically significant. In follow-up analysis, Milham (1988) evaluated ham operator mortality by five FCC license classes which served as surrogates for possible higher and/or chronic exposure with increased experience and expertise. No clear gradient by license class was found. The study by Szmigielski et al. (1988) reported increased rates of cancer, especially for specific sites in the hematopoietic system, among Polish military personnel exposed to RF and microwave radiation. Yet restrictions on the degree of detail for reporting results limit evaluation and interpretation of this study.

In general, epidemiologic studies of cancer and RF radiation show only a slight tendency for excess risk, especially for the hematopoietic system sites, but they present several methodological difficulties. The studies by Milham are the most persuasive in demonstrating positive and significant associations. In should be noted that the exposures evaluated by Milham differ in frequency (lower end of the RF portion of the EM spectrum) from the other studies which chiefly examined microwave frequencies.

3.3.2. 50- or 60- Hertz Exposures or Electromagnetic-Field Exposure to Unspecified Frequencies

3.3.2.1. Residential (50 or 60 Hertz)

Wertheimer and Leeper (1982) extended their wiring analyses in a study of adult cancer in four areas in Colorado, e.g., Boulder, Longmont, the City of Denver, and the Denver suburbs, In Boulder and Longmont, cancer cases were identified from death certificates between 1967 and 1975 for residents of those towns. A roster of potential controls was developed by drawing the next three certificates for noncancer deaths and for the same town. Controls were then selected for each case by matching on sex, age, and year of death within 5 years, and socioeconomic level (if possible). The address history of both cases and controls was traced and developed for 10 years preceding diagnosis of the case.

In addition, some living cases were drawn from the Colorado Cancer Registry. These cases were defined as persons with a life-threatening form of cancer that had been diagnosed five years or more prior to the study and were alive without known recurrence in 1979.

Life-threatening cancers were those for which more than half of the registrants had died within 5 years of diagnosis. Controls for these living cases were drawn from a random sample of persons identified in a telephone survey and were matched for age, sex, and socioeconomic level of residential census tract.

The approach for developing cases and controls was somewhat different for the Denver area. Death certificates for persons dying of cancer in 1977 in the Denver area were sampled. All cancer cases, except lung cancer, who had died before reaching 63 years of age, were included. Every other lung cancer death was included. Every other certificate was also drawn for deaths among persons older than 62 years.

Neighborhood controls were selected for the cases in the Denver area. Taken from a 1970 city directory, control addresses were randomly selected within two blocks in either direction of a case address. Apartment dwellers were matched. This approach provided a similarity in housing stock or other characteristics, yet could tend to minimize possible wiring, hence, exposure differences. Because of the latter, the method of categorizing wiring configurations was somewhat changed from the approach taken in the earlier study of children.

Cases and their controls were included only if address history could be traced for at least four years prior to diagnosis. The address at which a case and control had lived the longest during a period of 3 to 10 years prior to diagnosis was the address used in wire coding and analysis. There were 194 cases from Longmont, 321 cases from Boulder, 255 cases from the Denver suburbs, and 409 cases from Denver, totaling 1,179 cases.

Five major classes of distribution wires were considered: (1) Multiple (six or more nongrounded wires) or thick three-phase primary or high tension wires; (2) thin three-phase primary wires; (3) first-span secondary wires; (4a) second-span secondary wires; (4b) “short” first-span secondary wires; and (5) end-pole situations. Thin single-phase primaries were not treated; the authors stated they are ubiquitous and carry very low current. Wiring configurations for homes were coded into four groups that accounted for the distribution classes, noted above, plus distance. The codes were: (1) very high current configurations (VHCC) - Class 1 wires running past less than 15 meters (50 feet) and/or Class 2 wires running past less than 7.5 meters (25 feet); (2) ordinary high current configuration (OHCC) - Class 1 wires running past within 15-39.5 meters (50-129 feet, Class 2 wires running past within 7.5-19.5 meters (25-64 feet), or Class 3 wires within 0-15 meters (0-50 feet); (3) ordinary low current configuration (OLCC) - all other types of possible wiring configurations except

endpole configurations (homes beyond the endpole of a distribution line). Wires located more than 40 meters (130 feet) from a house were not coded. This ordering of the codes represents an estimate from high- to low-magnetic field level. Criteria were also established for case-control pairs to determine which member of the pair had lived in a home with a higher current configuration. Some pairs did have the same coded wiring configuration, and these pairs were excluded from matched pair analyses.

Analysis was made on the basis of wiring configuration code, but some selective measurements were made outside homes with side street access (Table 3-22). These measurements of magnetic fields generally supported the ordering of wire code current configurations.

From Table 3-22, it can be seen that even in the very high current configurations (VHCC), only 28.6% of the homes had actual magnetic field measurements over 3.0 mG (0.3μT), which suggest that these coding configuration categories may not be the best groupings for exposure since most of the residences falling in this very high category (VHCC) did not appear to have magnetic fields at the levels found to have been associated with effects in studies of children.

The authors looked at only total cancer (all sites combined) in the analysis. The four geographic areas were analyzed separately. When the distribution of cases and controls with respect to wiring code in four strata (VHCC, OHCC, OLCC, and endpole) was examined, the proportion of cases in each class generally decreased with decreasing estimates for current/magnetic field, denoted by wiring code (Table 3-23). This suggests a dose-response

TABLE 3-22. DAYTIME 60-Hz MAGNETIC FIELDS MEASURED NEXT TO THE PART OF THE HOUSE NEAREST TO DISTRIBUTION WIRES BY WIRE CODE

	VHCC (N = 56)	OHCC (N=134)	OLCC (N=186)	End-pole (N=41)
Maximum	10.0	8.0	3.0	1.4
Median	2.5	1.2	< 0.5	< 0.5
% >3.0 mG	28.6	10.4	1.1	0.0

SOURCE:

TABLE 3.23. WIRING CONFIGURATIONS AT THE HOMES OF CANCER CASES AND CONTROLS

	Type of configuration				Pair comparisons[a] Higher current configuration in:		C-ratio
	VHCC	OHCC	OLCC	End-pole	A. cases	B. controls	(A/B)
LONGMONT							
Cases	17	40	105	32	95	58	164 $p < 0.005$
Controls	12	28	114	40			
% Cases[b]	58.6	58.8	47.9	44.4			
BOULDER							
Cases	37	106	157	21	146	102	143 $p < 0.01$
Controls	19	101	173	28			
% Cases	66.1	51.2	47.6	42.9			
DENVER SUBURBS							
Cases	19	69	150	17	102	70	146 $p = 0.02$
Controls	12	57[a]	147	39			
% Cases	61.3	54.8	50.5	30.4			
CENTRAL DENVER							
Cases	35	115	230	29	166	137	121 $p = 0.11$
Controls	31	112	225	41			
% Cases	53.0	50.7	50.5	41.4			
TOTAL							
Cases	108	330	642	99	509	367	139 $p < 0.0001$
Controls	74	298	659	148			
% Cases	59.3	52.6	49.3	40.0			

[a] Pairs where the case and control had equivalent configurations were omitted from the pair-comparison data. VHCC = very high current configuration, OHCC = ordinary high current configuration, OLCC = ordinary low current configuration, End-pole = end-pole configuration.

[b] Percent of cases of the total of cases and controls by type of configuration and by geographic area.

SOURCE: Wertheimer and Leeper, 1982.

relationship; but, no statistical tests were reported. No estimates of risk were given in these tables. The authors presented other results in terms of a "C-ratio" ("C" stands for "configuration") which seems to be similar to odd ratio estimates for matched pairs. In this situation, the C-ratio was described as the number of pairs in which the case lived in the higher configuration home divided by the number of pairs in which the control lived in the higher current configuration home, then multiplied by 100. Significance was tested using the Sign Test. The results are like matched pair estimates of the odds ratios. The difference relates to how the data are described or categorized; that is, rather than arraying cases and their controls as with or without a factor, they are arrayed as to which has a higher or lower wiring code for their residence.

As shown in Table 3-24, some of the C-ratios were statistically significant by the Sign Test, indicating an association between higher wiring codes and total cancer. This effect was strongest in the youngest age group, i.e., persons under 55 years of age. The cases and controls were distributed with respect to urban versus nonurban residence, modified by age, that is, older persons were treated as having lower exposure to "urban factors." In this case,

TABLE 3-24. C-RATIOS FOR CANCER IN COLORADO ADULTS FOR RESIDENCE NEAR HIGHER WIRING CURRENT CONFIGURATIONS BY TOWN AND VARIOUS FACTORS

	Total	Longmount	Boulder	Denver Suburbs	Central Denver
Total	139*	164	143*	146*	121
Diagnosis Age:					
19-54 Years	201*	170	264*	200*	188*
55-69 Years	114	220*	129	97	191
70+ Years	137*	136	129	225	130
Male	NDR	NDR	NDR	103	NDR
Female	NDR	NDR	NDR	194*	NDR
Urban:					
Total	113				
Central Denver	121				
Male Suburban, 19-69 Years Old	81				
Low Urban:					
Total	162*				
Male Suburban, 70+ Years Old	500*				
Female Suburban	151*				

* p-value at least 0.05. NDR = No difference reported.

SOURCE: Wertheimer and Leeper, 1982

the risk was stronger in the “low urban” exposure group. Although not given in Table 3-24, this result was consistent across three age strata. The effect was also stronger in the highest socioeconomic group.

The authors considered all cancers together. But they noted that significantly high C-ratios were found for cancer of the nervous system, uterus, breast, and lymphomas. Elevated but nonsignificant ratios were found for cancer of the pancreas, bladder, kidney, and prostate. Except for nervous system tumors, these sites are different than those associated with magnetic field exposure in studies of children. Leukemia was not reported and presumably was not associated with magnetic fields, as estimated by wiring code.

The authors stated that they drew four main conclusions from their work, as follows: (1) a dose-response relationship was found; (2) the association was not an artifact of age, urbanicity, neighborhood, or socioeconomic level; (3) the association was most demonstrated where urban/industrial factors that may relate to cancer were least likely to obscure the effect; and (4) there was a distinct pattern of latency consistent with a promotion effect of exposure to alternating magnetic fields (AMFs). These broad generalizations may be unwarranted in view of the unusual methods used to design and analyze this study. The selection of cases and controls for inclusion in the study group was somewhat convoluted. The unusual manner in which certain subgroups (but not all) were included as cases, e.g., cancer survivors, as well as others who were excluded as controls, e.g., lung cancer deaths, makes it difficult to assess the direction and impact of selection factors on the results. Furthermore, the use of nonparametric testing methods to obtain point estimates (C-ratios) and assess significance (the Sign Test) instead of the more powerful odds ratio and Mantel-Haenszel testing procedures is strange. The latter statistical tools are ideally suited to case-control studies such as this. Why they were not used is not stated in the paper. The net result is to make it difficult to place a value on the usefulness of the conclusions in evaluating a carcinogenic effect.

Coleman et al. (1985) presented preliminary results of a case-control study of leukemia in London, England. Incident cases of leukemia registered in the Thames Cancer Registry for 1965-1980 were selected for study. Over 99% of the cases were histologically confirmed. Cases were limited to residents of four adjacent South London boroughs. Why the study was limited to these areas was not explicitly explained, but the authors noted the boroughs were densely populated, contained both urban and rural areas, and had no boundary changes in the study period. Two controls per case were randomly selected from all registered cases of

solid tumors (except lymphoma). If possible, a third control was also selected to hold in reserve. Controls were matched to cases for 5-year age group, sex, year of diagnosis, and borough of residence. The authors do not give the ages of the cases. There were 811 eligible cases; 42 were excluded because they could not be located or there were no matching controls, resulting in 769 final cases. There were 1436 controls after exclusion for, primarily, inability to locate either the control or the matched case. Unfortunately, 102 cases could only be matched to one control.

Exposure to EM fields at 50 Hz was estimated by mapping environmental electrical power supply sources and computing distance from residence to sources. For overhead lines, the distance used was the shortest distance between the residence and the line connecting pylons. Ordinance Survey grid maps were used to plot subject addresses and substations and overhead lines. Cases versus control status was blinded. Underground cables were not on the grid maps but data on their paths were obtained from utilities as well as was additional information on substations.

This paper presented only results for overhead power lines. Less than 1% of the population lived within 100 meters of lines at the time of cancer registration. When 100 meters was used as the demarcation distance for critical exposure, the odds ratio for leukemia was 1.31 (95% CI=0.50-3.45) but the result was not statistically significant; there were only 7 cases and 10 controls who lived less than 100 meters from an overhead power line. Distance to overhead power lines was also stratified further into groups living 0-24, 25-49, 50-99, and 100 or more meters, Taking the last group as having no exposure, the odds ratios for leukemias for these groups were 1.87, 1.87, and 1.07, respectively. Although the odds ratios, to some extent, increased with decreasing distance, the trend was not significant (p=0.24). The odds ratio remains 1.87 if the two low groups (0-24 and 25-49 meters) are combined. The lack of significance may be due to the small numbers of cases and controls at these close-in distances and a subsequent loss of statistical power. The authors noted that almost the entire local distribution network is underground. Since few people live near overhead power lines, it could be very difficult to detect small increases in risk.

The paper focused chiefly on proximity to overhead power lines which are uncommon in the region studied. Other than this proxy measure, exposure estimates were not given. Also, proximity of residence to lines was taken at the time of tumor registration which may not necessarily be the same residence as at onset of disease. Increased risk was seen for

leukemia for residences nearer to power lines. Statistical significance was not seen; this may reflect the small number of observed cases.

The authors updated this paper (Coleman et al., 1989) by enlarging the control group to include two referents chosen from the same Thames Cancer Registry from which the cases were chosen. The controls were to be picked from other registrants with solid tumors other than lymphoma. Using the same 769 plus 2 additional cases discussed in the earlier paper, 110 were matched to only one control because the address at registration could not be located on the primary control and no reserve control was eligible. The remaining 661 were matched to 1322 controls. A total of 1432 controls resulted. The surrogate for exposure was again distance from overhead power lines but now distance from substations was also considered. Distances were 0-24, 25-49, 50-99 and 100+ meters. Despite the large number of cases and controls, very few individuals lived within 50 meters of the overhead lines. Only three cases and three controls were found to live within 50 meters distance from power lines. This was enough to produce a nonsignificantly increased risk of leukemia (OR=2.00). On the other hand, for those residing within 25 meters of a substation the risk was nonsignificantly elevated (OR= 1.26) based upon 35 cases and 51 controls. No increased risk was seen in persons residing beyond 25 meters.

Included as part of this case-control study were 84 cases in children under age 18 who were matched with 141 controls. The authors performed a separate “nested” analysis of this subgroup in which they noted a trend of increasing risk of leukemia with decreasing distance from a substation, as follows:

RELATIVE RISK BY DISTANCE OF SUBJECT’S HOME FROM SUBSTATION IN CHILDREN UNDER AGE 18

	Meters				
	0-24	25-49	50-99	100+	Total
Cases	3	11	22	48	84
Controls	3	12	48	78	141
RR	1.63	1.49	0.75	1.00	

None of these risks are significant, however, but they appear to be supportive of the findings in the childhood cancer studies of an increased risk of leukemia from exposure to magnetic fields.

No actual measurements of magnetic fields were available to substantiate exposure in any of the designated distance categories. In other studies where measurement data were available, distances at and beyond 25 meters from most sources of magnetic fields have not been found to harbor magnetic fields of strengths much greater than those at 100 meters. Hence, it may not be unexpected that risks calculated in these locations are not elevated. Furthermore, implicit in these risk calculations involving distance is the assumption that no other sources of electromagnetic fields were producing magnetic fields at those same locations.

Another potential confounding effect can happen when referents are taken from the same cancer registry as are the cases. If exposure to EM fields is associated with cancers other than leukemia, then the referents with the associated cancers may be found to live closer to the source of the magnetic fields, and the risk estimate for leukemia will be reduced as a result.

And again as in most of these studies duration of exposure (length of residency in the magnetic fields) and latent effects have not been addressed by the authors.

However, despite the study's limitations, the observed relationship between proximity to the line and excess leukemia risk is consistent with a weak positive effect. However, the authors also pointed out that residence near overhead power-lines is not a major leukemia hazard for large numbers of people in the geographical area studied.

Using a cohort study design, McDowall (1986) investigated the mortality rate of persons who resided near electrical transmission facilities in East Anglia, England. The study period extended from the 1971 Population Census until the end of 1983. Sample size calculations (not provided) indicated approximately 8000 persons or 3000 households would be needed to detect a twofold increase in risk for most major cancer sites.

Subjects were entered into the study using a stratified random sampling scheme that served to identify houses from National Grid Maps. Houses (and, consequently their occupants) were selected if they were within a 50-meter radius of a substation or within 30 meters either side of an over head power cable. A total of 2839 houses were selected.

Census data were examined to identify and extract information about the resident householders in the 2839 dwellings. Abstracted information included name, address, date of

birth, sex, occupation, employment status, and address 1 year and 5 years prior to the census. Census data on 7920 persons were linked to the National Health Service Central Register (NHSCR), and 7631 persons were located, a tracing rate of about 96%. Of these, 814 (409 men, 405 women) had died by December 31, 1983, the end of the study period. The sampled population was generally similar to the whole East Anglia population with respect to sex and social class (based on occupation and employment status), but the sample was somewhat younger.

Cause of death was obtained from death certificates and was coded to the Revision of the *International Classification of Disease (ICD)* in effect at the time death. National coding rules were followed for comparability to the reference rates used in analyses. Standardized Mortality Ratios (SMRs) were calculated for certain specified causes of death. Expected deaths were calculated from East Anglia mortality rates. National rates for England and Wales were used to generate expected deaths due to hematopoietic neoplasms.

For both men and women, mortality for major causes of death was generally similar to what would be expected based on rates in East Anglia; SMRs for men were generally lower than expectation, and SMRs for women were generally higher than expectation. The only cause of death that significantly exceeded expectation was lung cancer among women. SMRs for leukemias and other hematopoietic neoplasms were elevated only for women (154 and 171, respectively), but the result did not significantly differ from expectation.

SMRs were also calculated for subsets of the population, categorized by distance in meters of the residence from electrical installations, e.g., 0-14, 15-34, and 35-50 meters. The sexes were combined in this analysis to try to obviate small numbers. For all groups, only the SMR for lung cancer (215) was significantly greater than expectation in the group who had lived 14 meters or less from an electrical installation. Deaths from respiratory disease were also slightly elevated (SMR 127). Elevated but nonsignificant SMRs were noted for leukemia (143) and other neoplasms of the hematopoietic systems (333) at this same distance based upon only a few deaths. The highest SMR was for breast cancer (122), and that occurred in the subgroup that resided 15-34 meters from an electrical installation. But, generally, there was little difference from expected values. The highest SMR for the subgroup that lived the farthest away from electrical installations (35-40 meters) was for nonleukemia hematopoietic neoplasms (144). The SMR for leukemia was, at 120, the second highest. The SMRs for

several other major cancer sites, including leukemia, exceeded unity, but overall cancer mortality was less than unity.

The sampled population was also examined with respect to address 5 years prior to the 1971 census, e.g., same address and different address. Again, the results for both sexes are combined. In both groups, only the deaths from circulatory disease significantly differed from expectation, and were less than expected. Although not significant, the SMRs for malignant neoplasms of the hematopoietic system, other than leukemia, were the highest in both address groups, e.g., 125 for same address and 138 for different address.

The two address groups were also further subdivided, and SMRs were calculated for persons who lived within 25 meters of an electrical installation at the time of the 1971 census, In this analysis, results for circulatory diseases remained significant only for the same address group. Also, for this group, only deaths from lung cancer occurred in excess. In the group who had resided at a different address 5 years prior to the census, many causes of death occurred in excess of expectation, but SMRs did not differ significantly from unity. The SMR for nonleukemia lymphatic neoplasms was 300, but there were only three cases and the 95% confidence interval was very wide.

Overall, the mortality level of the sampled population for all and specific causes did not differ from expected based on rates in East Anglia or on national rates. All-cause mortality was significantly lower than expected, primarily due to lower rates for death from circulatory disease. The author speculated that older housing units with older residents may have been under-represented in the sample, and this is responsible for the observed lower mortality in the study group. Generally, for all analyses, SMRs for leukemia and for other hematopoietic neoplasms were elevated, based on regional and national rates. This result was strong for females. These results were not significant, but the number of cases was small. The highest SMRs for these causes occurred among persons living the closest (15 meters) to electrical installations. Excess lung cancer was seen among women and among both men and women who lived less than 15 meters from an electrical installation.

In this study, residence near electrical installations (50 meters) or overhead lines (30 meters) was taken as the indicator for exposure. Field measurements, either single or continuous, were not made. All types of facilities were included regardless of type or current. It is interesting that only 19 of the 7631 residents lived within 30 meters of an overhead cable.

It seems that the methods employed yielded populations whose exposures were likely to be low or very low. Distance from a source was used as a proxy for field strength.

Although the author stated that his findings do not support the previously reported associations of exposure to EM fields with acute myeloid leukemia and other lymphatic cancers, he did report elevated, albeit nonsignificant, risks of leukemia and cancer of the hematologic and lymphatic tissue based on very small numbers in persons living less than 15 meters from electrical installations. This is a cohort study that basically had very little power to detect risks of rare cancers such as leukemia; the conclusions of the author must, therefore, be viewed in the context of the study's limitations. Electric and magnetic field measurements are lacking and so the EM field environment that characterizes each distance category is unknown. The author suggested that perhaps his study could not confirm associations noted by other investigators because exposures characterizing the study area are probably too low, or exposure was diluted by mobility, or there were inadequacies in the study design.

Severson et al. (1988) investigated the occurrence of acute non-lymphocytic leukemia and residential exposure to power frequency magnetic fields in adults in western Washington State. Cases were identified from the population-based Cancer Surveillance System of the Fred Hutchinson Cancer Research System. Cases were defined as all newly diagnosed cases, aged 20-79 years, of acute nonlymphocytic leukemia (of seven histological types) between 1981 and 1984 in three counties. Living and deceased cases were included in the study. Controls in the same region were selected by using random-digit dealing methods and were frequency matched for sex and age in 5-year groupings. Study subjects or their next-of-kin were interviewed with respect to residence history, ionizing radiation exposures, occupational history, medical history, medications and drug use, smoking and alcohol history, pet ownership, and various demographic characteristics.

An arbitrary reference date was randomly assigned to each control to try to make the recall period similar between cases and controls. This resulted in a uniform distribution of reference dates over the period of case diagnosis.

Three different and extensive methods of exposure assessment were used. The first method mapped external wiring configurations within 140 feet of each subject's residence (except apartment dwellings) over a 15-year period prior to the reference date. The technician who developed these maps was kept unaware of whether an address was a case or a control. Each map was then classified, according to a coding scheme similar to that of Wertheimer and

Leeper (1979, 1982), into one of four groups, e.g., endpoles, ordinary low current configuration, ordinary high current configuration, and very high current configuration, that presumably represent a gradient of increasing potential exposure.

The second method of exposure assessment was to measure magnetic fields in and outside the residences at the time of the interview for subjects who had lived in that residence at least one year or more prior to the reference date. Magnetic fields were calculated as root mean square (rms) of three measurements per location and were expressed in milligauss (mG, 1 mG=0.1 microtesla, μT). Measurements were made in the kitchen, the subject's bedroom, and the family room under conditions of low power use (most appliances off) and high power use (all appliances turned on in the room being measured). For both low- and high-power use conditions, two exposures were calculated, i.e., the mean of the three room measurements and the mean of the three room measurements weighted by the estimated time spent by the subject in each room.

The third method of exposure assessment was to measure magnetic fields over a 24-hour period in residences where the one-time-only measurements had been made. Using an assessment scheme developed by Kaune et al. (1987), the 24-hour meter readings were correlated to various aspects of the wiring configurations maps to estimate magnetic field levels within each residence.

Originally, 164 cases and 204 controls had been identified (Table 3-25). Refusals to participate, either by physicians, hospitals, or subjects, or other reasons for losses or nonparticipation resulted in 114 cases and 133 controls available for interview and analysis. The interview response rate was, thus, 69.5% and 65.2% for cases and controls, respectively. Although the level of response is similar for cases and controls, it is of concern that the rate is low.

The cases and controls were compared with respect to various demographic and other factors. It was found that cases tended toward lower socioeconomic status, measured separately by education and family income, and more cigarette smoking. No increased risk was found for pet ownership or estimates of ionizing radiation exposures. The cases and controls were similar with respect to length of residence in mapped dwellings. Persons who had lived in apartments for all 15 years prior to the reference date or had moved to the study area just prior to the reference date were excluded from the analyses.

TABLE 3-25. LOSSES/EXCLUSIONS IN A STUDY OF ACUTE NONLYMPHOCYTIC LEUKEMIA AND RESIDENTIAL EXPOSURE TO POWER FREQUENCY MAGNETIC FIELDS IN ADULTS IN WESTERN WASHINGTON STATE

	Cases		Controls	
	No.	%	No.	%
Number Identified	164	100	204	100
Number Interviewed	114	69.5	133	65.2
Exclusions/Refusals	50	30.5	71	34.8

SOURCE: Severson et al., 1988.

TABLE 3-26. RISK ESTIMATES OF ACUTE NONLYMPHOCYTIC LEUKEMIA IN ADULTS IN RELATION TO EXPOSURE BASED ON WERTHEIMER AND LEEPER'S WIRING CLASSIFICATION SCHEME FROM FITTED LOGISTIC REGRESSION MODELS, WESTERN WASHINGTON STATE, 1981-1984

Wiring Configuration	No. of Cases	No. of Controls	Odds Ratios[a]	95% CI [b]
Longest Residence 3-10 Years before Reference Date				
Very Low (Endpole)	42	44	1.00	
Ordinary Low	21	37	0.60	0.29-1.22
Ordinary High	21	23	0.77	0.35-1.68
Very High	5	6	0.79	0.22-2.89
Residence Closest to Reference Date				
Very Low (Endpole)	42	52	1.00	
Ordinary Low	26	38	0.81	0.41-1.61
Ordinary High	24	19	1.36	0.62-2.96
Very High	5	7	0.84	0.24-2.93

[a] Controlling for age, sex, cigarette smoking, family income, and race.
[b] CI = confidence interval.

SOURCE: Severson et al., 1988.

With one apparent exception, there was no increased risk of acute nonlymphocytic leukemia from exposure to magnetic fields under the exposure assessment schemes and methods of analysis applied in the study.

Two analyses of wiring configurations (based on residential mapping as previously discussed) were reported, that is, analysis of wiring configuration for the place of longest residence and for the residence closest to the “reference” date. Also, two analytic methods were used, i.e., fitting the data to a logistic model and estimating relative risk for exposure strata. Odds ratios were developed and controlled for age, sex, cigarette smoking, family income, and race. With the logistic model and for both types of residences, odds ratios did not generally exceed unity, and no increased risk was associated with residence in homes classified with a higher current configuration, the presumed highest magnetic field exposure. No estimate was, however, significantly different from expected. Results were fairly flat across all configurations from very low to very high. Similar results were obtained when subjects with underground residential wiring (called endpoles) were excluded from the analyses. Inclusion of this subgroup in the lowest exposure category would tend to underestimate the risk if any did (does) exist. It was suggested in a critique of this paper by Wertheimer and Leeper (1989) that if the two low exposure categories are combined and then contrasted with the two highest categories, combined, a weak but modest increase in the risk of this cancer will be seen, i.e., 1.2 for longest residence and 1.5 for “closest” residence. This is probably not an unreasonable exercise in view of the small numbers that the authors dealt with. The suggested recategorization by collapsing into only two groups does add some stability to the numbers. Savitz et al. (1988) did much the same thing to improve risk estimates and decrease variability of those estimates.

Analyses for both longest residence and most recent residence were also performed for exposure estimates in milligauss developed using the method of Kaune et al. The exposure estimates were categorized in three groups representing low (0.51-1.99 mG), and high (2.00 mG) exposure. With this approach, the odds ratios were again less than 1.0 and none were significant, Of note is that the authors table on this analysis lists 19 additional cases and 26 additional controls, in the category entitled “residence closest to reference date,” which is 41 more subjects than the total interviewed.

Risk estimates were also developed for the weighted and unweighted mean magnetic field measurements, divided into three groups (0-0.5, 0.51-1.99, and 2.00+ mG), under both low-

and high-power use conditions, although there was little difference (0.174) between them. The odds ratios were nonsignificantly higher in the exposure level 2.00+ mG. It was in this analysis that the only dose-response result was obtained, that is, an increase in risk was seen with increased mean exposure under the low power configuration (Table 3-27). Also, the trend was not observed when exposure was weighted by time spent in each measured room, based upon interview data. Application of logistic models suggested measure fields were not related to disease.

There was a borderline significantly increased risk (OR=2.4) of acute nonlymphocytic leukemia observed for use of electric blankets, water bed heaters, and electric mattress pads, elicited in the interviews, in subjects with an annual family income under $15,000.

This study has several drawbacks and weaknesses that need to be addressed before the results can be considered definitive. First, the study deals only with one type of leukemia, acute nonlymphocytic leukemia. Chronic nonlymphocytic as well as acute and chronic lymphocytic leukemia were not considered; the results from this paper do not pertain to them.

TABLE 3-27. RISK ESTIMATES OF ACUTE NONLYMPHOCYTIC LEUKEMIA IN ADULTS IN RELATION TO THE WEIGHTED AND UNWEIGHTED MEAN MAGNETIC FIELD MEASUREMENTS MADE IN THE KITCHEN, BEDROOM, AND FAMILY GATHERING ROOM OF THE SUBJECT'S RESIDENCE AT REFERENCE DATE, WESTERN WASHINGTON STATE, 1961-1964

Exposure Level (milligauss)[b]	Odds Ratio (95% CI [a])	
	Low power Configuration	High Power Configuration
Mean Exposure		
0-0.50	1.00	1.00
0.51 - 1.99	1.16 (0.52-2.56)	0.55 (0.25-1.22)
2.00 +	1.50 (0.48-4.69)	1.56 (0.49-5.04)
Weighted Mean Exposure		
0-0.50	1.00	1.00
0.51 - 1.99	1.17 (0.54-2.54)	0.91 (0.42-1.96)
2.00 +	1.03 (0.33-3.20)	1.25 (0.35-4.48)

[a] CI = confidence interval.
[b] 1 milligauss (mG) = 0.1 microtesla (μT).

SOURCE: Severson et al., 1988.

Second, a very small number of cases and controls were selected for inclusion into the study. In addition to the small sample size, a poor response rate was attained. Poor response among cases was chiefly due to physician and hospital refusals. No explanations were given regarding the reasons for the refusals. One must have some concern about the impact on the results of missing information from the approximately 35% of the population who were nonrespondents. The small sample size attained makes it somewhat questionable that the nonpositive results are indicative of the underlying risks for this type of leukemia. The study had little power. Third, magnetic field measurements taken many years later are not necessarily representative of actual exposure received by the cases prior to diagnosis. This problem is, of course, not unique to this study. Latency must be considered. Length of residency prior to the date of the measurement of electric and magnetic fields or the date when the next-of-kin was interviewed is not a proper measure of latency. Fourth, a potential source of bias is the use of live controls matched to dead cases. Data provided from questions asked of live controls may differ from the data provided by the next-of-kin of dead cases. Lastly, no mean and/or median magnetic field measurements were taken within each wiring code category to substantiate any potential trend of increasing exposure from “very low” to “very high.” The author’s own analysis of his wiring code does not correlate well with his 24-hour magnetic field measurements.

Preston-Martin et al. (1988) reported the results of a study of 116 adult acute and 108 chronic myelogenous leukemia (AML, CML) cases that examined effects of exposure to EM fields from electric blanket use. This was a case-control study that was not originally designed to examine potential risks from EM fields. But, because of high fields, prolonged exposure, and intimate contact from electric blankets, a source of EM fields, the authors stated they added questions on electric blanket use to ongoing studies

Cases were identified from the University of Southern California Cancer Surveillance Program, a population-based registry, and were Los Angeles County residents aged 20-69 years with histologically confirmed AML or CML diagnosed from July 1979 to June 1985 (Table 3-28). Cases had to be alive and able to be interviewed in English; this criterion was also applied to controls, There were 859 registered cases but only 458 were alive. Further selections were made only among the live cases. Exclusions were 122 patients or doctors who refused to participate and 68 cases who could not be located. After these exclusions were made, there were 295 cases for whom questionnaires were completed. The controls

TABLE 3-28. ELECTRIC BLANKET USE AMONG ADULTS (AGED 20-69 YEARS) WITH ACUTE AND CHRONIC MYELOGENOUS LEUKEMIA, RESIDING IN LOS ANGELES COUNTY, AND THEIR MATCHED NEIGHBORHOOD CONTROLS

Factor	Case	Controls	Odds Ratio
Ever used electric blankets regularly			
AML[a]	40	43	0.9
CML	38	42	0.8
Average usage duration, in years			
AML	8.5	7.0	
CML	9.0	10.0	
Years of first use			
AML	1971	1971	
CML	1970	1970	
Years since last use			
AML	3.2	4.1	
CML	2.7	2.8	

[a]AML=acute myelogeneous leukemia, CML=chronic myelogeneous leukemia.

SOURCE: Preston-Martin et al., 1988.

were individually matched neighborhood controls, matched on sex, race, and birth year ±5 years. The selection procedures procedures resulted in 293 matched controls for whom all questionnaires were completed.

Telephone interviews were conducted and, because the process for identification and selection was explained to the subjects, the interviewers were not blinded to case versus control status. Information was obtained on events up to the time of the interview, but analyses were restricted to events that took place at least 2 years prior to diagnosis. In addition to electric blanket use, i.e., year first used, year last used, and duration of use, the questionnaire solicited information on jobs, chemical use, radiation therapy, and diagnostic radiography. Procedures for matched-pair analyses and multivariate methods were used. Odds ratios were maximum likelihood estimates.

Because the survey's question on electric blanket use was added to the ongoing study, only 224 matched pairs answered the question on whether they had ever used an electric blanket regularly. Cases (both AML and CML) did not differ from controls with respect to regular usage of electric blankets (AML OR=0.9, CML OR=0.8). The cases and controls also

did not differ for patterns of blanket usage, as shown in Table 3-28. Adjustments for other risk factors, i.e., diagnostic radiography, work as a welder, and farm residence, did not alter the observed lack of association.

This study has some merit as a general study of leukemia in adults in Los Angeles, but several major problems limit its usefulness in judging the risks of EM fields. Although the study provides no support for the hypothesis that electric blanket use is associated with myelogenous leukemia, the authors pointed out that this hypothesis might be more effectively tested in an area with a harsher climate than Los Angeles with its year round warm climate. It also says nothing about the risk of lymphatic leukemia, which mainly affects children, The sample size just achieves the 80% power needed for a one-sided detection of a risk. Furthermore, deceased myelogenous leukemias were excluded from this study. Only live cases were considered. Hence, the results apply only to survivors, since there may be differential risks between surviving and deceased cases. Only 53% of all registered myelogenous leukemia cases survived to be included in the study. The use of only live cases represents a substantial loss of information about all leukemia cases. On the other hand, the accuracy of information on electric blanket use may be improved if the information comes from the subject himself rather than the next-of-kin. Another major problem is the very broad nature of the interview questions (Table 3-27) on electric blanket use which only provided a very crude surrogate of possible exposure. For example, detailed information on frequency of use other than “years” of use as well as detailed questions on use patterns would have been more informative. Also, as the authors point out, such blankets can generate fields from 12 to 50 mG (1.2 to 5.0μT). Individuals vary according to how often and how much they depend upon electric blankets for warmth and the intensity settings they prefer. Furthermore, the questions on electric blanket use were added, according to the authors, after 69 cases and 65 controls had been interviewed. This implies that the authors had not originally intended to study electric blanket use. The propriety of introducing a new hypothesis, midway through a scientific study for testing, must be questioned. Because of these issues, this study cannot be considered conclusive and adds little to our understanding of the cancer risks posed by this source of EM fields. As the authors state, it might be better if future studies use populations more dependent upon electric blankets than are residents of Los Angeles.

In summary, the results obtained from studies of cancer incidence or mortality in adults in relation to residential exposures to EM fields from 50- or 60-Hz power transmission frequencies

are not as strong as were the results obtained from studies of children. The only clearly positive study was conducted by Wertheimer and Leeper (1982). The other studies (Coleman et al., 1985; McDowall, 1986; Severenson et al., 1988) of power frequency fields are generally nonpositive or only show weak associations for increased risks of leukemias or hematopoietic cancers *in toto* from exposure to EM fields, estimated by proximity to lines or by wiring configuration codes. There has been discussion in the literature that recategorization of exposure groups in the Severenson et al. (1988) study may produce more strongly positive results. The study also exhibited poor response rates, although rates were comparable for cases and controls. The study by Preston-Martin et al. (1988) is of a different type in that it briefly examined electric blanket use rather than power transmission and distribution fields.

3.3.2.2. Occupational

This section examines studies on occupations and workplace exposures. It is organized by the cancer site, to the extent possible, that was the principal endpoint under study.

3.3.2.2.1. Multiple Sites. The following studies examined cancer mortality or incidence in general and for more than one site.

Wiklund et al. (1981) reported on the first use of the Swedish Cancer-Environment Registry to investigate cancer risk in an occupational group, that is, telephone operators for the Swedish Telecommunications Administration. The Registry represented linkage between the 1960 census and the National Cancer Registry for 1961-1973. The development of this joint registry was enabled by the assignment of individual personal identification numbers to Swedish residents. About 1% of registered cancer cases cannot be identified in the census. About 0.5% of linked cancer case census matches are believed to be inaccurate. Another quality control assessment compared death certification to incident case registration and found the total loss of cases to be approximately 3%-4%. But certain malignancies, including the leukemias (11.5%), exhibited a greater registry loss rate.

Cases were defined as telephone operators at the Telecommunications Administration identified as such in the 1960 Census and who were entered in the Cancer Registry with a diagnosis of leukemia; only 12 cases resulted. Sex was not identified. The expected number of cases was calculated by applying national rates specific for year of birth and sex; 11.7 cases were expected overall. Observed to expected ratios were evaluated by means of the

Poisson distribution. The observed cases were not found to differ significantly from expectation.

The development and use of national cancer and other registries is very important and useful. But the approach and results presented here do not seem to be fully satisfactory for examining carcinogenic risks among telephone operators, as discussed below. As the authors point out, many factors and different approaches should be applied to fully assess whether exposure to a suspected carcinogen may result in increased incidence of cancer. For example, the underregistration of leukemia cases to the cancer registry, in general, is of concern. It seems surprising that the national linked databases yielded only 12 cases between 1961 and 1973 (13 years) whereas the cluster of cases that prompted the study totaled 4 cases in one city between 1969-1974 (6 years). Employment was ascertained from the census; this could possibly misrepresent the number of operators. In any event, the census data is a point estimate for employment. While this study is valid on its own merits, other approaches might be applied in the future to further examine the Gothenburg leukemia cluster and/or to further examine whether any cancer risk is present for telephone operators or other telecommunications workers. For example, a cohort study among workers at the Telecommunications Administration might be useful.

Howe and Lindsay (1983) reported on a computerized system for linking records to monitor mortality among the Canadian labor force. Data were collected from all employers between 1965 - 1969 and 1971 on an approximate 10% sample of the Canadian work force, using social insurance (SI) identification numbers as the sampling frame. Occupations and industries were coded to 1961 (for 1965-1969 data) and 1971 (for 1971 data) census designations. Data from 1970 were not available; the reason was not stated. A file of three million records was generated. Because individuals could be identified over several sampled years, the records were sorted to develop a composite record per person. The file was also examined for errors. These procedures resulted in a final file of 700,335 records of individuals. The records contained information on surname; first and second given name; sex; day, month, and year of birth; mother's maiden name; and occupation(s) and industry(ies) of employment.

The data for the sampled population were linked to the national mortality registration system for the years 1965-1973. A scheme was developed to determine whether the linked data were in agreement, and, thus, whether a match had been found. If a match was

determined to have been made, data on date and cause of death, coded according to the operative ICD code, were added to the occupational file.

In the analysis, the 1971 sampled employees were excluded. Females were also excluded. These exclusions resulted in 415,201 records of males who were ever employed between 1965 and 1969 for which 19,374 deaths between 1965 and 1973 were identified.

Standardized mortality ratios were calculated for all causes, all cancers, and for 19 specific cancer sites. Expected rates were calculated by applying age-specific rates for a given cause for a reference group to the person-years of observation of the “exposed” group, grouped in 15-year age groups. Two reference groups were used, namely, the Canadian population and the whole occupational cohort.

Overall, the sampled population exhibited lower total mortality (SMR=0.83) than the Canadian population as might be expected given the “healthy worker” effect. The depression in mortality was less strong for death from cancer (SMR=0.88), from lung cancer (0.95) and from bladder cancer (SMR=0.89).

An individual was coded as belonging to a given occupation or industry if he had been recorded as being employed in the same for at least one year between 1965 and 1969. SMRs for major occupational groups were derived using the total cohort as the reference group. For 13 major occupational groups, the group for transport and communication workers is most likely to encounter electric and magnetic fields. In this subset, SMRs were elevated for 12 of the major cancer sites presented (SMRs were less than 1.0 for cancer of the pancreas and of the buccal cavity and pharynx, except lip), for all malignant neoplasms, and for all causes of death combined. Of the elevated SMRs, the SMR for leukemia and aleukemia (SMR=1.68, $p \leq 0.01$) was significantly elevated as were the SMRs for deaths from all malignant neoplasms combined (SMR=1.12, ≤ 0.05) and for deaths from all causes (SMR=1.04, $p \leq 0.05$).

For the 12 major industry groups examined, the industry of transportation, communication, and other utilities is the grouping that can be most readily linked to electric and magnetic field exposure. In this group, the potential excess risk is less clear than it was for the similar occupational grouping. Here, the SMRs were largely greater than one but no increase was statistically significant. The SMR for leukemia and aleukemia was 1.36.

For presentation of the more detailed occupational/job codes, the group with the greatest apparent potential for exposure to electric and magnetic fields was linemen and servicemen for telephone, telegraph, and power systems. The data presented only gave SMRs for those sites

for which an observed increase differed significantly from unity. For linemen and servicemen, significantly elevated SMRs were seen for cancer of the intestine (except rectum) (SMR=3.53, $p \leq 0.01$) and of the stomach (SMR=2.33, $p \leq 0.05$). These sites differ from those observed in other studies, i.e., are not leukemia or other neoplasms of the hematopoietic system. Unfortunately, the SMRs for these cancers are not given but were apparently not statistically significant. In a review, Coleman and Beral (1988) cite an SMR for all leukemias of 2.41 (CI=0.97-4.97) among these power and telephone lineman (N=4583); these data were obtained from a personal communication with Howe.

For presentation of detailed industrial codes, the group with the seemingly greatest potential for EM-field exposure is manufacturers of major appliances (both electric and nonelectric). Again, only data on sites with significantly elevated SMRs were given. For this industrial group, a significantly increased risk of death from neoplasms of lymphatic and hematopoietic tissues was observed (SMR=5.28, $p \leq 0.01$).

Olin et al. (1985) evaluated the mortality levels of 1254 electrical engineers who had graduated from Sweden's Royal lnstitute of Technology between 1930 and 1979 with a Master's degree. The study group was compared to the general Swedish male population. SMRs were derived for the engineers and for male architects who also had graduated from the same school over the same period of time. The mortality of the electrical engineers was lower than expected based on the general population for all causes and for all major disease groups; a very strong healthy worker effect seemed to be operative. The observed mortality in architects was also lower than expected on the basis of general population rates. For the most recent graduates (1979), follow-up was, at most, only about 5 years. The earliest graduates could have been followed up to about 55 years. Considering the differing follow-up periods plus the effects of secular changes on mortality, it would have been helpful if analyses had also been performed in different calendar times or birth cohorts.

Vagero et al. (1985) conducted a retrospective cohort study on cancer mortality among workers in one large Swedish telecommunications company, established in 1910, involved in research, development, and manufacturing of telecommunications equipment. Study subjects were all workers employed for at least 6 months during 1956-1960 at three work sites. It is not clear if these three sites were inclusive or only a subset of all places or employees of the telecommunications company. The subjects were ascertained from a company employee registry maintained by management at the three sites and consisted of 2918 subjects, 2051

men and 867 women. The follow-up period was from 1958 to 1979, resulting in 62,028 person-years (PY) at risk.

Company files were used to elaborate work histories throughout an individual's period of employment. Work histories included information on the departments in which a person worked by month and year. A group of senior engineers developed a scheme to describe the type of work or work practice in each department. The developed work information was then used to specify subcohorts formed by workers in departments with specific types of work. The potential exposures or work practices of interest to the investigators were soldering (N=1514, PY=30,940); oil mist (PY=1787); trichloroethylene (PY=7202); and grinding, polishing, and degreasing (PY=5366).

Tracing efforts were very successful (2916 out of 2918 total subjects). Cause of death could not be established for two persons who were, thus, excluded from analyses of the resultant 2914 persons. The four losses were all male subjects.

The data on the study population were linked to information in the Swedish Cancer Registry to identify cases of cancer between 1958 and 1979. SMRs (here, standardized morbidity ratios) and 95% confidence intervals were calculated, and expected cases were developed by applying age-, sex-, and calendar year-specific Swedish incidence rates. Cases were coded according the Seventh Revision of the ICD.

There were 102 cases of all cancers among men, and 37 cases of all cancers among women. The number of cases for both sexes was close to expected with both SMRs essentially at unity. No excess of lung cancer was observed in either sex. For men. SMRs for several types of cancer were elevated, but only the SMRs for malignant melanoma of the skin (SMR=25) and Brill-Symmer's (SMR=17.6) (nodular lymphoma) were statistically significant. For the latter, two cases were diagnosed in the population whereas only 0.1 cases were expected based on Swedish incidence rates. Among women, cases of cancer of the small intestine (SMR=16.0), corpus uteri (SMR=2.2), and malignant melanoma of the skin (SMR=2.8) were greater than expected although only the SMR for intestinal cancer was statistically significant.

Given the observed excesses in malignant melanoma for both sexes, further analyses were performed for this type of cancer. All cases were confirmed by biopsy. When the sexes were combined, the calculated SMR was 2.6 with a 95% confidence interval of 1.3-4.5. An analysis of all cases that assumed at least 3 years of exposure (work) and a 10-year latency period was

performed. The assumptions yielded 10 cases (7 men, 3 women) for any work and 6 cases (4 men, 2 women) for workers involved with soldering. The overall SMR was 2.8 (95% CI=1.3-5.1), but the SMR for soldering work was 3.9 (95% CI=1.4-8.5). The cases were clustered at work site A.

This is another Swedish study that used cancer registry data to investigate the risk of cancer in telecommunications workers. The focus of the study was chemical exposures rather than EM fields. The study seemed to have good information on employment histories. Observed excesses in malignant melanoma in both sexes were concentrated among workers at one location who were involved with soldering. However, more detailed evaluation of soldering jobs was not done. Exposures from soldering can involve several potentially important agents, including EM fields. The excess risk of cancer of the small intestine in women was not subjected to a more detailed work history analysis. The age distribution of the cohort was not given in the paper.

A study conducted by Barregård et al. (1985) investigated mortality and cancer incidence among workers exposed to static magnetic fields (Table 3-29). The subjects were employed at a Swedish chloralkali plant. Chlorine is produced by electrolysis using a direct current of about 100 kA which can create strong magnetic fields. This work presumably took place in what was called the “cell room.” As identified by foremen, workers in the cell room were selected for study if they had worked there at least one year between 1951 and 1983. Also included were electricians who spent at least 25% of their work time for at least one year over 1951 and 1983. There were 157 subjects. Mortality was assessed by developing observed vs. expected ratios (SMRs although not so stated) using calendar-year and age-specific (5-year age groups) mortality rates of Swedish males as the standard. Cancer incidence among the workers was compared to the incidence expected based on rates for Swedish males and for men in the county where the plant was located. An accounting for a latency period (5 or 10 years) was incorporated into the analyses and was calculated from the first year of exposure. For the examination of incidence, analyses were made for work $\geq$ 1 year and $\geq$ 5 years; these durations do not seem reflect a range.

No association of exposure with either mortality or incidence was observed. The results are shown in Table 3-29. The obtained ratios are similar to what is usually expected if a healthy worker effect is operative. Cancer mortality was not examined; there were three cancer deaths. The source of the mortality and incidence data was not stated, and it is not

TABLE 3-29. PERSON-YEARS AND OBSERVED AND EXPECTED ALL-CAUSE MORTALITY OR CANCER INCIDENCE BY LATENCY AND EXPOSURE DURATION FOR SELECTED SWEDISH MALE CHLORALKALI WORKERS, WITH EXPECTED VALUES BASED ON NATIONAL AND REGIONAL RATES FOR MALES

	Duration[a]	Latency	P Y	O	E_N	E_C	O/E
Mortality	-	≥ 5	2142	17	22	-	0.8 (0.4-1.2)[b]
	≥ 5	≥ 10	1272	14	18	-	0.8 (0.4-1.3)
Incidence	≥ 1	≥ 5	1990	6	8.6	7.7	0.8 (0.3-1.6)[c]
	≥ 5	≥ 10	1157	5	7.0	6.3	0.8 (0.3-1.9)

[a]Duration and latency in years, PY = person-years, O =observed, E = expected, E_N = expected values based on national rates, E_R=expected values based on county rates.
[b]95% confidence interval.
[c]O/E ratio computed here used expected values based on county rates.

SOURCE: Barregård et al., 1985.

clear if the subjects, including the cases, were still actively working. It is stated there were no losses to follow-up.

Static magnetic fields were measured in the factory in 1984, taken at 10, 110, and 170 cm above the floor. The fields ranged from 4 to 29 millitesla (mT) or 40 to 290 gauss (G). The cell room averaged 14 mT (140 G). The control or rectifier room averaged 6 mT. The authors noted that the concern of most other studies has been fields from AC. The chloralkali plant used DC, but the authors indicated that currents could be induced by the movement of people, and these currents could possibly be stronger than those induced by AC magnetic fields.

Detailed data on duration of cell room work, beyond the summary data presented, were not presented and might have been helpful in determining the extent of potential exposure. For example, it would be interesting to know how many men worked in the cell room only one year versus how many worked the most number of years. Follow-up in this study may also have been quite short since it is possible, from the definition of the cohort, that a worker may have been employed beginning in 1982 and followed for only a year. There was no information provided as to what the distribution of the length of follow-up was, i.e., how many were followed one year, how many followed two years, and so forth. Although electricians have been identified in other studies as a potential high-risk group, in the study it is possible that the inclusion of electricians may dilute any response, if one exists, because they spent less time in the cell room. It would have been useful to have compared the foremen's determinations as to who worked in the cell room with actual personnel records. The

foremen's determinations are certainly open to subjective bias, particularly considering that they were asked to recall for a 32-year period. Finally, the size of the cohort was extremely small (N=157) to be able to detect any significant effects

Törnqvist et al. (1986) investigated the incidence of cancer among a cohort of electric power linesmen and power station operators. The Swedish Cancer-Environment Registry was used. Occupational data were derived from the 1960 census. Record linkage with the Cancer Registry covered the period 1961-1979 which is an extension of the calendar period reported in the earlier study Wiklund et al. (1981). Cancers were coded according to the Seventh Revision of the ICD (ICD7).

There were 3358 power linesmen and 6703 power station operators in the electric power industry identified in the 1960 census. The workers were Swedish born men aged 20-64 at the time of the census. There were 236 cases of cancer recorded in the Cancer-Environment Registry among linesmen and 463 among the station operators between 1961-1979. After stratification in 5-year age groups and for county, expected values were "based on the cumulative incidence for all 986,408 men classified as blue collar workers by the census."

SMRs were calculated separately for the linemen and the station operators. Results for 13 cancer sites and all sites combined (ICD7:140-204) were given. For linemen, SMRs were elevated for stomach cancer (SMR=1.2, 90% CI=0.8-1.7), prostate cancer (SMR=1.2, 90% CI=0.9-1.5), kidney cancer (SMR=1.3, 90% Cl 0.8-2.0), cancer of the urinary organs, excluding kidney (SMR=1.2, 90% CI=0.8-1.8), skin cancer excluding melanoma (SMR=1.5, 90% Cl=0.7-2.6), cancer of the nervous system (SMR=1.5, 90% Cl=0.9-2.4), and leukemia (SMR=1.3, 90% CI=0.7-2.1). For all sites combined, the risk was slightly elevated with an SMR of 1.1 (90% Cl=1.0-1.2). All of these increases were small and for no site did the lower limit of the 90% confidence interval exceed unity. The authors did not state why they used 90% confidence limits rather than the more typically applied 95% limits.

SMR values were generally lower for power station operators. Again no increased SMR had a 90% confidence interval for which the lower limit exceeded unity, although the results for urinary cancer were marginal. Increased SMRs were seen only for laryngeal cancer (SMR=1.6, 90% Cl=0.9-2.7), testicular cancer (SMR=1.8, 90% Cl=0.8-3.6), kidney cancer (SMR=1.3, 90% CI=0.8-1.7), and cancer of the urinary organs excluding kidney (SMR=1.3, 90% CI=l.0-1.7). The overall SMR was 1.0 (90% CI=0.9-1.0).

This study has certain methodologic limitations. The calculation or estimation of the cumulative incidence of blue collar workers, used to derive expected values, was not explained. Although there were more than 10,000 individuals in the cohort with 19 years of follow-up, the work classification was made as of 1960; hence, the duration of employment for these individuals is not known. The age distribution of the cohort is not known. No attempts to examine issues pertaining to latency or dose-response were reported. For these reasons, this study neither confirms nor refutes the carcinogenicity of EM fields.

In summary, this study failed to show any statistically significant excess risks, although SMRs were modestly elevated for cancer at several specific sites. Generally, more excesses were seen for linemen than for power station operators, although this may be a function of age or other factors which are unknown. Cancers of the nervous system and leukemias, among other sites, were nonsignificantly elevated for linemen.

Gubéran et al. (1989) examined disability, mortality, and cancer incidence among painters and electricians who lived in the Canton of Geneva in Switzerland. The original purpose of the study was to compare the incidence of neuropsychiatric disabilities (known as “painters’ syndrome”) among painters and electricians, but the study was extended to investigate cancer mortality and incidence in both groups. The discussion here will focus on the cancer results for electricians.

The two work cohorts of men were identified from 1970 census files, traced through various registers, and included 1993 painters and 1992 electricians. There were 77 painters and 44 electricians excluded from this base population either because they were foreigners not included in population records, they had died or emigrated before follow-up was initiated, or errors were found in records due to misclassification of occupation, duplications, and so forth. After these exclusions, the study cohort was reduced to 1916 painters and 1948 electricians.

The electricians included electricity installers and repairmen, telephone installers, linemen and cable jointers, and car electricians. Electrical and electronic fitters and assemblers as well as radio and television repairmen were not included.

The 14-year follow-up period included the calendar years from January 1, 1971, to December 31, 1984. The authors did not present detailed data on follow-up. The two cohorts had a large proportion of foreigners, i.e., non-Swiss workers. The nationalities comprising these subgroups were not described. There were 763 foreign painters (39.8% of the painter

cohort). Of these, 230 (30%) left Switzerland and were lost to follow-up. This loss represents 12% of the total painter cohort, There were 649 foreign electricians (33.3% of the electrician cohort). Of these, 174 (27%) left Switzerland and were lost to follow-up, This loss represents 8.9% of the total electrician cohort. Only 13 Swiss painters and 31 Swiss electricians emigrated; all but one electrician could not be traced and were included in the study.

Coded death certificates were provided by the national office in Switzerland responsible for vital statistics. Coding was according to the Eighth Revision of the ICD. Cause of death for 10 deaths occurring abroad was obtained from various informants in addition to death certificates. Incident cases were identified from the General Cancer Registry.

Expected deaths and expected cases of cancer were calculated from regional rates, e.g., the Canton of Geneva. Standardized mortality ratios and standardized incidence ratios (SIRs) were developed. One-sided statistical significance was tested under the Poisson distribution. Ninety percent confidence intervals were calculated for SMRs and SIRs. Use of 90% limits is appropriate but somewhat atypical. Expected death rates and incidence rates in electricians were calculated based on 24,807 and 23,387 person-years, respectively.

Among electricians, no cause of death, including all causes together and specific types of cancer, was found to be significantly greater than expected. Deaths from several cancers were, however, elevated, i.e., all malignant neoplasms (SMR=114), esophagus (SMR=176), stomach (SMR=130), intestine/rectum (SMR=140), pancreas (SMR=143), larynx (SMR=273), brain (SMR=154), Hodgkin's disease (SMR=250), and leukemias (SMR=143). All of these excesses were based on less than six cases. A similar pattern was seen for the calculated SIRs which were generally lower than the SMRs. The incidence and mortality of lung cancer were not elevated.

Although this study failed to show any significant excesses in cancer mortality or cancer incidence, it has a number of methodologic limitations: (1) follow-up yielded 24,807 person-years of observation, which may not be sensitive enough to observe excesses in lymphomas and brain cancers; (2) 14 years of follow-up may not be long enough for the latency of these cancers; (3) no age distribution of the study cohort was provided, thus, it is not known whether this cohort had more younger workers or otherwise; (4) there were no data available on actual exposures. The occupation was identified from the 1970 census. Therefore, the length of employment was not known. The above factors preclude dose-response or latency analyses. Lastly, given potential ethnic, national, or regional

differences in mortality and incidence, the relatively high withdrawal rates among foreign workers, and use of Geneva rates as the standard schedule of rates for certain analyses, it is questionable whether the non-Swiss workers should have been included in the cohorts. The benefit of increased sample size could be offset by the introduction of biases. Additional analyses for nationality subcohorts or controlling for nationality might have indicated whether there was a problem. However, it is interesting to note that higher cancer risks found in other studies were also seen in excess in this study.

Matanoski et al. (1989) examined cancer incidence among New York Telephone Company employees. By limiting the population to those actively working, the study was designed to examine risks in younger persons; the mean age was 40 years. Cases were identified through the New York State Cancer Registry. Person-years were accumulated and events were counted if there was confirmation that an individual was still employed during the period of follow-up, 1976-1980. There were 50,582 male employees who accumulated 206,067 person-years.

Two standard schedules of rates were used to develop SIRs. Age-specific New York cancer rates and cancer rates of nonline workers for (comparison to line workers) applied to person-years to determine expected numbers of cable splicers, central office technicians, outside plant technicians, and workers on installation, maintenance, and repair. Statistical significance was evaluated at the 95% level under the Poisson distribution.

In the analysis that used rates of New York State males as the standard schedule of rates, the SIRs for all cancers combined for all men and across job types were less than unity, except for cable splicers (see Table 3-30). This is likely demonstrative of a healthy worker effect. Similarly, for all men, SIRs at specific cancer sites were less than 1.0, except for acute and unspecified leukemia, considered together, and for breast cancer. There were only two cases at both sites, but the result for breast cancer in males is of interest. Excesses do occur among specific job categories, although none are statistically significant. Of the 16 cancer end points examined, all but four-multiple myeloma, breast cancer, bladder cancer, and stomach cancer-- were in excess for cable splicers. With respect to these four end points, there were no cases of multiple myeloma, stomach cancer, or breast cancer, and the one bladder cancer case was less than expected,

Cancer among certain types of workers was also examined with respect to rates in nonline workers to serve as an internal control (see Table 3-31). Such an analysis enhances

TABLE 3-30. STANDARDIZED INCIDENCE RATIOS (AND NUMBER OF CASES) FOR SPECIFIC CAUSES OF CANCER BY TYPE OF WORK AMONG MALE NEW YORK TELEPHONE EMPLOYEES: 1976-1980, STANDARD: NEW YORK STATE MALE RATES

	All Men	All Line	Cable Splicer	Central Office	Outside Plant	Install Repair
All cancers	0.81* (391)	0.83* (265)	1.27 (40)	0.88 (96)	0.86 (9)	0.67 (86)
Gastrointestinal	0.85 (107)	0.83 (68)	1.30 (10)	1.19 (24)	1.92 (5)	0.60 (20)
Oral	0.66 (20)	0.71 (14)	1.03 (2)	1.36 (9)	1.61 (1)	0.12* (1)
Stomach	0.58 (9)	0.88 (9)	- (0)	1.13 (4)	3.03 (1)	0.97 (4)
Colon	0.63 (36)	0.77 (20)	2.11 (5)	0.65 (6)	2.40 (2)	0.50 (6)
Lung	0.76* (85)	0.87 (63)	1.20 (8)	0.75 (19)	0.44 (1)	0.78 (23)
Leukemia	0.77 (12)	0.88 (9)	2.65 (3)	0.58 (2)	- (0)	0.96 (4)
Lymphoid	0.87 (5)	1.34 (5)	5.18 (2)	0.79 (1)	- (0)	1.32 (2)
Acute & Unspecified	1.16 (2)	1.76 (2)	7.14 (1)	- (0)	- (0)	2.14 (1)
Chronic	0.75 (3)	1.15 (3)	4.17 (1)	1.11 (1)	- (0)	0.95 (1)
Myeloid	0.85 (7)	0.74 (4)	1.59 (1)	0.56 (1)	- (0)	0.90 (2)
Brain	1.00 (13)	0.70 (6)	2.00 (2)	1.42 (4)	- (0)	- (0)
Lymphomas	0.79 (25)	0.86 (18)	1.96 (5)	1.18 (8)	- (0)	0.35 (3)
Multiple Myeloma	0.69 (4)	1.07 (4)	- (0)	0.78 (1)	8.40 (1)	1.30 (2)
Breast	1.44 (2)	- (0)	- (0)	6.48 (2)	- (0)	- (0)
Prostate	0.85 (21)	1.06 (17)	2.45 (3)	1.45 (9)	1.95 (1)	0.49 (3)
Bladder	0.66 (21)	0.53 (11)	0.51 (1)	0.70 (5)	- (0)	0.36 (3)

*Statistically significant at the 95% level, two tail, Poisson distribution.

TABLE 3-31. STANDARDIZED INCIDENCE RATIOS (AND NUMBER OF CASES) FOR SPECIFIC CAUSES OF CANCER BY TYPE OF WORK AMONG MALE NEW YORK TELEPHONE EMPLOYEES: 1976-1980, STANDARD: NONLINE WORKERS

	Cable Splicer	Central Office	Outside Plant	Install Repair
All cancers	1.81* (40)	1.15 (96)	1.15 (9)	0.91 (86)
All gastrointestinal	1.76 (11)	1.02 (28)	2.05 (5)	0.84 (24)
Oral	1.38 (2)	2.45* (9)	2.31 (1)	0.20 (1)
Stomach	- (0)	# (4)	# (1)	# (4)
Colon	2.23 (5)	0.54 (6)	214 (2)	0.55 (6)
Lung	2.16 (8)	1.26 (19)	0.73 (1)	1.41 (23)
Leukemia	7.00* (3)	1.07 (2)	- (0)	1.77 (4)
Lymphoid	# (2)	# (1)	- (0)	# (2)
Myeloid	2.33 (1)	0.53 (1)	- (0)	0.89 (2)
Brain	1.79 (2)	0.90 (4)	- (0)	- (0)
Lymphomas	3.59* (5)	1.94 (8)	- (0)	0.53 (3)
Multiple myeloma	- (0)	# (1)	# (1)	# (2)
Breast	- (0)	# (2)	- (0)	- (0)
Prostate	4.38 (3)	3.48* (9)	4.54 (1)	1.02 (3)
Bladder	0.60 (1)	0.78 (5)	- (0)	0.40 (3)

* Statistically significant at the 95% level, two tail, Poisson distribution.
\# No cases expected based on nonline rates.

comparability and minimizes the healthy worker effect that can be seen in working populations when compared to general populations. In this analysis, SIRs for cable splicers were elevated across many sites. Total cancers, leukemias, and lymphomas were significantly in excess. SIRs for installers and repairers were generally not elevated. Few cancers were observed for workers whose work was classified as “outside plant.” Central office workers also demonstrated an excess of cancer at most sites, and oral cancer was significantly in excess. The breast cancers were all found in this group of employees. SIRs could not be calculated for breast cancer among central office workers because expected values were so low as to be virtually zero.

Exposure was assessed for the different job functions by making measurements over the workshift of a sample of U.S. telephone workers. Of the five job groupings examined, the time-weighted average magnetic flux density was highest for cable splicers (4.3 mG or 0.43 µT). This group, with the highest average magnetic field exposures, exhibited the highest risk ratios. The second highest time-weighted average magnetic field levels were found for central office employees (2.7 mG or 0.27 µT). Risks for various sites were also elevated in this group, although leukemias were not found to be in excess. The mode of exposure is different in these central office workers; that is, the type of work (call switch rooms) involved brief but continuous exposure to high spiked fields (Personal communication with G. Matanoski at DOE/EPRI contractor’s review, November 1990). The two breast cancer cases found in the study were in this group. Breast cancer is extremely rare for males. It is interesting to note that Stevens (1987) hypothesized an increased risk for breast cancer with exposure to EM fields, based on laboratory results pointing to effects on the pineal gland and melatonin production. Average exposures for the other types of jobs (“outside plant,” installation and repair, and miscellaneous [supervisor, clerk, etc.]) were similar (1.6-1.7 mG or 0.16-0.17 µT).

This study was well-designed, appropriately analyzed, and presented improvements in exposure assessment. Exposure measures for types of work are given. Although the work categories are somewhat broad, an apparent dose-response relationship was seen, i.e., risks are highest among the groups most highly exposed. Also, different modes for delivery of exposure seem to produce differential risks which, if not yet confirmed, serve to illustrate the difficulties in evaluating exposure- and dose-response characteristics of EM fields. Mortality comparisons using both external (New York State cancer rates) and internal (New York Telephone Company nonlinesmen) comparison groups. Excesses were heightened with the

internal comparisons. The study has a relatively short follow-up period which may not be critical, however, if EM fields have a promotional effect on cancer. There are small numbers in some instances. The primary weakness of the study is that potentially confounding exposures could not be evaluated.

3.3.2.2.2. Cancer of the Hematopoietic System. As part of an update of occupational mortality for Washington State, Milham (1982, 1985a) noted excess deaths from leukemia among men who worked with electric and magnetic fields. PMRs, standardized by age and year of death, were calculated for Washington State male residents aged 20 years or more, from 1950 to 1979, and for 158 cause-of-death categories and 218 occupational classes. Ten occupational classes with presumed exposure to electric and magnetic fields exhibited elevated PMRs for all leukemia [Seventh Revision of the ICD (ICD7):204], ranging from 111 to 259. PMRs for three of the these occupations (electricians, power-station operators, and aluminum workers) were statistically significant based on expected values for Washington State white males for all leukemia (ICD7:204) and for acute leukemias (ICD7:204.3). Also presumed to have electromagnetic exposures, the welders and flame cutters had a PMR of 67.

Wright et al. (1982) evaluated leukemia cases in men with jobs involving exposure to electric and magnetic fields, using data from a population-based registry, the Cancer Surveillance Program, in Los Angeles County, California. Occupational information was obtained at the time of diagnosis. Categories for this analysis followed those used by Milham. Proportional incidence rates (PIRs) were computed for all leukemias, acute leukemias, and AML for white males in Los Angeles County from 1972 to 1979. There was a general trend for increased PIRs in all the 12 occupational groups used, including all jobs combined. For all groups, PIRs were highest for AML. Statistically significant PIRs were found for power linemen (acute leukemia and AML), for telephone linemen (AML), and for all jobs combined (acute leukemia and AML).

McDowall (1983) evaluated the proportionate mortality of males, age 15-74 in England and Wales, using 1970-1972 data from a report on occupational mortality. Electrical occupations were broken down into 10 occupational subgroupings. PMRs were computed for all leukemias (ICD8):204-207), lymphocytic leukemias (ICD8:204), acute lymphocytic leukemias (ICD8:204.0), myeloid leukemias (ICD8:205), and acute myeloid leukemias (ICD8:204.0). Considering all electrical occupations together, the PMRs were not significantly elevated for any disease group. Expected values were based on all Welsh and English men aged 15 to 74

in 1970 to 1972. But McDowall noted consistently elevated PMRs among electrical engineers (noted as “so described”), telegraph radio operators, electrical engineers (professional), and electronic engineers (professional). The PMRs were most increased for all myeloid leukemia and acute myeloid leukemia. Lymphocytic leukemia was elevated in electricians. The results of statistical tests of significance or confidence intervals were not given.

In the same paper, the results of a case-control study were also given (McDowall, 1983). Cases were the 537 deaths occurring in England in 1973 among males age 15 or more with AML given as the underlying case of death. Controls were randomly selected from males age 15 year or older dying from all causes of death, excluding leukemia, in 1973 and then matched within 5 years of age. Two controls were matched per case (537 cases, 1074 controls).

Seven occupational groups were defined, including “all electrical occupations” and “all electrical occupations plus men in any occupation engaged in an electrical or telecommunication industry.” These were identified from death entries rather than from the occupational data used in the PMR analyses. The results were stated to be “relative risks” rather than “odds ratios.”

These risks were elevated in all seven occupational groups and ranged from 1.6 to 4.0. Except for the two summary classifications, the number of cases was small, resulting in broad 95% confidence limits that spanned 1.0. Confounding exposures within the various electrical occupations were not examined. In addition, some individuals were classified as belonging to more than one occupational group, but it is not stated whether deaths were counted in more than one group. If true, the alternatives of limiting deaths to one unique job category could substantially change the risk ratios.

Coleman et al. (1983) evaluated the incidence of leukemia among men aged 15 to 74 in 10 types of electrical occupations in southeast England for the period 1961-1979. Data were taken from the South Thames Cancer Registry, and “proportional registration ratios” (PRRs) were calculated. Job classification codes were based on hospital record data and were similar to the groups analyzed by McDowall (1983). Since only 88% of tumor reports could be assigned a job code, presumably the remaining 12% were excluded from the study. Cancer sites were coded according to the 8th Revision of the ICD and were all leukemias (ICD8:204-207), acute lymphocytic leukemia (ICD8:204.0), chronic lymphocytic leukemia, acute myeloid leukemia (ICD8:205.0), and chronic myeloid leukemia. The chronic leukemias included all cases specified as chronic, plus cases unspecified as acute or chronic. In a matrix

of 40 calculated PRRs, the vast majority exceeded unity; only seven ratios were less than one, and seven PRRs were significantly elevated, including the ratio for all leukemias for all occupational groups combined. Within the occupational groups, no pattern or particular group stands out as evidencing increased incidence.

Another study was conducted in New Zealand by Pearce et al. (1985). A case-control design was used and drew on Cancer Registry data - 546 male leukemia cases registered during 1979-1983 aged 20 years or more. Four male controls per case were matched on age registration year to yield 2184 controls. Eight occupational groups with presumed exposure to electric and magnetic fields were defined. The authors believed the number of cases by occupation (18) were too small to warrant investigation of specific leukemia cell types. Over all occupations, an excess of leukemia was seen, but it was not statistically significant (OR = 1.70, 95% Cl = 0.97-2.97). A significant excess was seen, however, for electronic equipment assemblers (OR = 8.17) and radio and television repairers (OR = 4.75). In a later report (Pearce et al., 1989), it was noted that these job categories had been miscoded and should have been labelled as radio and television repairers and electricians, respectively. There were no cases among electronic equipment assemblers.

Calle and Savitz (1985) examined mortality from leukemia among 10 occupational groups, using data from the state of Wisconsin. The occupational groups were those used by Milham and Wright, e.g., electrical engineers, radio and telegraph operators, electricians, linemen (power and telephone), television and radio repairmen, motion-picture projectionists, streetcar and subway motormen, power station operators, and welders and flamecutters. The source of the occupational information was not stated; one might assume that the information was taken from death certificates. Deaths were Wisconsin white men, 20 years of age or older, who had died between 1963 and 1978. Proportional mortality ratios were calculated for each occupation using all deaths from 1963 to 1978 among Wisconsin white males aged 20 years or more.

Mortality from all leukemia [41 cases; Seventh Revision of the ICD (ICD7):204.3] was presented. Excess mortality was not consistently observed over all 10 occupational groups. No cases were found for several groups. For all leukemias, the highest PMR (2.35) was seen for radio and telegraph operators, and this result was statistically significant. The PMR for electrical engineers (1.86) was also significantly elevated. Two other occupational groups exhibited elevated PMRs that were not statistically significant. The two groups were linemen

and electronics technicians. For acute leukemia, again, the largest PMR (3.0) was seen for radio and telegraph operators, but the result was not statistically significant. The PMR for electrical engineers was also again elevated (2.57) and was statistically significant. Mortality for acute leukemia was elevated among linemen (1.43) and welders and flamecutters (1.04); neither was statistically significant.

In a case-control study, Gilman et al. (1985) evaluated leukemia in a population of 19,000 U.S. male coal miners. This population of workers was identified as potentially exposed to EM fields because power distribution lines are strung overhead in mines, stepdown transformers and converters provide power (600-2000V) to mining equipment, and transportation is provided by electrically-operated trolleys. The miner population database had previously been studied by the National Institute for Occupational Safety and Health (NIOSH) and had been divided into four cohorts based on length of follow-up for mortality, e.g., 5, 10, and 15 years, and the fourth was an autopsy cohort.

Forty cases of leukemia [Eighth Revision of the ICD (ICD8:204-207)] were identified among 6066 death certificates. Each case (white males) was matched to four controls within the same cohort who died of causes other than cancer or accidents. Matching was on age at death and year of birth (± 3 years). No information on EM-field exposure was known. Length of employment in underground mining was used as a surrogate of exposure.
EM-field-exposed workers were defined as those miners with underground employment of 25 years or more. Miners who had worked less than 25 years were classified as unexposed. Cigarette smoking and work history information had been collected via questionnaires when the cohorts were initially ascertained. Although not clearly stated, it also appears that radiological examinations for coal dust deposition in lungs had been performed to define coal work pneumoconiosis. Odds ratios were calculated, and statistical significance was assessed either by the Chi-Square or the Fishers Exact Test.

Excess risk for death from leukemia for multiple cell types was found for underground mining employment of 25 years or more, taken as a surrogate of potential EM-field exposure. Of observed excesses, statistical significance was achieved for all leukemias (ICD8:204-207; OR=2.53), chronic leukemias (ICD8:204.1, 205.1, 206.1, 207.1; OR=8.22), chronic lymphocytic leukemia (ICD8:204.1; OR=6.33), and myelogenous leukemia (ICD8:205; OR=4.74). No risk was observed with respect to cigarette smoking or pneumoconiosis for all leukemias

considered together. The only risk estimate that was depressed was for acute lymphocytic leukemia (ICD8:204.0; OR= 0.63); only two cases were identified.

In an extension of an earlier investigation, Flodin et al. (1986) have reported the results of a case-control study in Sweden that examined the incidence of acute myeloid leukemia in relation to various types of exposure. The chief exposure of interest was background levels of ionizing radiation. Cases were persons of Swedish ethnicity aged 20 to 70 years, diagnosed with acute myeloid leukemia between 1977 and 1982 from five hospitals. In addition, the subjects had to be alive in the catchment area of the diagnosing hospital and be alive and able to answer a questionnaire; therefore, very ill or deceased cases were excluded. A total of 59 cases met the study criteria.

Two sets of control subjects were elaborated. The first set was drawn from the general population and matched (four controls per case) with respect to sex, age within 5 years, and parish residence. There were 236 control subjects in this set. The second set was randomly selected from the general populations of the hospitals' catchment areas and was restricted to adults aged 20 to 70 years. This series was comprised of 118 individuals (two controls per case).

Information about various exposures was obtained via a questionnaire that was apparently self-administered, The questionnaire addressed medical care, especially the use of drugs, x-ray treatment, and x-ray examinations; occupational exposures; chemical and solvent exposures; smoking habits; house building material to evaluate background ionizing radiation exposure by means of a gamma radiation index; and other environmental and leisure time exposures, Approaches to account for dose and/or duration of exposure were applied.

The authors stated that risk estimates were similar with respect to the two comparison groups; therefore, they presented the results of pooled analyses,

An increased risk for acute myeloid leukemia was seen for a history of long-term residence or work in concrete buildings, x-ray exposure and radiological work. No excess risk was noted for pesticide exposure, cigarette smoking, engine exhausts, plastics or rubber chemicals, the occupation of painting, and contact with cats or cattle. However, weak but nonsignificant increases in risk were observed for some of the above agents when long-term exposure or latency was considered, i.e., 25 years of contact with cattle, at least 5 years of exposure to motor gasoline, and a 25-year induction-latency for pesticide exposure.

Of chief interest to this review are the results with respect to potential exposure to EM fields. Electrical workers were found to have an elevated risk for the development of acute myeloid leukemia. Electrical work was defined according to Swedish occupational codes and comprised the following subgroups: electrical technicians (code 002), electrical workers (code 755), and computer and telephone mechanics (code 764). The logistic rate ratio was 3.8 for electrical work with 8 cases and 14 controls.

Concern has been expressed in the literature that electrical work can also involve work with or exposure to chemicals, including solvents and the observed risks from EM fields either may represent an interaction with chemicals or may represent an indirect measure of a true underlying risk posed by chemicals alone. In this study, separate analyses for chemical exposure found a significantly elevated risk for exposure to styrene (minimal subjects, however) but not to any other solvents. Use of psychopharmacological drugs also posed an increased risk. Joint analyses of multiple exposures, except with respect to gamma radiation, were not reported.

Stern et al. (1986) conducted a case-control study of leukemia mortality among on-shore workers at the Portsmouth Naval Shipyard in New Hampshire. The cases and controls were drawn from a previously developed cohort of 24,545 white males employed between January 1, 1952, and August 15, 1977. The goal of the study was to determine if there was an association between death from leukemia and occupational exposure to ionizing radiation or organic solvents (Table 3-32).

Cases were defined as all persons who had died by the end of 1980 with an underlying or contributory cause of death of leukemia. Cases were not included if medical records could not confirm death certificate coding for leukemia. Controls were selected from the rest of the work force cohort after excluding persons who had died from hematopoietic or lymphatic malignancies, Controls were matched to cases. Controls had to have lived as long as the cases. Matching criteria were the absolute difference in years between birth dates, dates first employed, and duration of employment. The differences in these three values between cases and potential controls were summed and used as a score. The four persons with the lowest score were selected as controls to a given case. There were 53 leukemia deaths and 212 matched controls. The authors stated that the 4:1 matching ratio yielded 80% power for detecting a true relative risk of 2.2.

TABLE 3-32. BACK GROUND INFORMATION ON SHIPYARD WORKERS
AT PORTSMOUTH NAVAL SHIPYARD, NEW HAMPSHIRE

		Cases	Controls
Birth year	Mean	1904	1904
	Range	1892-1939	1692-1940
Year employed	Mean	1940	1940
	Range	1914-1963	1914-1963
Duration of employment (yrs)	Mean	22	22
	Range	0-47	0-46
Average number of jobs		1.96	2.08

SOURCE: Stern et al., 1986.

Job history information was coded for cases and controls. Shops and jobs were classified and grouped by the commonality of processes, materials handled, and occupational exposures. Information was derived from shipyard staff, personnel records, a NIOSH industrial hygiene survey, and historical industrial hygiene data from the shipyard. Both shop and job codes were developed per work assignment per person. There was no exposure monitoring data for individuals except radiation film badges for certain workers.

Mantel-Haenszel odds ratios were calculated for the evaluated exposure groups. All leukemias and specific cell type were examined. To control for potentially confounding exposures and to evaluate interactions, a conditional logistic regression model was also employed.

In the Mantel-Haenszel or univariate analyses for ionizing radiation and (likely) solvent exposures, certain odds ratios were elevated, especially for solvent exposure, but no estimate was statistically significant. If at least three cases had ever worked in a given job or shop, those job types and shops were also examined, with comparisons made to employees never in the subject job or shop. In these analyses when all leukemias were considered together, several job types and shops yielded odds ratios greater than 1.0, but the largest and only significant odds ratios were obtained for the job of electrician and work in the electrical shop. The effect was not as strong when myeloid leukemia and lymphatic leukemia were examined separately but the estimated risks remained elevated. Astatistically significant odds ratio (13.0) for lymphatic leukemia for the class of supervisors, regardless of job, was observed.

The odds ratios for myeloid leukemia (1.53) and for all leukemia combined (2.36) were elevated, but not significantly. The authors noted that 5 of the 13 supervisors who died of leukemia had at some time worked as electricians or welders. (Elevated odds ratios were also observed for welders and the welding shop.) Tables 3-33 and 3-34 give partial results for some of the jobs and shops that exhibited the highest risk estimates,

The data were also evaluated using conditional logistic regression analyses. Based on the previous analyses, electrical and welding jobs were included in the model. Again, results for ionizing radiation and solvent exposures were not strong. In analysis of categorical variables, the jobs of electrician and welder again demonstrated significantly elevated odds ratios. Exposure was also examined as a continuous variable using years as a welder or electrician. Similar results were obtained although the magnitude of the risk estimates were not as large as in the categorical analysis and the odds ratios for electricians only were significant for all leukemias combined.

Many jobs and shops were evaluated and so the results for electricians and welders could be a chance occurrence. Yet, the results were similar and consistent when examined from the two perspectives of job type versus shop and across all methods of analysis,

This study had well-developed work history information derived from various sources although no measurement or exposure data were available except for ionizing radiation film badges. The work history information enabled evaluations of various types of workplace exposures by job or shop, of potential confounders, and of interactions, While different jobs may have multiple exposures that cannot be fully isolated, the analyses point to significantly elevated risk of leukemia for electricians and electrical work and, to a lesser extent, welders, Where predominating work with solvents could be identified, the risks were elevated but not significantly, and the excesses were usually less pronounced than those for electricians and welders,

Another study has taken advantage of the information available from Sweden's system that links cancer incidence data from the National Swedish Cancer Registry with census data, including employment information. Incidence data for 1961-1979 is linked to occupational data from the 1960 census. Linet et al. (1988) used the Swedish Cancer-Environment Registry (CER) to investigate leukemia and occupation (Table 3-35). The CER uses the Seventh Revision of the ICD. For purposes of this analysis, the leukemia cases were recoded into the currently recognized categories of acute lymphocytic (ALL), chronic lymphocytic (CLL), acute

TABLE 3-33. RESULTS OF MANTEL-HAENSZEL ANALYSIS OF LEUKEMIA FOR SELECTED JOBS AND SHOPS (WITH THE HIGHEST RISK ESTIMATES) FOR SHIPYARD WORKERS

	All Leukemias			Myeloid Leukemia			Lymphatic Leukemia		
	Cases	OR	95%CI	Cases	OR	95%CI	Cases	OR	95%CI
Jobs Ever Held									
Electrician	11	3.00*	1.29-6.98	6	2.33	0.77-7.06	5	6.00*	1.47-24.45
Carpenter	7	2.50	0.91-6.90	4	2.50	0.71-8.83	3	3.33	0.56-19.83
Supervisor	13	2.36	0.95-6.90	8	1.53	0.54-4.40	5	13.00*	1.31-28.96
Welder	7	2.25	0.92-5.53	6	3.83*	1.28-11.46	0	---	---
Sheetmetal	4	2.14	0.64-7.19	2	3.50	0.49-24.96	2	2.00	0.41-9.83
Shipfitter	11	1.54	0.67-3.54	8	1.71	0.62-4.72	3	2.00	0.41-9.76
Engineer	6	1.40	0.53-3.70	3	1.00	-	3	2.20	0.51-9.44
Shops Ever Worked									
Electrician	10	2.57*	1.11-5.96	5	2.12	0.64-7.10	5	3.80*	1.13-12.76
Welding	7	2.25	0.92-5.53	6	3.83*	1.28-11.46	0	---	---
Public Works	3	2.40	0.60-9.61	1	4.00	0.31-51.79	2	2.67	0.48-14.89
Sheetmetal	4	2.08	0.64-7.19	2	3.50	0.49-24.69	2	2.00	0.35-12.35
Shipfitting	14	1.53	0.71-3.31	8	0.21	0.46-3.18	4	1.83	0.39-8.54
Woodworking	4	1.30	0.037-4.41	2	1.00	---	2	3.00	0.27-33.35
Rigging	6	1.00	---	1	0.22	0.02-1.75	4	2.60	0.57-11.86
Electrical	7	0.89	0.37-2.11	4	1.44	0.38-5.55	2	0.40	0.10-1.53

*= Significant.
OR=odds ratio, CI=confidence interval. There were 11 job types and 14 shops listed in the paper.

SOURCE: Stern et al., 1986.

TABLE 3-34. RESULTS FROM CONDITIONAL LOGISTIC REGRESSION ANALYSIS FOR SOLVENT ELECTRICAL, AND WELDING WORK, TREATED EITHER AS A CATEGORICAL OR CONTINUOUS VARIABLE (YEARS USED AS INDEX OF EXPOSURE), AMONG SHIPYARD WORKERS

	All leukemias		Myeloid leukemias		Lymphatic leukemia	
Exposure	OR	95% CI	OR	95% CI	OR	95% CI
Categorical [a]:						
Solvent job	2.32	0.85-6.29	2.56	0.58-11.35	1.99	0.46-8.67
Electrician	3.39*	1.40-8.18	3.03	0.92-10.03	6.11*	1.38-27.10
Welder	3.19*	1.09-9.37	6.23*	1.64-23.64	---	---
Continuous [b]:						
Yrs in solvent job	1.82	0.93-3.58	2.16	0.79-5.95	1.53	0.56-4.22
Yrs as electrician	1.67*	1.01-2.78	1.57	0.83-2.96	1.90	0.89-4.07
Yrs as welder	2.86*	1.02-8.04	5.53*	1.52-20.09	---	---

[a]Considered if "ever worked" in these jobs.
[b]Calculated from average "exposure." Averages were 8.59 years for solvent jobs, 6.46 years for electricians, and 13.16 years for welders.
*=significant. OR=odds ratios, CI=confidence interval.

SOURCE: Stern et al., 1986

TABLE 3-35. SELECTED STANDARDIZED INCIDENCE RATIOS (SIRS) FOR LEUKEMIAS BY MAJOR DIVISION OF INDUSTRY AND OCCUPATION, BY GENERAL MANUFACTURING INDUSTRIES, AND BY GENERAL CRAFTSMEN-TRADESMEN OCCUPATIONS, AMONG SWEDISH MALES 1961-1979

	ALL		CLL		ANLL		CML	
	Cases	SIR	Cases	SIR	Cases	SIR	Cases	SIR
Industry:								
Electric, gas, water, and sanitary services	1	0.4	44	1.3	26	1.0	14	1.0
Transportation and communications	16	1.3	151	0.9	141	1.1	84	1.1
Occupation:								
Transport and communication workers	12	1.0	126	0.9	129	1.0	78	1.0
Manufacturing Industry:								
Machine and electrical	13	1.1	164	1.0	108	0.8	68	0.9
Craftsmen-Tradesmen Occupation:								
Toolmakers, machinists, plumbers, and welders	23	1.5	178	1.0	153	1.0	100	1.0
Electrical workers	4	1.0	52	1.2	42	1.1	27	1.1
Electrical line workers	NG	NG	13	1.9[a]	8	1.4	NG	NG

[a] $p < 0.05$

NG = not given.

SOURCE: Linet et al., 1988.

nonlymphocytic (ANLL), and chronic myelocytic (CML). Standardized cumulative incidence ratios were computed. Expected values were derived by applying 5-year birth-cohort, sex-, region-, and type-specific leukemia incidence rates for Swedish males for 1961-1979 to 5-year birth cohort-and sex-specific distributions of industrial and occupational groups. The 1960 Swedish census employment classifications, which followed international standards of the United Nations International Labor Office, were used to define industrial and occupational groups.

There were 5351 leukemia cases identified (ALL=3%, CLL=45%, ANLL=33%, and CML=19% of the total cases.) Although many results were presented, only the results of possible pertinence to this document will be discussed. It was found that electrical line workers had a significantly increased risk of CLL (OR=1.9, 13 cases). The authors noted that this result differs from other studies in that other studies had reported an excess risk from ANLL, not CLL. Linet et al. (1988) also found ANLL to be elevated among electrical line workers (OR=1.4, 8 cases), but the excess was not statistically significant. The authors noted that, in Sweden, electrical line workers have exposure to many solvents and other chemicals such as creosote, lead, isocyanates, and silicon. Significantly increased risk was not seen in the broader occupational category of electrical workers but all odds ratios were 1.0 or greater.

The authors pointed out recent data indicating that underreporting of leukemia cases to the CER may be 18%. They also noted that the lack of significant association in the study by Tornqvist et al. (1986) may be due to restricting the study population to workers 20 to 64 years of age; CLL incidence is highest in the oldest age groups. Törnqvist et al. (1986) also used the CER.

Juutilainen et al. (1988) examined cancer incidence in Finnish males employed in electrical occupations. Data were taken from the Finnish Cancer Registry and the Central Statistical Office of Finland. The eight occupational groupings examined were electricians (indoor installation), electric fitters and repairmen, telephone installers and repairmen, linemen and cable jointers, electric and electronic equipment assemblers, and the residual, other electrical occupations. Standardized incidence ratios (SIRs) were calculated using rates for all Finnish males as the standard schedule of rates. The authors stated that other occupational groups, similar in socioeconomic status to electrical occupations, were also as a reference, but no information on these groups was presented in the paper. Only results for leukemia were

reported. Neither the applicable ICD codes nor the time period under study were stated. This study seems to have been reasonably designed but is poorly reported.

Only 17 leukemia cases among all electrical occupations were identified, and the SIR was 1.23; confidence limits or statistical test results were not given. Bearing in mind that the observed number of cases is very small, the SIRs for specific electrical occupations were generally elevated, or else there were no observed cases. The highest SIR (3.13) was determined for linemen and cable jointers, considered together. There were four cases in this group. The residual grouping of all other electrical occupations yielded an SIR of 2.63, but there was only one case.

Pearce et al. (1989) examined the incidence of cancer, especially leukemias, among New Zealand electrical workers in a case-control study using a population-based cancer registry. Cases were all male patients aged 20 years or older at the time of their registration in the New Zealand Cancer Registry. For each person, the current or most recent occupation was described in Registry files and coded according to the New Zealand Standard Classification of Occupations. Analyses were restricted to the 19,904 eligible registrants for whom there was occupational information. This number is 80% of all eligible registrants (N=24,762). This population overlaps with a previously studied population which was registered between 1979 and 1983 (Pearce et al., 1985). The percent of cases for whom occupation was available ranged from 73% to 92%, but there did not seem to be any unusual underreporting of occupation by cancer site. Reporting of occupational information was typically available for 80% to 84% of the cases within specific cancer types. Occupational information was available for 82% of all leukemia cases. The occupations examined were electrical and electronic engineers, electrical and electronic technicians, electrical fitters, electronic equipment assemblers, radio and television repairers, electricians, telephone installers, linemen, and power station operators.

Controls were males within the population of 19,904 who had a diagnosis of any cancer site other than the particular site under test. This study, thus, represents a series of many case-control studies conducted within the Registry population of adult males. The authors stated that age-adjusted odds ratios were estimated by the Mantel-Haenszel method and confidence intervals were calculated using Miettinen's approximate method.

Odds ratios were elevated for all electrical workers, considered together, for several cancer sites. These sites were buccal cavity and pharynx (OR=1.25), stomach (OR=1.06), colon

(OR=1.06), rectum (OR=1.16), liver (OR=1.52), larynx (OR=1.23), soft tissue sarcoma (OR=1.26), urinary bladder (OR=1.00), brain (OR=1.01), leukemia (OR=1.62), and a residual category of miscellaneous sites (OR=1.28). The odds ratio for leukemia was the only risk estimate for which the 95% confidence interval exceeded unity (1.04-2.52). Brain cancer was not significantly in excess in this composite group.

More specific types of electrical jobs, previously mentioned, were also examined with respect to leukemia (see Table 3-36). The odds ratios were elevated for all specific job types except equipment assemblers (no cases), telephone installers (no cases), and a residual category. The 95% confidence interval encompassed unity for the odds ratios for radio/television repairers and, marginally, for power station operators. The jobs of motion picture projectionists and welders were not specifically identified in the tables, but the authors noted that there was one case of leukemia among seven projectionists (OR=7.8, 95% CI=1.23-49.46) and no cases among 44 welders. Brain cancer was not elevated in the total group of electrical workers but was elevated among electrical engineers (OR=4.74, 95% CI=1.65-13.63) and electricians (OR=1.91, 95% CI=0.84-4.33).

Risks for specific types of leukemia within two broad age groups (20-64 years and 65 years or older) were also examined (see Table 3-37). It should be cautioned that numbers are small. For the older age group, odds ratios were elevated for all specific leukemia types, but not significantly. But the 95% confidence interval for the summary odds ratio exceeded unity (OR=1.85, 95% CI=1.03-3.32). The results are somewhat more variable for the younger age

TABLE 3-36. AGE-ADJUSTED ODDS RATIOS FOR LEUKEMIA BY TYPE OF ELECTRICAL WORK AMONG NEW ZEALAND MALES AGED 20 YEARS OR OLDER

Type of Electrical Job	Exposed Cases	Exposed Controls	Odds Ratio	95% Confidence Interval
Engineers	2	47	1.54	0.38-6.27
Technicians	1	34	1.03	0.14-7.32
Fitters	1	23	1.56	0.21-11.41
Equipment assemblers	0	9	---	---
Radio/TV repair	2	10	7.86	2.20-28.09
Electricians	6	125	1.68	0.75-3.79
Telephone installers	0	18	---	---
Linemen	5	77	2.35	0.97-5.70
Power station operators	2	20	3.89	1.00-15.22
Other	2	104	0.70	0.18-2.78
Total	21	467	1.62	1.04-2.52

SOURCE: Pearce et al., 1989.

TABLE 3-37. AGE-ADJUSTED ODDS RATIOS FOR LEUKEMIA AMONG NEW ZEALAND MALE ELECTRICAL WORKERS, BY AGE AND LEUKEMIA SUBTYPE

	Age 20-64 Years			Age ≥65 Years		
	Cases	OR	95% CI	Cases	OR	95% CI
Acute lymphatic (ICD 204.0)	0	---	---	1	3.05	0.44-20.97
Chronic lymphatic (ICD 204.1)	4	3.36	1.27-8.89	4	1.67	0.62-4.53
Acute myeloid (ICD 205.0)	3	1.21	0.38-3.85	2	1.09	0.27-4.44
Chronic myeloid (ICD 205.1)	1	0.88	0.12-6.38	2	2.55	0.64-10.10
Other	1	1.73	0.24-12.67	3	2.65	0.86-8.18
Total	9	1.39	0.71-2.71	12	1.85	1.03-3.32

OR=odds ratio, CI=confidence interval.
SOURCE: Pearce et al., 1989

group, except the odds ratio for chronic lymphatic leukemia (CLL) was significantly elevated (OR=3.36, 95% CI=1.27-8.89). CLL is most typically a disease of older persons. CLL is extremely rare under age 30; rates slowly increase between ages 30 and 50, and rates exponentially rise in older age groups (Linet, 1985).

These results are generally consistent with previous studies, although risks are greater in older age groups, except for CLL. Use of other cancer cases as controls can present selection bias if exposure relates to other cancer sites. The authors did not believe any potential bias would be a major consideration because, based on other analyses of New Zealand electrical workers, age-adjusted total cancer mortality was 8% lower than for other employed males.

3.3.2.2.3. Cancer of the Nervous System. Preston-Martin et al. (1982) reviewed the characteristics of 3215 cases of central nervous system (CNS) neoplasms diagnosed from 1972 to 1977 and registered in the Los Angeles County (CA) Cancer Surveillance Program. The Registry contains information on age, sex, race, address, religion, birthplace, occupation and industry, and pathological diagnosis abstracted from hospital records. More than 95% of the diagnoses are histologically confirmed. For descriptive analyses, the authors calculated incidence rates using the direct method for 10-year age groups with the U.S. 1970 population taken as the standard. Employment of the cases at diagnoses was coded according to the 1970 U.S. Census Occupational Classification System. The analysis of industry and occupation considered cases among white males age 25 to 64 years, and PlRs were

calculated as the ratio of the number of observed cases to the number of cases expected in a subgroup. Statistical significance was measured by use of a summary Mantel-Haenszel chi-square test. Results were presented for various characteristics, but only the occupational results are discussed here.

The distribution of all CNS neoplasms, considered together, by industry of employment at diagnosis was examined. The industries for which at least five cases were seen, and the PIR was significantly elevated were: beverage, lumber and wood products, apparel, printing and publishing (excluding newspaper), transportation equipment, colleges and universities, insurance, and petroleum refining. Of these industries, the lowest PIR was for the petroleum refining industry (1.11, 8 cases). The highest PIR (2.63, 7 cases) was seen in the beverage industry. Most cases (N=85) were employed in the transportation equipment industry, and the aircraft industry accounted for 73 of the 85 cases. The PIRs for the transportation equipment industry and its aircraft subset were 1.40 and 1.46, respectively. For analyses by cell type (not tabulated for presentation in the paper), the PIRs for both gliomas and meningiomas were also significantly elevated in these industries.

The job title at diagnosis of the cases was also examined. Two groups which contained at least five cases and demonstrated significantly increased PIRs were electricians (PIR=1.42, 11 cases) and engineers (PIR=1.28, 47 cases). Engineers were noted to have been found to be the predominant job title in the aircraft industry, accounting for 38% of those cases. The authors stated that the excess incidence they observed for electricians corresponds to the excess mortality among electricians and electronic workers observed in Britain (Registrar General, 1971).

Lin et al. (1985) evaluated a possible association between occupational exposure to EM fields and death from brain tumors in white male Maryland residents who died between 1969 and 1982. Although 1043 cases were originally identified by ICD codes on death certificates, analyses were based on the recorded histologic type to yield 951 cases - 370 gliomas, 149 astrocytomas, and 432 nonspecified brain tumors. Tumors known to be from metastasis were excluded; nonspecified tumors were analyzed separately because of the possibility of secondary tumors occurring in this group. Occupations were those recorded on the death certificates.

The cases were evaluated in several different ways. Seventy-eight of the cases had electrical or electronic or utility occupations. As a preliminary step, the number of deaths in

the three electrically-related occupational groups was compared to the number expected based on the proportion of these occupations repotted in the 1970 Maryland population census. In all comparisons, observed deaths always exceeded the number of deaths expected for these occupations. Considering gliomas and astrocytomas together, the expected values differed significantly from observed for all three job groups, separately and in combination. For nonspecified brain tumors, significance was achieved only for the group that included electric or electronic engineering and technician occupations and for all occupations in combination.

Because of probable problems in the validity of the above approach, a case-control study was also conducted and reported in the same paper. The cases were the same, i.e., 951 white male Maryland residents who died of brain tumor between 1969 and 1982. Controls were selected from a 10% computer-randomized roster of Maryland decedents. Death certificates were obtained for white adult Maryland residents who died of causes other than cancer. Controls were matched to cases for age and date of death. There were equal numbers of cases and controls. The report does not state whether the controls were only men. If not, the inclusion of women could seriously misrepresent the distribution of controls according to type of occupation.

The distribution of types of occupations was compared in glioma and astrocytoma cases and controls, Occupations with potential exposure to electromagnetic fields occurred more frequently in the case group. This was not seen for nonspecified brain tumors, There were fewer cases than controls in composite groups, namely, “other occupations” and “unknown occupation.” The only significant excess in glioma and astrocytoma cases compared to controls occurred for one job class, electrician or electronic engineer or technician occupations.

In a third approach, the occupations were classed according to the level of potential exposure to electromagnetic fields. A panel of experts defined what kinds of occupations would fall in the classes. These groups were definite, probable, possible, or none. Cases and controls were blindly assigned to the exposure categories. The calculated odds ratios for gliomas and astrocytomas demonstrated a gradient across the exposure categories; the odds ratios increased as exposure potential increased. While measured or typical exposures are not available for these broad job categories, these results provide some limited evidence of a potential dose-response relationship. Odds ratios for the highest class - definite EM

exposure and for the third group - possible EM exposure were statistically significant. The results with nonspecified brain tumors were essentially negative.

Lastly, the mean age at death was examined for the cases by EM exposure category versus no exposure. Only one difference was noted. Glioma and astrocytoma cases classed as having definite EM exposure died at significantly younger ages than did cases classed as without EM exposure.

Thomas et al. (1987) conducted a case-control study of deaths from brain tumors in northern New Jersey; Philadelphia, Pennsylvania, and surrounding counties; and southern Louisiana to investigate occupational risk factors. There were 435 cases and 386 controls; both were identified from death certificates of residents in the three geographic areas. Cases were white males age 30 years or older who died of brain or other central nervous system tumors between January 1, 1978, and December 31, 1981. Diagnoses were verified by reviewing hospital records. One control per case was selected from men who died of causes other than brain tumor, stroke, suicide, or homicide. Cases and controls were matched on age at death, year of death, and area of usual residence. Job histories for the study subjects were obtained by interviewing next-of-kin; the response rate for cases was 74% and 63% for controls. How eliminations occurred and how they were handled to result in 435 cases and 386 controls were not discussed in the report. Risk ratios were reported as relative risks in the paper, but are referred to as odds ratios here.

Two methods for classifying exposure to EM radiation were used. The first method defined occupations with exposure to EM radiation after the classifications used by Lin and Milham. These jobs were electronics and telecommunications engineers; electronics technicians and teachers; radio, radar, and telegraph operators; electricians; electrical linemen; electrical and electronics equipment repairmen; aluminum production workers; welders; and motion picture projectionists. Men never employed in these jobs were considered unexposed. The second method involved classification by an industrial hygienist of jobs with presumed exposure to EM radiation, with exposure to lead, and with exposure to soldering fumes. This method represented an attempt to sort out exposures to other agents also associated with occupations involving EM radiation. Unexposed men were those classified as never working with any of the three agents.

Under the first method for classifying exposure, the odds ratio for subjects who ever had a job with EM exposure was 1.6, but it was not significant. Significant excess risk (OR=2.3) was

seen in the subset of subjects who had worked in a job involving the design, manufacture, installation, or maintenance of electrical or electronic equipment.

The occupations were further evaluated by partitioning the jobs into two classes: (1) jobs involving the manufacture and repair of electronic equipment, including engineers, teachers, technicians, repairers, and assemblers and (2) jobs in the electrical trades, including electricians, power linemen and servicemen, and telephone linemen and servicemen. The former group was considered to have had mixed exposure to EM radiation and solvents and fumes from soldering. Excess risk was reported for the first class of jobs with a significant odds ratio of 3.9, as compared to an odds ratio of 1.9 in the tradesmen group. Furthermore, the risk was concentrated among the electronics equipment repairers

Significantly increased risk (OR=1.7) for death from brain tumors was observed in occupations that had involved EM-radiation exposure, as classified under the second method. However, when subjects who also had exposure to lead and soldering fumes were removed from the analysis, the odds ratio dropped to 1.4 and was not significant. Removal of additional subjects, those who had also worked with organic solvents, resulted in further reductions in risk, with the odds ratio falling to 0.4. The methods for classifying jobs on the basis of exposure to organic solvents was not discussed in the report. The results seem to indicate that the risk of death from brain tumors relates more to the other agents associated with jobs involving EM radiation, than to EM radiation alone.

The excess risk associated with electronics manufacture and repair jobs was due to excess deaths from astrocytic tumors. When exposures to lead and soldering fumes in any job were evaluated separately, no risk was found for lead exposures.

This study attempted to separate exposures to various agents seen in occupations involving work with EM-radiation sources and systems. However, the authors stated that, although their data showed elevated brain tumor mortality risk among men occupationally exposed to soldering fumes, the effects of all the agents associated with electronics jobs still could not be separately evaluated. It is possible that electrical and electronic occupations may present risks that result from an interaction of exposure to various potential carcinogenic agents, but further refinements in exposure assessment, if possible, will be required to address this question.

In their report, Thomas et al. (1987) refer to exposure to EM radiation as exposure to microwave and RF radiation. This may be misleading because the radiation frequencies

involved in the evaluated jobs probably encompass many portions of the spectrum. When electrical tradesmen were separated, it was noted exposure would be to ELF radiation. But the other jobs may have involved exposures to emissions or modulations to frequencies other than the primary or carrier frequency of a given set of equipment. In any event, the exact frequency of radiation exposure is not always obvious for broad occupational classes.

Speers et al. (1988) conducted a case-control study of occupational exposures and brain cancer among east Texas residents. Persons who had died of primary malignant brain tumor (glioma, ICD8:191) between 1969 and 1978 were identified from death certificates of residents in 40 counties in east Texas. The number of cases ascertained and included in the study totaled 440; 202 male cases were the subject of analyses. All were white and between 35 and 79 years of age. One control was selected per case. The next death certificate listed in State numerical files was selected as a control if the same criteria of race, east Texas residence, age 35-79, and time period of death were met. Deaths from brain tumors were excluded as controls. Male controls totaled 238. Descriptive information abstracted from death certificates included usual occupation and industry which was coded according to the 1980 Census classification system.

Deaths were examined deaths in broad industry categories, classified according to the system used by the US. Bureau of Census. Industrial subcategories and certain occupation were also examined. Odds ratios and their confidence intervals were computed. A given “exposed” industry was compared to the total sample (all other industries combined) less the industry then under examination. Significantly increased risk of death (OR=2.26) from glioma was observed in the broad census group of transportation, communication, and utility employees. Although not stated in the report, this category presumably represents a broad industry grouping that most likely contains occupations with potential exposure to EM fields. The odds ratio for utility employees considered alone was 13.10 and was statistically significant. The risk among workers employed in occupations (including electricians and electronic workers) associated with electricity or EM fields was elevated (OR=2.11), but the increase was not significant. It is not clear whether the persons identified with these occupations were all drawn from the broad industrial category of transportation, communication, and utilities. When utility workers were considered with the group with potential EM-field exposure, the odds ratio was 3.94, and this increase was statistically significant.

Loomis and Savitz (1989) examined 1985 mortality data from 16 states participating in the National Center for Health Statistics industry and occupation coding program with respect to EM-field exposure. A case-control design was used to study occupation among men and mortality from malignant brain tumors (N=1095), leukemias (N=1694), and acute myeloid leukemias (N=474). Controls were drawn in a 10:1 ratio to cases from all other causes of death. Adjusted mortality odds ratios were calculated. For all electrical workers, excess risks were found for brain cancer. The observed excess was concentrated among electrical and electronic technicians and electric power repairers and installers. No increases in expected deaths for leukemias, and specifically for acute myeloid leukemias, were found among the total group of electrical workers, although some subgroups, i.e., electricians and electrical and electronic technicians, had elevated mortality odds ratios. This limited information (see Table 3-38) is taken from an abstract; a more detailed paper is under development. The authors stated that the results were consistent with other data on brain cancer but not leukemia.

Reif et al. (1989) examined occupational risks for brain cancer in New Zealand, in a case-control design using data from a national cancer registry. The criteria and methods for case and control selection and methods of analysis are the same as those previously described for the leukemia study conducted by the same authors (Pearce et al., 1989). In this

TABLE 3-38. MORTALITY ODDS RATIOS (MORs)[a] FOR BRAIN CANCER, LEUKEMIAS AND ACUTE MYELOID LEUKEMIAS AMONG MALE ELECTRICAL WORKERS FROM 16 STATES

Occupation	Brain Cancer	Leukemias	Acute Myeloid Leukemias
Electrical Workers	1.5 (1.0-2.1)	0.9 (0.6-1.3)	0.9 (0.5-1.8)
Electrical & electronic technicians	3.1	NG	1.9
Electric power repairers & installers	2.4	NG	NG
Electricians	1.8	NG	NG

MORs and 95% confidence intervals (in parentheses) were not given for all subgroups.
NG = not given.

SOURCE: Loomis and Savitz, 1989.

study however, cases were males, aged 20 years or more, registered with a diagnosis of brain cancer [Ninth Revision of the ICD (ICD9:191)] or of cancer of other and unspecified parts of the nervous system (ICD9:192). There were 506 total cases, and 452 cases (of both rubrics) for whom occupational information was available. Again, controls were cases of other cancer types. Risks among both broad occupational groups and more specific jobs titles were examined.

Elevated odds ratios were seen for several occupational groups and types of jobs, but only those results that may relate to EM fields or electrical work will be given. Odds ratios were elevated for men with professional and technical occupations (OR=1.32, 95% CI=1.02-1.69). Within this group, elevated odds ratios were found for physical scientists (OR=1.37, 95% CI=0.33-5.77) engineers and architects (OR=1.16, 95% CI=0.73-1.82), and aircraft and ship officers (OR=1.76, 95% CI=0.64-4.83). Although not presented in the published tables, risks were stated to be significantly elevated among electrical engineers (OR=4.74, 95% CI=1.65-13.63), which was a subset of engineers and architects. To examine the potential for a bias from improved diagnosis (and access to medical care) among white collar workers, risks were also estimated for specific professional and technical jobs using only all professional technical workers as the reference group. For this analysis, the magnitude of the association for electrical engineers (and other jobs) only slightly decreased and the lower limit of the confidence interval remained above 1.0 (OR=4.06, 95% CI=1.36-12.01).

Elevated risk was not seen for the broad occupational grouping of laborers, production workers, and transport workers. More specific job types within this broad group were examined. The odds ratio for electrical workers was not elevated (OR=0.78, 95% CI=0.39-1.59), but risks for a further delineated subset of electricians were in excess (OR=1.91, 95% CI=0.84-4.33). The number of cases among electricians was not stated, but was likely small since there were only eight cases among all electrical workers. It is interesting to note that the risks among plumbers and welders were confined to plumbers (OR=2.02, 95% CI=0.99-4.12).

Swerdlow (1983) presented data on “eye cancer” in adults in England and Wales. Incidence data between 1962 and 1977 was obtained from 14 population-based cancer registries which submit their information to a National Registry. The general goal of the study was to investigate the epidemiology of “eye cancer,” largely of melanoma histology, and describe trends over time by sex, age, region, level of urbanization, and latitude. Registration

rates were directly age-standardized using the European population (Doll et al., 1970; Waterhouse et al., 1976) as the standard.

For persons aged 15 years or older, there were 2159 cases of “eye cancer” registered for men and 2125 cases for women. Linear regression analyses revealed that the age-adjusted incidence had significantly increased over the time period. Social class and occupation were also evaluated. Age-standardized proportional registration ratios were developed and tested as Poisson variables.

Generally, “eye cancer” incidence was higher in higher social classes (which ran in six groups from professional to unskilled manual). Occupation was examined with respect to the 26 occupational orders or groupings established by the Registrar General. Significantly increased proportional registration ratios were observed in three occupational orders, e.g., electrical and electronic workers; administrators and managers; and professional, technical workers and artists.

The author stated that caution must be applied to interpretation of the results for social class and occupational group because of a small number of cases and the necessity of excluding cases for whom occupation was unknown or could not be classified. The possibility of errors in coding and occupational ascertainment was also noted. In contrast to the other occupational groups, the observed excess incidence among electrical and electronics workers is somewhat at odds with the results seen by social class since these occupations largely fall in the medium to low end of the social class groupings (in skilled manual and partly skilled manual). Thus, Swerdlow felt that these results were of particular interest.

3.3.2.2.4. Malignant Melanoma of the Skin. De Guire et al. (1988) investigated the incidence of malignant melanoma of the skin in telecommunications workers in Canada, following several case reports, The study population consisted of all the workers (N=9590) in Montreal plants of one telecommunications company who were employed for at least 6 months between January 1, 1976, and December 31, 1983. Persons newly hired during this period were included as well as persons who had been working before the study began, The start of the study, thus, does not represent the data of first employment.

Cases of malignant melanoma among employees were ascertained by linking employee lists with name, sex, date of birth, and social insurance number to case lists of Montreal area residents. The malignant melanoma case lists had been developed by identifying all cases newly diagnosed in the same time period from records in 30 local hospitals. This list was

cross-checked against the Quebec Tumor Registry. Pathological and histological reports were examined, and, if equivocal, were reviewed by a consulting dematopathologist. Histological types included were malignant melanoma not otherwise specified, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, amelanotic melanoma, and acral lentiginous and “epitheloid cell type” melanoma. The underlying population was obtained from national census data for 1976 and 1981, and was used to construct incidence rates for malignant melanoma for the greater Montreal area for the study period.

Person-years of observation were calculated from date of first employment and date of work termination, or other means of withdrawal from follow-up. Montreal rates were applied to the person-years for workers to develop expected values after standardization for age and sex. The ratio of observed cases among workers to expected cases formed an SIR, and 95% confidence intervals and p values were calculated. The latter were not reported.

Ten cases of malignant melanoma were diagnosed among the male telecommunications workers during the study period; 3.68 cases were expected. The distribution of histological types was similar to published data from various countries. There were no cases among women. There were 52,456 person-years of employment for men. The SIR was 2.7 (CI=1.31-5.02) and was statistically significant.

Risk with respect to latency period was also examined. Here, latency period corresponds to length of employment divided into two groups, years and 20 years. Among the cases, the minimum number of years worked was 5 years (two cases), and the maximum number of years worked was 38 years (two cases). For persons who had worked less than 20 years, the SIR was 5.0 [observed (Obs)=5, expected (Exp)=0.99, Cl=1.63-11.75] and was statistically significant. In contrast, the SIR for persons who had worked 20 years or more was 1.9 (Obs=5, Exp=2.69, CI=0.60-4.34). Length of any latency period and duration of employment often reflect age. This is true with this population, except for one case. Four of the five cases who had worked less than 20 years were age 42 years or less; two were in their twenties. Therefore, excess risk is seen in the subset of the cohort that was younger and had worked in the company for the least amount of time. The authors discussed the implications of these results. The greater risk in the “short latency” subgroup argues against a causative occupational exposure. The range of years employed in this group ran from 5 to 18. A causative exposure, requiring a given latency period, may have occurred prior to employment or, for some, during childhood. On the other hand, melanomas are generally diagnosed in

middle or older ages. For example, the median age of diagnosis for Montreal males was 54.4 years. This small case group seems to exhibit a slightly younger age at diagnosis than is typically expected. The authors noted that, in addition to change, the results could also be explained by either some highly potent carcinogenic agent or an additive agent, both of which could accelerate expression of cancer.

Detailed job or exposure data were not available. The title of the last job held and the longest held position were not available for all 10 cases, but, it appears that about half of the cases were involved with technical work for some period of time. Bearing in mind the small number of cases, the “low latency” group had somewhat more technical employees than the “high latency” group which had generally more office or unspecified jobs. The tumor location was also slightly different in the two latency groups. Limbs predominated in the low latency group. The abdomen and back predominated in the high latency group.

Nine other cases and one case of choroidal melanoma were not included in the study because they did not meet the location and time criteria for inclusion. The authors pointed out that continued follow-up would be necessary to determine if the risk of malignant melanoma continue among this company’s employees or whether the observed risk disappears, perhaps indicating a cluster or elimination of the responsible risk factor.

Some of the studies previously discussed also have identified excesses for skin cancer. These studies are Szmigielski, 1987; Vagero et al., 1985; and Törnqvist et al., 1986. The eye cancers reported by Swerdlow (1983) were stated to be of melanoma histology.

There are several interesting features of the reported results for malignant melanomas of the skin. The excesses occurred in occupational groups that are younger than typical cases. The location of the cancers included parts of the body not always exposed to sunlight or ultraviolet (UV) radiation, at least on a long-term basis, although short-term high level exposure is possible. The effect has been seen in various types of jobs, with various primary frequencies of putative exposure, and, as a consequence, with various potentials for differing confounding exposures. In other words, the effect has been seen in different jobs with different primary EM-field exposures that may not all have the same potential for the same potential confounders. As such, no single agent or limited number of agents could necessarily explain the results. Except for servicing linemen, there is no reason to believe that workers with some sort of exposure to EM fields would work outdoors more than other types of

workers, Therefore, it is possible that exposure to EM fields or NIR radiation may present some risk for developing malignant melanomas of the skin.

3.3.2.2.5. Summary of Occupational Studies. Many studies in the United States, New Zealand, and Europe have shown cancer incidence or mortality among workers in electrical and electronic occupations to exceed general population levels. Such workers are likely to encounter exposures to various frequencies of nonionizing or electromagnetic radiation, including electric and magnetic fields at the power frequencies of 50 or 60 Hz. All of the studies have strengths and weaknesses, some of which are common to most epidemiologic studies.

Many of these studies are hypotheses-generating in nature for several reasons. For example, some of the studies were not designed, nor were the populations originally formed, to test the hypothesis of whether EM radiation relates to an increased risk of cancer. Some were re-examinations of existing studies or evaluations of vital records, registry, or occupational databases, and so proportional mortality or incidence ratios (PMRs/PIRs) are often the derived estimate of risk. Data on work histories and exposures are very limited; consequently, some of the observed associations may be indirect. Most of the studies drew occupational data from death certificates. Occupation as drawn from death certificates can be very broad, raising the possibility of exposure to an array of agents including EM radiation. It should be noted that there are problems associated with the reporting of occupation or job on death certificates where the accuracy of the recorded occupation may be affected by difficulties in recall or lack of information or understanding of the decedent's job by informants, the recording physician, or others. Although the standard certificate asks for usual occupation, rather than last or current occupation, the usual occupation may not be recorded.

Confounding by other occupational exposures has not been thoroughly addressed in the occupational studies, and more research to improve exposure assessment would be an important improvement. It is possible that many different chemicals could be present in the occupational setting, and the types of chemicals may be different for different jobs. On the other hand, it is not fully known what chemical exposures would be strongly associated with leukemia or brain cancer. While there may be exceptions, it should be noted that human data on chemical carcinogenesis are limited, in the broad sense, and one cannot simply assume that concomitant chemical exposures may explain these results. Similarly, it is difficult to conceive that other possible explanatory factors, such as socioeconomic or behavioral factors,

would be consistently present to an important degree in all the occupations, jobs, and populations that have been studied. Mechanisms that could involve cancer promotion or enhancement have been hypothesized. If such theories can be confirmed, other exposures may not be confounders but may be necessary.

Several studies attempted to address multiple exposures in various ways in the face of limited industrial hygiene information and no monitoring or measurement data on EM fields, chemicals, or other factors. Two, in particular, made a fairly good effort of sorting out various exposure by type of work performed. Stern et al. (1986) found significant excess risks of leukemia among shipyard electricians and for shipyard electrical work. Results were not as pronounced for work with solvents. Thomas et al. (1987) found that brain cancer risks among workers with jobs involving EM-field exposure were reduced when subjects with exposure to lead, soldering fumes, and solvents were removed from the analyses. That approach does not necessarily refute or support the potential carcinogenicity of EM fields (it may have merely eliminated subjects with the clearest mixed workplace exposures), but it is useful to examine potential differential risks.

The potential for confounding exposures is a critical issue. An important point must be kept in mind. For a factor to be a confounder, it must relate to exposure and to the effect or end point under study. Two perspectives can be explored: what is known about the epidemiology of the end point (specific cancer type or site) and what is known about other putative causal agents in the environment of the exposed subject. Smoking is a major factor for cancer in adults. Absence of data on smoking histories is always problematic. However, the cancers identified in these studies are not strongly associated with smoking. Occupations involving RF radiation and EM fields also involve exposure to other agents (chemicals), some of which have evidence as to their carcinogenicity. Some of the putative confounding agents are associated with the end points identified in these EM-field studies, while others are not. It is not yet clear what agent(s) is strongly associated with the specific cancers to serve to explain the results. Just as the extent of EM-field exposure is largely undefined in the occupational studies, the extent and type of exposure to chemicals in electrical jobs and occupations is not yet clear.

Although the many occupational studies have noted increases in various cancer sites, three broad types of cancer predominate, i.e., neoplasms of the hematopoietic system, especially leukemias, and, to a lesser extent, lymphomas; nervous system cancers, including

brain cancer; and, to some extent, malignant melanoma of the skin. For those studies that examined specific types of leukemia, acute myeloid leukemia (AML) predominates, although a few studies have noted increased risks for chronic lymphatic leukemia (CLL). There is, thus, some degree of site specificity.

As mentioned previously, further research is needed to improve exposure assessment and to define relevant exposure parameters. Few studies provided measurements. While it is clear that the studied populations are exposed to NIR, it is not clear to what degree or what exposures are biologically relevant. To date, the study that best addresses the occupational exposure environment was conducted by Matanoski et al. (1989). Although firm dose-response gradients were not reported, excess risks, especially for leukemias, were found in the group with the highest average magnetic field exposure. To some extent, risks became less pronounced with lower average exposures.

The occupational studies can involve exposures to multiple frequencies of NIR and exposures to 50 or 60 Hertz. Excesses have been reported for many types of jobs, not only electricians. Frequency of exposure cannot be readily discerned for job titles or job classifications. The predominating exposures are probably to extremely low frequencies, but jobs involving radio, TV, radar, and so forth entail exposure to modulated RF radiation.

The lack of supportive quantitative exposure data in the occupational studies makes it difficult to determine harmful levels, if a true risk exists, and to test for dose-response relationships. Therefore, dose-response has not yet been characterized. However, many studies have attempted to evaluate dose response in a qualitative fashion, e.g., by examining risks across work or job subgroups that represent a gradient of potential relative exposures. Admittedly, the approaches have been necessarily crude, and exposure misclassification is a distinct possibility, but qualitative approaches have yielded some evidence of greater risks with greater potential exposure. Some results from laboratory-based studies have identified frequency and intensity windows for certain effects (see chapters on mechanisms and on supporting evidence) which point to the possibility of nonlinear dose-response relationships. If further animal and cellular level research continue to build support for that evidence, the lack of quantitative dose-response evidence from epidemiologic studies may be of less importance in weight-of-evidence assessments that draw upon classical criteria for causality. Furthermore, nonlinear dose-response may be difficult to discern in epidemiologic studies.

Yet, despite limitations of the current data, the results of the occupational cancer studies are remarkably consistent. Similar results in different geographic regions, countries, age groups, industries, and occupational classifications have been reported. Given this diversity, plus the likelihood that, across studies, the work denoted by broad job titles is probably not uniform, it is difficult to identify any single agent or group of compounding exposures that could explain the consistently positive results. Exposure misclassification is a distinct possibility, but, if a true risk exists, that sort of bias forces risk estimates toward the null, and observed risks would be underestimated. The magnitude of the risk estimates is similar across studies. The specific cancer sites associated with excess risk are similar across studies, In addition, similar results have also been obtained using different study designs.

The strengths and weaknesses of the many epidemiologic studies on jobs and occupations involving work with EM-radiation sources and EM-field exposure have been discussed above. Despite their limitations and the clear need for more research, especially to improve exposure assessment, the consistency and specificity of the findings provide evidence that EM-field exposure in the workplace may pose a carcinogenic risk for adults. The results from occupational studies are supportive of the positive results noted in most of the studies of children exposed residentially.

3.4. SUMMARY

3.4.1. Introduction

This chapter reviewed the available epidemiologic literature with respect to evaluating the relationship between exposure to EM fields and cancer. More than 40 studies of EM fields have appeared in the literature in the last 15 years. They can be divided into four basic categories as follows: (1) studies of children exposed residentially to 50- or 60-Hz magnetic fields, (2) studies of adults exposed to RF radiation, (3) studies of adults residentially exposed to EM fields from 50 or 60 Hz, and (4) adults potentially occupationally exposed to electromagnetic radiation.

3.4.2. Childhood Cancer

Nine studies were reviewed, eight case-control studies of childhood cancer and one case report involving adolescent girls. Six of the case-control studies examined residential exposure from power transmission and distribution systems and the other two studies have

examined childhood cancer in relation to paternal occupation. Five of the six residential exposure studies showed positive associations with exposure to EM fields. Three of these reported statistically significant results. One of these three dealt with wiring configurations that were reasonably correlated with actual measurements of magnetic fields in the vicinity of the residences of the children. The two remaining significant studies also reported similar findings at similar levels as low as 2 mG, or 0.2μT. Where different cancer sites were evaluated, leukemia, lymphoma, and nervous system tumors were found to be in excess in the five residential studies showing positive associations. However, the author of one of the two nonsignificant positive studies concluded that his findings did not support the results of the three significant studies based upon his tests of significance. Failure to find significance may be due to small numbers and the error of including children in his control group who were most likely exposed to magnetic fields similar to his "exposed" children, i.e. within 100 meters of overhead lines. The second nonsignificant positive study from Taiwan did not have sufficient power to detect a positive risk as significant. The sixth nonpositive study based on wiring configurations was methodologically flawed because of the use of multiple dwellings for case children and single addresses for control children, which would tend to dilute exposures and risk estimates. The study also overestimates the degree of fall-off of field levels with distance, which again would dilute exposure and response. This device will, by necessity, force risk estimates toward the null.

The two paternal occupational studies found statistically significant associations between neuroblastoma and brain cancer among children whose fathers' job likely involved exposure to electric and magnetic fields. The case report of a cluster of endodermal sinus tumors in five adolescent girls in close proximity to power distribution lines was not helpful. No measurements of actual fields were done. Although the girls lived near such power lines, coincidental environmental factors that were not identified could be responsible.

The case-control studies of children residentially exposed to magnetic fields provide evidence of a positive association of a risk of certain types of cancer, namely leukemia, central nervous system cancers, and lymphoma. Unfortunately, detailed information regarding specifics of these cancers is not available in these studies, Because these measured risks are low in all of these studies, the possibility that some unknown confounder is responsible cannot be eliminated. However, because of the consistent positive findings and suggested site concordance, chance is not likely to be the explanation, Furthermore, one of the positive

studies extensively examined several possible confounders and did not find another explanation for the association between childhood cancer and wire code and magnetic fields. Questions still remain regarding what length of residency would be required before one could conclude that residency in a magnetic field is likely to be the cause of a cancer. Only a few of these studies discuss this in a cursory fashion. Residency at time of diagnosis is not necessarily a valid surrogate without information about how long the child lived there.

3.4.3. Adult Cancer

There have been many studies of adults potentially exposed to different frequencies of EM radiation or in different exposure environments. These studies can be grouped into three categories, that is, RF radiation, residential exposure to EM fields, and occupational exposure to EM radiation (see Table 3-39).

3.4.3.1 Radiofrequency Radiation

Among eight studies of radiofrequency radiation exposure in adults, five cohort studies reported statistically significant risks of lymphatic and hematopoietic neoplasms, especially acute myeloid leukemia, in amateur radio operators based on proportional mortality ratios and standardized mortality ratios, and of total cancers in Hawaii residents living in close proximity to RF towers based on standardized incidence ratios, and of hematopoietic system cancer, including leukemia, lymphoma and lymphosarcoma, as well as melanoma from exposure to RF radiation, primarily from radar, in Polish military officers. For the Hawaiian study, leukemias were nonsignificantly elevated, but small numbers made the leukemia estimates unstable. Two studies (of U.S. Embassy employees in Moscow exposed to microwave radiation and U.S. Naval personnel exposed to radar) suggested a slight tendency toward an increased risk of cancer in general and the hematopoietic system specifically. Excesses were, however, not statistically significant in either study. The remaining cohort study of participants in a radar research and development project at the Massachusetts Institute of Technology, where the subjects were exposed to RF radiation estimated to be about 2 to 5 mW/cm^2, produced few significant findings of mortality in the subjects. Some elevated risks of certain site-specific cancers, most notably Hodgkin's disease, were found.

All of these studies, although suggestive of an elevated risk, suffer from design and methodological problems, which in their entirety preclude any definitive statement regarding

TABLE 3-39. STUDIES OF CANCER IN ADULTS

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
RADIOFREQUENCY RADIATION EXPOSURE						
Lillenfeld et al. (1978)	US Nationals abroad	Cohort, SMRs	US Foreign Service employees (both of State Department and non-State Department) and dependents stationed at the Moscow Embassy in the Soviet Union	Other similar employees serving at other East European posts. SMRs based on US mortality rates	Mortality In both groups generally lower than expected based on US mortality. Some elevations for cancers, Including leukemias. More excess cancers In females.	Good efforts to trace and locate populations. Low response rates for questionnaire. Relatively short follow-up dictated by study requirements. Very low exposures.
Robinette and Silverman (1977) Robinette et al. (1960)	US military	Cohort, SMRs	About 4000 Navy Veterans (Korean War) from military occupational specialties that work with radar.	Divided Into low and high exposure groups with further ranking of high group Into a "hazard ranking system." Low exposure group estimated to have received < 1 mW/cm^2; high exposure group experienced higher RF exposures. Cohort mortality for subgroups compared to expected mortality based on group as a whole.	Mortality ratio of 1.64 (nonsignificant) for subgroup In hlgh exposure group, based on **8** deaths. Also. elevated but nonsignificant leukemia mortality.	Large well-defined cohort. Attempted limited exposure measurements and applied an exposure ranking system. Mortality ratio biased down since Included exposed groups In calculating expected cancers (could not exceed approximately 2). Longer follow-up would be useful. This group has a good potential for further follow-up with Improvements In design and methods.
Milham (1985b)	US (Washington State & California)	Cohort, PMRs	Amateur radio operators who were members of the American Radio Relay League and died in Washington or California	Expected values from 1976 US age-speclflc white male death frequencies.	Significantly elevated PMRs for all leukemias and acute and chronic leukemia. For operators from Washington, PMR=2.64 if death certificate cited electrical work. If no such work, PMR=2.1.	Deaths identified from obituary listings In League's member magazine; an innovative approach but could Introduce bias or underascertainment. Amateurs also are exposed to lower frequencies, includlng 60 Hz, so probably cannot distinguish differential effects of RF vs. ELF radiation.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Milham (1988a,b)	US (Washington State & California)	Cohort, SMRs	Amateur radio operators licensed with the Federal Communications Commission (FCC) who lived In California or Washington and died between January 1. 1979 - December 31. 1984. Identified from FCC operator licensee lists.	a: Expected values based on US male death rates. b: Expected rates from U.S. male population. Internal comparisons by FCC license class. License category explored as potential measure of exposure and duration.	a and b: SMRs elevated for several cancer sites and statistically significant for acute myeloid leukemia (SMR=1.76) and multiple myelomas and miscellaneous neoplasms of the lymphoid tissues (SMR=1.62). Hodgkin's Disease elevated (SMR=1.23) but not statistically significant. Significantly lower SMRs for several diseases Including all causes combined and all malignant neoplasms combined. b: Lowest FCC license category (presumably shortest term operators) showed lowest risks. No trend across other categories.	a and b: Large well-defined cohort (N=68,000 men. PY=233,000). Level of exposure unclear. Deaths only sought In California and Washington. Amateurs also are exposed to lower frequencies, including 60 Hz, so probably cannot distinguish differential effects of RF vs. ELF radiation. b: Extension of earlier study to attempt to identify possible exposure or duration groupings. Link between exposure level and license category not clear.
Environmental Epidemiology Program, State of Hawaii (1986)	US (Hawaii)	SIRs, "Ecological." Incidence	Residents of Honolulu living in census tracts with RF radiation towers (TV. FM. AM).	Residents in Oahu living In census tracts without RF towers. Expected values based on State rates.	Significantly elevated total cancer in "exposed group." Leukemia In excess but not significantly	Small numbers precluded concurrent age, sex, race adjustments. Exposures only broadly defined In census tracts. Urban/rural differences possible.
Hill (1988)	US	Cohort	MIT scientists and engineers in radar R&D facility in World War II.	US white males and cohort of physician specialists (to reduce socioeconomic differences). Internal controls grouped by work assignment to estimate exposure.	Overall survival better than expected. In comparison with physicians, Increased risk for lymphomas, particularly Hodgkin's Disease (SMR=10.3, Risk ratios proportional hazards model=4.0). Differential risks not seen across exposure categories that ranked potential exposure.	Typical exposures for time period developed, i.e., 2-5 mW/cm^2, or SAR of about 0.4 W/kg. General follow-up over 40 yrs. but had to be censored to compare to physicians to 1974. For the latter. further follow-up would be an Improvement.
Szmiglelski et al. (1967)	Poland	Cohort	Military personnel with RF and microwave exposure. primarily from radars.	Internal controls. Divided Into exposed and unexposed subgroups.	Numerical striking excesses for lymphatic and hematopoietic neoplasms (6 times more) and most all sites In exposed group vs. unexposed group.	Information lacking to describe methods, exposures, population size and make-up, etc. that limits interpretability. Potentially important and further information should be obtained.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
RESIDENTIAL EXPOSURES, 60 HERTZ						
Wertheimer & Leeper (1982)	US (Colorado)	Case-control. Matched design.	Cancer decedents and survivors in Colorado cities.	Non-cancer decedents and geographically matched persons	Strong excess of total cancers in high exposure group. denoted by wire code (size and distance of wired from homes). Excess lymphomas. No association with leukemia.	Exposure based on electrical wiring code configuration. Use of surrogate supported by limited measurement data. Rather complicated methods of case selection, Including both death certificate and incidence records; this may complicate analysis and interpretation.
McDowall (1986)	England (East Anglia)	Cohort, mortality. SMRs	Residents whose homes were selected by random sampling from National Grid Maps and included if within 50 m. of substation or 30 m. of overhead line. Followed between 1971-83 to yield 409 male deaths and 405 female deaths.	Expected values based on East Anglia mortality rates and. for hematopoietic neoplasms. from national rates for England & Wales.	Statistically significant SMR for lung cancer in women. SMRs for leukemias (1.54) and other hematopoietic neoplasms (1.71) elevated for women but not statistically significant. When stratified by distance from electrical installations, various SMRs were elevated including for leukemia and other hematopoietic neoplasms especially in group living closest to electrical installations.	Small number of deaths for specific cancer sites. Low power. Small numbers of exposed persons, further reduced by use of four exposure strata. Exposure misclassification possible and referent group possibly exposed to other sources. No exposure measurements and less description of sources than Wertheimer & Leeper. Author suspected under representation of older age groups.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Coleman et al. (1985. 1969)	England (London)	Case-control	Incident cases of leukemia between 1965-80 in Thames Cancer Registry in London, limited to four South London boroughs.	Cancer controls (generally two per case) drawn from same registry, matched for age. sex. year of diagnosis, and borough of residence.	Updated In 1989. OR=1.25 for residence within 25 m. of a substation but not statistically significant: no excess risks beyond 25 m. OR=2.0 for resident within 50 m. of overhead power line but not statistically significant. Also included some results for children; nonsignificant excess risks below 50 m. from substations.	Exposure estimated by mapping sources and their distance from residences. Few persons lived near sources. Low statistical power
Severson et al. (1988)	US (Washington State)	Case-control	Newly diagnosed cases aged 20-79 yrs. of acute nonlymphocytic leukemias between 1981-84 in three counties identified from population-based surveillance system. N=164 identified, N=114 participated.	Regional controls selected by random digit dialing, frequency matched for sex and age. N=204 identified. N=133 participated.	Excess risks not observed by and large. Nonsignificant increase In risk with increasing mean magnetic field exposure that disappeared when weighted by time spent in each measured room. Borderline risk (OR=2.4) for appliance use in lower Income families.	Well-designed study. One type of leukemia. Poor response rate for questionnaire but similar response rate for cases and controls. Three methods of exposure assessment.
Preston-Martin et al. (1988)	US (California)	Case-control	Los Angeles County residents aged 20-69 yrs. with histologically confirmed acute myelogenous leukemia diagnosed July 1979-June 1985. (859 registered cases, 458 alive, 295 completed questionnaires and included in analyses)	Neighborhood controls matched on sex. race, birth year. N=293 with completed questionnaires.	Interviewed on use of electric blankets (four broad questions). No differences between cases and controls.	Not originally designed to evaluate EMFs. Only living cases included. Very general questions: no exposure estimates. Limited usefulness for assessing EMF risks.
OCCUPATIONAL EXPOSURES TO 50/60 HERTZ AND POSSIBLY OTHER HIGHER FREQUENCIES						
Multiple Cancer Sites						
Wiklund et al. (1981)	Sweden	SIRs	Telephone operators from Telecommunications Administration identified from 1960 census and entered in cancer registry with diagnosis of leukemia.	Expected values based on national rates specific for year of birth and sex.	No excess observed; only 12 cases Identified, 11.5 expected.	Possible underascertainment of leukemia cases and number of telephone operators. No exposure Information. Sex not reported.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Howe and Lindsay (1983)	Canada	SMRs	10% sample of Canadian workforce from 1965-69 and 1971 (N=700,335) but analyses limited to 415,201 males). Records linked to national mortality registration system.	Expected values based on specific national rates and the total cohort for occupation-specific analyses.	Analyses for all causes, ail cancers, and 19 cancer sites. Transport & communication workers: SMRs elevated for 12 sites, significant excess risk of leukemia and aleukemia (SMR=1.68). Transportation, communication, and other utility industry: some elevations but not statistically significant. SMR=1.36 for leukemia and aleukemia. Linemen & servicemen for telephone, telegraph, & power systems: significant SMRs for intestinal cancer (3.53) and stomach (2.33), borderline results for leukemias (SMR=2.41). Appliance manufacturers: significant SMR (5.28) for neoplasms of lymphatic and hematopoietic tissues.	Large comprehensive study. No exposure Information. only potential for work with fields identified by industry, occupation, and job.
Olin et al. (1985)	Sweden	Cohort, SMRs	1254 electrical engineering graduates (1930-79) with Master's Degree from Royal Institute of Technology.	Expected values from national males rates	Observed mortality lower than expected for all causes examined.	Small study. No details on ultimate work or possible exposures. Short follow-up for recent graduates. no allowance for cancer latency. More detailed analyses, numbers permitting. for time and birth cohorts would be more useful.
Vagero et al. (1985)	Sweden	Cohort	Employees who worked at least six months during 1956-60 at three locations of a large telecommunications company with research. development, and manufacturing activities. N=2,914, 2047 men and 867 women.	Expected values based on national rates specific for age. sex. and calendar year.	Males: Elevated SMRs at several sites but only significant for malignant melanoma (SMR=25) and Brill-Symmer's (nodular lymphoma (SMR=17.6). Women: Excesses for cancer of small intestine (SMR=16.0, statistically significant), corpus uteri (SMR=2.2). and malignant melanoma (SMR-2.8). Malignant melanoma: (a) significant excesses for both sexes combined (SMR=2.6). (b) If worked at least three yrs. and allowed 10 yrs. for latency, significant excesses overall (SMR=2.8) and specifically for soldering work (SMR=3.9); all cases at one workplace.	PY=62,028. follow-up from 1958-1979. Ages not stated. intended to study chemical exposures. Developed information on type of work or work practice. Good work histories but no information on chemical or other exposures.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Barregard et al. (1985)	Sweden	Cohort, SMRs & SIRs	Workers in chloralkali plants in jobs involving static fields. i.e., electricians and workers In electrolysis process.	Expected values based on national and regional rates.	Results only for all-cause mortality and total cancer Incidence. No difference from expected values.	Work with static fields. Population too small to detect differences and too small to draw Inferences.
Törnqvist et al. (1986)	Sweden	Cohort (from census), SMSRs	3,300 electric power linesmen and 6,730 power station operators.	Expected rates based on rates In Swedish blue collar workers, using national cancer registry data.	Mixed results. Where elevated, SMRs not statistically significant. For linemen. SMR=1.3 (90% CI 0.9-2.4). SMRs for power station operators generally lower.	Well-defined population but low power to detect Increases In risk. Duration of employment. potential exposure level. and accuracy of employment records not addressed.
Obrams (1988)	us	Case-control, mortality	222 AT&T employees who worked at least two yrs. and died of leukemia other than chronic lymphocytic leukemia.	687 controls from Bell System Personnel Data Base, matched on age. sex. company and year of hire.	No increased risk observed for acute myelogenous leukemia or chronic myelogenous leukemia among linemen.	Well-defined population. Population mostly retirees and sufficiently aged so that early withdrawals may not have been detected; deaths could be underascertained. Exposure misclassification or dilution possible by combining types of Jobs with different levels of exposure.
Gubéran et al. (1989)	Switzerland	Cohort, mortality and incidence	1,900 electricians	Expected values derived from local rates.	SMRs elevated at several sites but not statistically significant. SMR=2.5 for Hodgkin's Disease. SMR=1.43 for leukemia.	Occupation derived from census so no Information on duration of employment or other detail. Follow-up only 14 yrs.; < 25,000 PY; low power. Foreign workers about 1/3 of cohort. Their inclusion makes relevance of local rates to foreigners unclear, may introduce uncontrolled factors, and resulted in substantial loss to follow-up from their high mobility.
Matanoski et al. (1989) (poster)	US (New York)	Cohort, SMR	Actively working male telephone workers.	Expected values based on New York male rates and on rates among "nonline" workers.	Elevated risks at several sites and largest for cable splicers. most highly exposed. Using nonline rates for expected cases, cable splicers had significant excesses for leukemia (SMR=7). lymphomas (3.59). and total cancers (SMR=1.81). Breast cancer among male central office technicians; expected values negligible.	Well-defined large population (N=50,582, PY=206,067). Not retirees, therefore, younger actively working population (mean age 40 yrs). Cases from NY State cancer registry. Exposure data with information on job/type of work and mean magnetic field exposures for Jobs.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Cancer of the Hematopoietic System						
Milham (1982, 1985a)	US	Proportional mortality (PMR)	Male Washington State residents who died between 1950-79	Compared different occupational groups to whole population	Significant excess of all leukemias and acute leukemias for electricians, power station operators and aluminum workers	Large data base, high statistical power. Occupational information limited on death certificates. PMR methods Influenced by rates of other diseases no under study. Statistical significance or confidence Intervals not given.
Wright et al. (1982)	US (California)	Proportional incidence (PIRs).	Cancer cases in a population-based surveillance registry, Los Angeles, CA, categorized by occupation	White males in Los Angeles County, 1972-1979	Generally increased Incidence of leukemia [especially acute myelogenous leukemia (AML)] for persons with jobs with presumed exposure to electric and magnetic fields. Statistically significant PIRs for power linemen [acute leukemia (AL) and AML], telephone linemen (AML). and all jobs combined (AL,AML) thought to have EMF exposure.	Methodology (use of register) may be more specific than PMR death certificate calculations. Influenced by rates for other cancers. 12 occupations with potential EMF exposure.
McDowall (1983)	England, Wales	Proportional mortality (PMRs). using occupational mortality database.	Male decedents aged 15-74 yrs., 1970-72. Ten subgroups for electrical occupations.	Expected values from all deaths among Welsh and English males of same age and time period.	Elevated PMRs among electrical and electronic engineers and telegraph radio operators, for all leukemias and the four specific types examined. Highest values for myeloid leukemia and acute myeloid leukemia. Lymphocytic leukemia elevated in electricians. Acute myeloid leukemia elevated in radio & radar mechanics and linemen & cable jointers.	Relatively large data base. PMR methods influenced by rates of other diseases no under study. No statistical tests or confidence intervals given. Reexamination of an earlier report on occupation.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
McDowall (1983) (continued)	England, Wales	Case-control	537 deaths in male decedents ≥ 15 yrs. old from acute myeloid leukemia in 1973.	1074 deceased males age ≥ 15 yrs., drawn randomly from all 1973 male deaths. excluding leukemias, matched on age within five years.	Significant excess seen In composite occupational categories: all electrical occupations and any occupation In electrical or telecommunications Industry (OR=2.3, 36 cases); all electrical occupations (OR=2.1, 30 cases). Elevated but nonsignificant ratios for five more specific occupations: electricians & electrician's mates (OR=1.6), electrical & electronic engineers (OR=1.8), Post Office & telephone engineers (OR=3.0), other telecommunications engineers (OR=4.0), and power station. substation, & all electricity board occupations (OR=2.0)	Relatively large data base, hlgh statistical power. Occupational Information taken from death entries.
Coleman et al. (1983)	SE England	Proportional incidence, called proportional registration ratios PRR)	Males age 15-74 yrs. with leukemia identified from South Thames Cancer Registry.	Per occupation examined, expected values based on proportions among all other occupations.	Significant PRRs for all leukemias for all electrical occupations combined (PRR=1.17). for electrical & electronic fitters (PRR=1.89). and telegraph/radio operators (PRR=2.46); six other electrical occupations had elevated but nonsignificant PRRs. For all occupations. nonsignificant excesses seen for acute and chronic lymphoid leukemia and acute myeloid leukemia, but not for chronic myeloid leukemia. Excesses were also seen for four groups for acute lymphoid leukemia (two significant), for six groups for chronic lymphoid leukemia (one significant), for seven groups for acute myeloid leukemia, and for four groups for chronic myeloid leukemia (one significant).	Used cancer registry. Job data from hospital records. 12% of tumor registrations excluded due to no information on jobs. Small numbers for specific types of leukemia.
Pearce et al. (1985)	New Zealand	Case-control	546 male leukemia cases registered 1979-83 and 20 yrs. old or more.	Four male controls per case matched on age and registration yr. N=2,164.	Defined nine occupational groups with presumed exposure; overall OR=1.7, CI=0.97-2.97, Significant excesses for radio and TV repairers (OR=8.17) and electricians (OR=4.75).	Used cancer registry. Two few cases to Investigate specific types of leukemia. Affected Job titles corrected in later 1989 paper.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Calle and Savitz (1985)	Wisconsin	Proportional mortality, PMRs	White males ≥ 20 yrs. old who died from leukemia between 1963-78.	Expected values from all Wisconsin deaths among white men ≥ 20 yrs. old.	Used occupational groupings after Milham and Wright. 41 cases of leukemia. Mixed results across ten occupations. Significant excess of all leukemias for radio & telegraph operators (PMR=2.35) and for electrical engineers (PMR=1.86); elevated but not significant for linemen and electronics technicians. For acute leukemia. same pattern observed: radio & telegraph operators (PMR=3.0, significant), electrical engineers (PMR=2.57, significant), linemen (PMR=1.43, not significant), and flamecutters (PMRs=1.04, not significant).	Source of occupation data unclear. Proportional rates Influenced by rates of other disease. Small number of cases.
Gilman et al. (1985)	US	Case-control, mortality, nested in cohort.	40 leukemia cases (white males) identified from 6,066 death certificates drawn from a population of 19,000 male coal miners.	4 within-cohort controls per case matched on age at death and year of birth and died of causes other than cancer or accidents.	Length of employment in underground mining used as surrogate for exposure: < 25 yrs=unexposed, ≥ 25 yrs.=exposed. Significantly elevated estimated risks for all leukemias (OR=2.53), chronic leukemia (OR=8.22), chronic lymphocytic leukemia (OR=6.33), and myelogenous leukemia (OR=4.74). No excess risk for acute lymphocytic leukemia (OR=0.63, 2 cases).	Mines have overhead power lines, transformers, converters, and electric trolleys. Examined 2 other potential risk factors, smoking and pneumoconiosis; no risk observed. Radon exposure possible.
Flodin et al. (1986)	Sweden	Case-control	59 cases of acute myeloid leukemia ages 20-70 yrs. diagnosed between 1977-82 at 5 hospitals.	(a) Four general population controls per case, matched for sex. age. and parish residence; N=236. (b) Two controls per case randomly selected from study hospitals' population catchment areas; N=118. Results not differ for the two control groups so pooled data: N=354.	Excess risk: long-term residence/work in concrete buildings, X-ray exposure, radiological work. No excess risk: pesticides (unless 25 yrs. latency), cigarette smoking, engine exhausts (unless 5 yrs exposure minimum), painting, contact with cats, contact with cattle (unless 25 yrs. contact). Electrical workers had elevated risks for acute myeloid leukemia (OR=3.8). Electrical workers were electrical technicians. electrical workers, and computer & telephone mechanics.	Primary focus Ionizing radiation but various other exposures assessed via questionnaire. Complicated detailed analyses. High control to case ratio.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Stern et al. (1966)	US (New Hampshire)	Case-control, mortality. nested in cohort.	White males who died by 1980 from leukemia In a cohort of 24,545 shipyard workers employed between January 1, 1952 - August 15, 1977.	Four within-cohort controls per cases. matched for birth date. date first employed, and duration of employment, using a scoring system to maximize similarities.	Extensive detailed analyses. Univariate analyses: For all leukemlas, largest and only significant excesses for electrician jobs (OR=3.0) and electrician shop (OR=2.57). Significant excess risk of myeloid leukemia for welders (OR=3.83) and welding shop (OR=3.83). Significant excess risk of lymphatic leukemia for electricians (OR=6.0) and electrician shop (OR=3.8). Similar results obtained for logistic regression analyses.	lonizing radiation and solvent risks were original objective of study. 80% power for 2.2 risk. No measurement data but very extensive well-developed work history data: analyzed for different shops and jobs. Results consistent between shop and job types and different analytical methods. Examined confounders and interactions.
Linet et al. (1988)	Sweden	SIRs	Incident male leukemia cases (5,351) for 1961-79 from national cancer registry.	Expected values from national rates specific for birth cohort. sex. region. and type of leukemia.	Linked with Cancer-Environment Registry to identify occupation. Significant excess risk of chronic lymphocytic leukemia for electrical line workers (SIR=1.9): acute nonlymphocytic leukemia also elevated but excess not significant. SIRs elevated for broader category of electrical workers but not significant.	Possible under-reporting of leukemia in Swedish register. Small number of cases. Chronic, not acute leukemia, observed to be in significant excess.
Juutilainen et al. (1986)	Finland	SIRs	Male incident cancer cases from national cancer registry classed into eight occupational groups. N=17.	Expected values based on national male rates.	Over all occupations, SIR=1.23. SIRs also generally elevated for the specific occupations. Highest SIR (3.13) for linemen and cable jointers and SIR=2.63 for all other occupations combined.	Only reported positive leukemia results. Electrical occupations taken from census. Strongest effect among linemen & cable jointers. No statistical tests or confidence intervals given. Small number of cases.
Loomis & Savitz (1989)	US	Case-control, MOR	Males who died of malignant brain tumors (N=1095), leukemias (N=1694), and acute myeloid leukemias (N=474). Listed in 16 State NCHS industry and occupation coding program.	Men who died from all other causes of death.	For all electrical workers combined, no excess risk for leukemias and acute myeloid leukemia but significant excess for brain cancer. Excess of acute myeloid leukemia for electrical and electronic technicians. Excess mortality from brain cancer for electrical work subgroups. i.e.. electrical and electronic technicians (MOR=3.1), electric power installers & repairers (MOR=2.4), and electricians (MOR=1.8).	Large multi-State study, national occupational database. Large case to control ratio (10:1). MORs and confidence intervals not reported for all occupational or disease subsets. Abstract only. Described In text under cancers of the nervous system.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHT/DEFICIENCIES
Pearce et al. (1989)	New Zealand	Case-control	19,904 men age $\geq$ 20 yrs. with cancer drawn from national cancer registry and had occupational information (60% of all eligible registrants).	When evaluating leukemia cases, male cancer registrants with cancer other than leukemia.	Examined electrically-related occupations. For all electrical workers considered together, elevated ORs for several types of cancer but only significant for leukemia (OR=1.62). ORs elevated for most of the specific electrical occupations but only significant for radio and TV repairers (OR=7.86) and were borderline for linemen (OR=2.35) and power station operators (OR=3.89). Also examined two age groups. For ages 65 yrs. or more, ORs elevated for all leukemia types but not significantly; significant (1.85) for all leukemias together. For ages 20-64 yrs. ORs elevated except for chronic myeloid leukemia. Significant excess for chronic lymphatic leukemia (OR=3.36).	Used cancer registry. Small number of cases. Interesting observation of significant excess of chronic lymphatic leukemia In younger age group: more typically a disease of older persons. Suggests need for more research to examine potential for early onset.
Cancer of the Nervous System						
Preston-Martin et al (1982)	US (California)	PIRs	3,215 cases of central nervous system neoplasms diagnosed from 1972-77 drawn from the Los Angeles County Cancer Surveillance Program. industry and occupational analyses restricted to white males age 25-64 yrs.	Expected values based on us 1970 population.	PIRs for total CNS neoplasms significantly elevated for eight industries. including transportation equipment Industry (PIR=1.4) and its aircraft component (PIR=1.46). Gliomas and meningiomas also significantly elevated in those two Industries (not tabulated). For jobs, significant increases were seen for electricians (PIR=1.42) and engineers (PIR=1.28). For the latter, 36% were in the aircraft industry.	Information on industry. occupation. and other factors from hospital records: industry and job title at diagnosis. Cancer registry data.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Lin et al. (1985)	US (Maryland)	Case-control	951 cases with histological type recorded out of 1,043 deaths from brain tumors in white male Maryland residents from 1969-82.	Proportional analysis of occupation: expected values from 1970 Maryland population census. Case-control analysis: 10% computer-randomized roster (N=951) of white adult Maryland residents who died of causes other than cancer, matched for age and date of death.	Four sets of analyses. (1) Proportion of deaths In three electrically-related occupations was greater than the proportion of the occupations In census: held for all tumors combined and specific cell types. (2) Occupations with potential EMF exposures more frequent in cases and significant excess of glioma and astrocytomas cases for one class: electrician. electronic engineer, technican. (3) Occupations ranked by experts into categories of differential potential exposure: ORs for gliomas and astrocytomas increased as potential increased. (4) Mean age at death significantly younger for glioma and astrocytoma cases than for control deaths.	Case identification from death certificates but restrictions such as including only records with histological types and separate analyses by specific vs. nonspecific cell types improves the method; minimized possibility of secondary or metastasized tumors. Sex of controls unclear; may bias occupational distributions. Better definition of occupation in cases than controls: may reflect general population sampling. Blind assignment of cases and controls into expert-ranked classes of likely exposure. Qualitative evidence of dose-response.
Thomas et al. (1987)	US (New Jersey, Pennsylvania, Louisiana)	Case-control	435 white males, identified from death certificates. who died from brain or other CNS tumors between January 1, 1978 - December 31,1981 and for whom next-of kin responded to interviews (74% of all cases).	386 men who died of causes other than brain tumor, stroke, suicide, or homicide, matched on age at death, year of death, and area of usual residence and for whom next-of-kin responded to interviews (63% of all controls).	Two methods to classify exposure or occupation, first, after methods of Lin and Milham, and, second, classification by an industrial hygienist of jobs with presumed exposure to EMFs, lead, or soldering fumes (unexposed men=no jobs with either any of the three agents). (a) Increased but not significant risk (OR=1.6) if ever had EMF job. Significant excess (OR=2.3) if job involved design, manufacture, installation, or maintenance of electrical or electronic equipment. Risks greater In manufacturing/repair subgroup (OR=3.9) (due to astrocytomas) vs. trades subgroup (OR=1.9): former presumed to have exposure to multiple agents. (b) Significant excess (OR=1.7) for EMF Jobs but decreased and lost significance (OR=1.4) when removed subjects with other exposures. No risks for lead exposures.	Reviewed diagnoses with hospital records. Job histories by interviewing next-of-kin. Attempted analysis of confounders and excess risk dropped. Could reflect true risk is from the other agents, interactions, poor reporting by kin. or loss of power; cannot be determined.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Speers et al. (1988)	US (Texas)	Case-control, mortality	Persons who resided in 40 counties in East Texas who died of gliomas between 1969-78, identified from death certificates. 202 white males 35-79 yrs. old evaluated.	238 males who died of causes other than brain tumors, selected as next record from numerical State death files that was of same sex, race, age, region. and time period of death.	For census Industrial categories (one Industry compared to all others), significant excess of glioma deaths for workers from transportation, communication, and utility industry (OR=2.26) and for utility industry alone (OR=13.10). Risks elevated but not significant in occupations involving electricity (OR=2.11). Adding utility workers with all others potentially exposed, OR=3.94 and was significant	Cause and occupation from death certificates.
Loomis & Savitz (1969)	US	Case-control, MOR	Males who died of malignant brain tumors (N=1095), leukemias (N=1694), and acute myeloid leukemias (N=474). Listed in 16 State NCHS industry and occupation coding program.	Men who died from all other causes of death.	For all electrical workers combined, no excess risk for leukemias and acute myeloid leukemia but significant excess for brain cancer. Excess of acute myeloid leukemia for electrical and electronic technicians. Excess mortality from brain cancer for electrical work subgroups. i.e., electrical and electronic technicians (MOR=3.1), electric power installers & repairers (MOR=2.4), and electricians (MOR=1.8).	Large multi-State study, national occupational database. Large case to control ratio (10:1). MORs and confidence Intervals not reported for all occupational or disease subsets. Abstract only. Described In text under cancers of the nervous system.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Reif et al. (1989)	New Zealand	Case-control	19,904 men age ≥ 20 yrs. with cancer drawn from national cancer registry and had occupational information (60% of all eligible registrants). 506 total cases with brain or other nervous system tumor: 452 cases with occupational data included In the study.	When evaluating brain and other nervous system tumors, male cancer registrants with other cancers served as controls.	(a) Significant excess for men In professional and technical occupations (OR=1.32) and In excess for subsets therein for physical scientists (OR=1.37). aircraft and ship officers (OR=1.76), and engineers and architects (OR=1.16). Within the latter group. there was a significant excess for electrical engineers (OR=4.74). When compared only to white collar professional technical workers, the OR for electrical workers dropped to 4.06 but remained statistically significant. (b) Among laborers and production & transport workers, no risk. From broad group, no risk for electrical workers combined (OR=0.78). For more delineated subset, electricians, OR=1.91 but not significant. Elevated borderline risk for plumbers and welders together (OR=2.02); cases only in plumbers.	Used national cancer registry. Attempted to control for socioeconomic factors: risk remained for electrlcal engineers. Small numbers for specific Job types.

TABLE 3-39. STUDIES OF CANCER IN ADULTS (continued)

AUTHOR(S) (YR.)	COUNTRY	STUDY DESIGN	STUDY POPULATION	COMPARISON GROUP	RESULTS	HIGHLIGHTS/DEFICIENCIES
Swerdlow (1983)	England, Wales	PRR	2,159 cases of eye cancer in men over age 15 yrs. between 1962-77 identified from 14 population-based cancer registries. and 2,125 cases in women.	Expected values based on the European population. age-standardized.	Significant increase In Incidence over the time period. Higher incidence In higher social classes. Examined 26 occupational groupings. Significantly increased PRRs for electrical and electronic workers; administrators and managers; and professionals, technical workers, and artists.	Different from other studies because is of eye cancer. Proportional rates influenced by rates of other diseases not under study. Large study in toto of a rare disease. No Information on exposures. Results for electrical & electronic workers unusual given social class results, i.e., these workers tend to be classed as skilled manual; author found this to be of interest.
Malignant Melanoma of the Skin						
DeGuire et al. (1988)	Canada (Montreal)	Cohort, SIR	All workers (N=9590) in Montreal plants of a telecommunications company employed at least six months between January 1, 1976 -December 31, 1983. New and past hires included. Newly diagnosed malignant melanoma cases identified from 30 hospitals and linked with Quebec Tumor Registry.	Expected values based on incident rates for the greater Montreal area.	No cases in women. Ten cases among men, 3.68 expected, SIR=2.7, Cl=1.31-5.02. Significant excess risk (SIR=5.0) in subset who worked less than 20 yrs (low latency group) and were younger but excess not seen in older group who worked over 20 yrs (high latency group). Given very limited information on jobs, about half of the cases involved with technical work and more so in low latency group. High latency group had more office workers or unspecified jobs. Different tumor locations between groups.	Hospital and registry data. Regional rather than national rates used as the standard schedule of rates. Differences between two latency (and age) groups may mean no relationship between cancer and job or presence of a potent carcinogen or an accelerating agent resulting in disease in the newer younger workers. Small number of cases. Study undertaken because of an earlier cluster of 9 cases, not in this study.

Notes: cm=centimeter, CNS=central nervous system, Cl-confidence interval, EM=electromagnetic, EMF=electromagnetic fields, mW=milliwatt, MOR=Mortality Odds Ratio, PIR=Proportional Incidence Ratio. PRR=Proportional Registration Ratio or Rate, similar to PIR, PMR=Proportional Mortality Ratio, NCHS=National Center for Health Statistics, OR=odds ratio, PY=person-years, RF=radiofrequency, SIR=Standardized Incidence Ratio, SMR=Standardized Mortality Ratio.

carcinogenicity of RF radiation. In some studies, follow-up was not sufficiently long. Identification of actual exposure was not possible in most cases; only estimates of microwave radiation were available. Proximity to or work with radar or microwave sources, census tract residency near RF sources, or membership in a ham radio club or listing on Federal amateur radio licensing rosters provided the basis for classifying subjects into cohorts of "exposed" persons. Hence, misclassification of nonexposed persons into these cohorts could have contributed substantially to the absence of the finding of a risk. The studies of amateur radio operators are the most persuasive in demonstrating positive significant associations. The frequencies to which amateur radio operators are exposed at the lower end of the RF portion of the EM spectrum, while the remaining studies in this group generally dealt with higher microwave frequencies; therefore, the potential risks among amateur radio operators may or may not be directly applicable to higher frequency exposures. Based upon the findings from these RF radiation studies, there appears to be little evidence to conclude or deny that a cancer risk exists from exposure to RF radiation.

3.4.3.2. Adults Residentially Exposed to Electromagnetic Fields

Five studies of adults residentially exposed to EM fields of 50 or 60 Hz were reviewed. Four of these were case-control studies; the fifth was a cohort study. Three of the four case-control studies were studies of leukemia only. The fourth case-control study consisted of a series of adult cancer cases and deaths sequentially recorded in vital records offices and to a cancer register during a given period of time, Two of the leukemia case-control studies found no elevated risk of acute nonlymphocytic leukemia in residents of western Washington State exposed to power frequency magnetic fields or risk of myelogenous leukemia with use of electric blankets. However, the third case-control study found a nonsignificant increase in the risk of leukemia to residents of South London in close proximity to overhead lines. The fourth case-control study reported significant risks of CNS cancer, uterine cancer, breast cancer, and lymphoma in Colorado residents living near power lines termed by the investigators as high current configuration. A cohort study of South London residents living in the vicinity of mainly low-voltage substations produced an excess risk of lung cancer in residents living close to the power facilities, but not leukemia. Cohort studies are insensitive to the detection of elevated risks of relatively low incidence diseases such as leukemia, unless large numbers of subjects make up the cohort.

The five studies discussed suffer from several problems that may explain the mixed results that were evident. The two nonpositive case-control studies of leukemia were studies with small numbers of cases, less than 120 in one and 225 in the second, for which the measured exposure in the first was less than 2 mG in the large majority of the residences considered, and in the second study of electric blanket exposure, it was suggested by even the author that their hypothesis might better be tested in a colder, harsher climate than Los Angeles. Presumably this would mean greater exposure to magnetic fields might be found elsewhere. The third suggestive (for leukemia) case-control study of some 769 cases in South London, still reported less than 1% of the population live within 100 meters of overhead power lines. The vast majority of cases were not close enough to overhead power lines to be considered exposed. The remaining case-control study of Colorado residents around Denver, although including 1179 cases of various types of cancers, probably contained few leukemia cases in accordance with normal chronologically recorded incidence and mortality patterns over a specified period of time. Hence, with probably few leukemia cases identified with this method, the study would have little power to detect as significant an elevated risk of leukemia. Similarly, the cohort study, notwithstanding 12 years of observation, only expected approximately six cases of leukemia, and, as a consequence, had little power to detect a significant risk.

In short, these residential studies of adults, although showing mixed results, either tacked evidence of any substantial EM-field exposure to members of the study groups to which they belonged or else lacked sufficient power to detect a significant risk of leukemia. These studies cannot be used to support or refute a possible association of EM radiation with an elevated risk of leukemia, CNS cancer, lymphomas, or even possibly other types of cancer.

3.4.3.3. Occupational Exposure to Electromagnetic Radiation

Twenty-eight studies have been evaluated dealing with cancer incidence or mortality in workers in the electrical, electronic and similar occupations with a high potential for exposure to EM fields, The EM-field exposures in these occupations chiefly involve extremely low frequency fields including 50- to 60-Hz powerfrequency fields.

Eight are cohort studies involving the investigation of mortality in the Canadian labor force, Swedish telecommunication workers, cell room workers in a Swedish chloralkali plant, Swedish male electrical engineers and architects, Swedish power linesmen and power station

operators, Swedish telephone operators, New York telephone workers, and, lastly Geneva painters and electricians. In several of these studies, although they involve jobs that have a potential for exposure to EM fields, many of these workers probably had little exposure because of the ways in which they were chosen, e.g. census data or cancer registry data. The decision to include persons was not based upon actual exposure to EM fields, but rather was based on whether a given broad occupational category, as identified from a cancer registry or census record, includes persons who probably have exposure to EM fields. This means there may have been, and usually are, many persons erroneously included who were not exposed to magnetic fields. These studies border on being called ecological in nature. Two of these cohort studies (transport and communication workers and cable splicers) exhibited a significant excess risk of leukemia. In the former study telephone, telegraph, and power workers demonstrated a high risk of stomach cancer, but not leukemia. The study of New York telephone company employees found an elevated risk of leukemia in cable splicers compared to New York age-specific cancer rates, but when compared to other nonline workers in the same company, the risk was significant based on three cases. The risk of lymphoma was also significant compared to the nonline workers.

However, most of the studies lacked the power necessary to detect even large risks of leukemia given small sample sizes and short observation intervals. Two of these studies demonstrated elevated risks of melanoma in telecommunication workers and in electrical engineers; one was significant. The single most important methodological problem in all of these cohort studies is the lack of definitive personal exposure information. It is probable that actual exposure to EM fields varied considerably within even those subgroups having the highest potential exposure. Without such information and the likelihood of misclassification of exposure in all of the cohort studies, the results from these studies are equivocal.

Ten case-control studies of adults who were diagnosed with either leukemia or central nervous system (brain) cancer were conducted to determine if prior exposure to EM fields may have contributed to the risk of these two site-specific cancers. Six evaluated the risk of leukemia and five evaluated the risk of central nervous system (brain) cancer.

Five of the six leukemia case-control studies reported significantly elevated risks associated with jobs having a high potential for exposure to EM fields. These are: (1) electronic equipment assemblers and radio/ television repairmen in New Zealand, (2) miners working underground for 25 or more years, (3) electrical workers in Sweden, (4) electricians

and welders at U. S. naval nuclear shipyards, and (5) New Zealand electrical workers, namely radio and television repairers, electricians, linemen, and power station operators. No excess risk of leukemia was found, however, in any groups of workers who were part of a 16-state National Center for Health Statistics (NCHS) survey of industries and occupations.

Five of the ten case-control studies were devoted to determining if an excessive risk of central nervous system cancer was in any way associated with jobs having a high exposure to EM fields. Four of the five noted significantly elevated risks of cancer in the following categories of employment: (1) gliomas and astrocytomas in Maryland electricians, telephone servicemen, linemen, railroad and telecommunication workers, engineers as well as electronic engineers; (2) primary brain cancer in workers of Philadelphia, northern New Jersey, and south Louisiana involved with design, manufacture, repair, or installation of electrical and electronic equipment; (3) brain cancer in East Texas male workers involved in highly exposed (EM fields) occupations in the transportation, communication, and the utilities industry; (4) brain cancer in workers identified in a 16-state NCHS survey of industries and occupations. The remaining case-control study did not exhibit any excess risk in New Zealand electrical workers in toto with jobs coded to a Standard Classification of Occupations, but excess risks were found for the more specific job of electricians, and statistically significant excesses were seen for electrical engineers.

All of the case-control studies discussed have problems with respect to who had significant exposure to EM radiation. Simply identifying a job from a register, census listing, death certificate, or questionnaire as having potential exposure is not enough. No measurements of actual exposure have been done in any of these studies. However, there does appear to be some evidence of an increased risk associated with employment in job categories where there is a likelihood of EM-field exposure.

There were four studies that could be characterized as either incidence or standardized incidence studies. Three of these were leukemia studies while the remaining one dealt with a study of melanoma. Of the three leukemia studies, only one reported a significantly elevated risk of chronic lymphocytic leukemia in Swedish electrical line workers, but not electrical workers as a general occupation, based upon census data and the Swedish Cancer Registry. The second reported a nonsignificant elevated risk of leukemia in a broad group of Finnish occupational categories that are assumed by the author to have a high potential for exposure to EM fields. The highest of these was in linemen and cable splicers. The third, a

hypothesis-generating study, was an effort to identify occupations in the Portland-Vancouver Standard Metropolitan Statistical Association (SMSA) that appear to be at a high risk of leukemia based upon census bureau data, hospital records, and cases reported to a cancer registry. A fourth study reported a significant risk of melanoma in male Montreal telecommunication workers derived from hospital records reporting a diagnosis of melanoma. The mean age at diagnosis was younger than usual.

There are four proportionate incidence studies, one dealing with central nervous system cancer (CNS), the second with leukemia, a third and fourth dealing with eye melanoma and leukemia, respectively, in England and Wales. The first found a significantly increased proportionate incidence rate (PIR) of CNS cancer (all types) in Los Angeles electricians and engineers based upon data from the Los Angeles County Cancer Surveillance Program. This same database provided evidence of a significant risk of leukemia, chiefly acute myelogenous, in a second independent study of occupations with likely exposure to electrical and magnetic fields similar to those of Milham. Occupation was that given at the time of diagnosis. The third noted a significantly increased risk of eye cancer in electrical and electronics workers identified as such by the Registrar General of Great Britain. The fourth noted a significant risk of leukemia in 10 electrical occupations based upon data from the South Thames Cancer Registry. These latter two studies the authors term proportionate registration ratio studies (PRR) because the diagnosis is “registered” in a cancer registry.

All four of the proportionate mortality ratio (PMR) studies deal with leukemia as the cancer site. Three of these reported significant risks of leukemia in Washington State residents and in Wisconsin State residents who were occupationally exposed to electric and magnetic fields, that is; electricians, power station operators, and aluminum workers in Washington State and electrical engineers and radio and telegraph operators in Wisconsin. One of these three studies also reported a significant risk of non-Hodgkin’s lymphoma in the same group of potentially exposed occupations. The remaining PMR study reported increased risks of myeloid leukemia in specific electrical occupations, i.e., electrical and electronic engineers, and telegraph and radio operators in England and Wales without providing any significance tests.

It should be kept in mind that PIR and PMR studies have inherent methodological weaknesses. Estimates of site-specific cancer risks that are derived from such studies are not independent of each other, since the sum total of all observed events must equal the

expected. Furthermore, no measurements of actual exposure were available in any of these studies. The authors are forced to rely on surrogates, such as employment in occupations that have a potential for exposure to EM fields, without any proof to substantiate if any or how much exposure actually took place. Under these circumstances it is impossible to do dose-response analyses. This problem is further compounded by use of information on occupation from cancer registers or death certificates. Random misclassification is probably endemic in all of these studies. This particular form of bias will, in all likelihood, lead to a reduction of the estimated risk toward the null. The actual risk, if true, is likely to be higher.

3.4.4. Conclusions

The strongest evidence that there is an association of certain forms of cancer (namely leukemia, cancer of the CNS, and lymphoma) with exposure to magnetic fields comes from the childhood cancer studies. Several studies have consistently found somewhat elevated, statistically significant risks and elevated nonsignificant risks of these three site-specific cancers in children whose exposure to magnetic fields has been estimated by the types of wires near their homes or magnetic field measurements of 2 mG (0.2 μT) or higher. Children do not have the same confounding influences that plague adults in the occupational studies. In fact, the potential confounders and biases that might have had an effect on the data were examined by the authors in some detail and found not to be a serious problem. No other agents have been identified to explain this association. However, there are contradictory results within these same studies, and dose-response relationships could not be substantiated, except in Savitz et al. (1988), based upon limited information on wiring codes. Furthermore, there is little information on personal exposure and length of residency in areas exposed to EM fields.

The studies of residential adult exposures to EM fields provide somewhat mixed evidence of a risk of leukemia, although they lack power and there is little evidence to substantiate exposure to levels of EM fields hypothesized as being associated with cancer. For these reasons these same studies cannot be used to argue that there is support for denying that such an association exists. On the other hand, the case-control study of cancer in Colorado residents does support an association of CNS cancer and lymphoma if proximity to high-current electrical wiring configurations is assumed to be a adequate surrogate for exposure.

Additional, but weaker, evidence that there is an association of leukemia, cancer of the CNS, and perhaps other sites comes from the occupational studies of EM-field exposure. Although many of these studies have found an excess risk of these forms of cancer with employment in certain jobs that have a high potential for exposure to EM fields, but few or no measurements have actually been taken in those occupations. Furthermore, information about occupation has come generally from sources that could be characterized as sketchy. The likelihood that misclassification bias or information bias is present in these studies is a distinct possibility.

The studies of RF radiation in adults exposed to microwave radiation or radar, particularly ham radio operators, produced mixed results. Again, the lack of definitive information about the kind, level, and length of exposure, as well as other confounders that may be responsible for the excess risks seen in the positive studies, precludes conclusions that a positive association exists with exposure to RF radiation.

In conclusion, after an examination of the available epidemiologic data over the last 15 years, there is evidence of a positive association of exposure to magnetic fields with certain forms of site-specific cancer, namely leukemia, cancer of the CNS, and, to a lesser extent, lymphomas. This is supported by many studies of children and adults across many different populations and subgroups, and in jobs and conditions in which there is a high potential for exposure to EM fields. Attempts to identify potential confounders have been made, but no single confounder has been identified that could explain the positive results. Much more work needs to be done to better refine exposure. This is more problematic for adults than for children. A dose-response relationship with magnetic field strength has not been firmly established, and potentially confounding influences have not entirely been ruled out; therefore, a sufficiently strong case for causality has not yet been made. However, there is a link between exposure to EM fields and certain forms of site-specific cancer, namely leukemia, CNS, and lymphoma.

3.5. OTHER END POINTS

Several epidemiologic studies have evaluated end points other than cancer, chiefly reproductive effects in work environments or in relation to specific products such as video display terminals, electric blankets, and heated water beds. These reports were not reviewed here because the purpose of this review was to focus solely on cancer.

3.6. ONGOING RESEARCH

Many epidemiologic studies are now being conducted and should be completed over the next few years. These studies are being conducted in several countries and examine children and adults and residential and occupational exposures. This research is summarized in Table 3-40.

TABLE 3-40. ONGOING EPIDEMIOLOGIC STUDIES ON ELECTROMAGNETIC FIELDS AND CANCER

Institution	PI	Sponsor	End Point	Study Type:Cases/ Controls	Exposure Assessment	Confounders	Due Date
I. Occupational Studies							
USC USA	Joseph Bowman	EPRI	ALL, ANLL, CLL, CML	CC[c]	D	Ch, IR, RF/MW	1990
JHU-SPH USA	Genevieve Matanoski, Patrick Breysee	EPRI	All L except CLL	CC:200/800	D	J	1990
JHU-SPH USA	Genevieve Matanoski, Patrick Breysee	NIEHS, EPRI	All CA	Co:391 CA	D	Age, J	1990
Univ. of Bern[d] Switzerland	Christoph Minder	Swiss National Fund	L lymphoma	CC:23/177 & 207	D/I	IR	1990
Mohash MS[e] Australia	Michael Salzberg	N/A	Glioma	CC:425/850	I	Ch, SC, Sm	1991
McGill University Canada	Giles Theriault	HQ, QH, EDF	L, BC, skin melanoma	CC:6000/17000	D	Sm, IARC-Ch carcinogens	1991
UNC USA	David Savitz	EPRI	L, BC	Co:215L, 186 BC	D/I	PBCs, Sv	1991-1992
NSPH-OCF Brazil	Sergio Koifman	FINEP	All CA	CC:347/1129	I	Sm	1992
Wellington MS New Zealand	Neill Pearce, Peter Bethwaite	Wellington MS	ALL, AML, ANLL	CC:300/800	I	E, SC, Sv	1992
NIOH Sweden	Birgitta Floderus	NEA. NIOH	ALL, AML, CLL, CML, Glioma	CC:200BC, 300L/1000	C/I	Bz, Fm, PD, SC, Sv	1992

TABLE 3-40. ONGOING EPIDEMIOLOGIC STUDIES ON ELECTROMAGNETIC FIELDS AND CANCER (continued)

Institution	PI	Sponsor	End Point	Study Type:Cases/ Controls	Exposure Assessment	Confounders	Due Date
II. Residential Studies							
Univ. of Leeds UK	David Clayden	GEGB	All CA/c	CC:374/388	I	H	1989
USC USA	John Peters	EPRI	UC	CC:232/232	D/I	Ch, IR, PO, Ps, SM	1990
Univ. of Leeds UK	Ray Cartwright	CEGB	ALL, AML, CLL, CML, DHL	CC:3200/3200	I	H	1990
Maastricht MS The Netherlands	Jan Meijers	Maastricht MS	All L, BC	Co:3549 people, 32-yrs. follow-up	I	None	1991
Karolinska Inst. Sweden	Anders Ahlborn	Karolinska Institute, NBE	L/a, BC.a, all CA/c	CC:(300 L, 425 BC)/725; (20-0 CA/c)/ 140	D/I	E, H, PD, PO, SC	1991
NTU Taiwan ROC	Ruey Lin	National Science Council	L/c, BC/c	CC:216/422	D/I	Al, Ch, IR, MP, PO, Sm	1991
USC USA	Susan Preston-Martin	State of California	BC/c	CC:300/300	D/I	Ch, IR, MP, PO, Ps, SC, W	1993
Univ. of Toronto Canada	Anthony Miller	OH	L/c	CC:200/400	D/I	IR, PO	1993
Univ. of Helsinki	Markku Koskenvuo	Imatran Voima Oy[b]	CA/CA/C	CC[c], Co[c]	I	J, SC, Sm	1993

TABLE 3-40. ONGOING EPIDEMIOLOGIC STUDIES ON ELECTROMAGNETIC FIELDS AND CANCER (continued)

Institution	PI	Sponsor	End Point	Study Type:Cases/ Controls	Exposure Assessment	Confounders	Due Date
II. Residential Studies (continued)							
NCI/CCSG USA	Martha Linet, Zdenek Hrubec	NCI	L(ALL)/c	CC: 1000/1000	D/I	Bz, Ch, E, EB, Fm, H, IR, MP, Pb, PD, Po, Pa, PVC, SC, SmSv	1994
CCACA Canada	Richard Gallagher	EPRA, DEA, HWC	L/c	CC:395/395	D/I	Bz, IR, PO, Pa	1994
IARC France	Peter Boyle	LARC	All L	CC:1500/1500	D/I	Bz, EB, Fm, H, IR, PCBs, PO, Pa	1994

Abbreviations used in Table 3-40:

Al:	Alcohol	Co:	Cohort
ALL:	Acute lymphocytic leukemia	D:	Direct measurements of individuals or workplaces
AML:	Acute myelogenous leukemia	E:	Ethnicity
ANLL:	Acute non-lymphocytic leukemia	EDF:	Electricite de France
BC:	Brain cancer	EPRI:	Electric Power Research Institute
BC/a	Adult brain cancer	FINEP:	Brazilian Research Funding Council
BC/c	Childhood brain cancer		
Bz:	Benzene	H:	Type of housing
CA:	Cancer	HQ:	Hydro-Quebec
W C :	Childhood cancer	HWC:	Health and Welfare Council
CC:	Case-control	I:	Indirect estimate of exposure
CCABC:	Cancer Control Agency of British Columbia	IARC:	International Agency for Research on Cancer
CCSG:	Children's Cancer Study Group	IR:	Ionizing radiation
DEA:	Canadian Electrical Association	J:	Job history
CEGB:	Central Electricity Generating Board	JHU-SPG:	Johns Hopkins University School of Public Health
Ch:	Chemicals	L:	Leukemia
CLL:	Chronic lymphocytic leukemia	L/a:	Adult leukemia
CML:	Chronic myelogenous leukemia	L/c:	Childhood leukemia

Abbreviations used in Table 3-40 (continued)

MP:	Medication of parents
MS:	Medical school
N/A:	Not available
NBE:	National Board of Energy, Sweden
NCI:	National Cancer Institute
NEA:	National Energy Administration, Sweden
NHL:	Non-Hodgkin's lymphoma
NIEHS:	National Institute of Environmental Health Sciences
NIOH:	National Institute of Occupational Health
NSPH-OCF:	National School of Public Health, Osvido Cruz Foundation
NTU:	National Taiwan University
OH:	Ontario Hydro
Pb:	Lead
PCBs:	Polychlorinated biphenyls
PD:	Population density
PO:	Parents occupations
PS:	Pesticides
PCV:	Polyvinyl chloride
RF/MW:	Radiofrequency/microwave radiation
ROC:	Republic of China
SC:	Social class
Sm:	Smoking
Sv:	Solvents
UNC:	University of North Carolina
USC:	University of Southern California
W:	Drinking water

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4. ANIMAL STUDIES

This section evaluates the published reports of lifetime bioassays that have studied radiofrequency (RF) and modulated RF radiation. These studies are:

- University of Washington (Guy et al., 1985) rat study of pulsed 2450-megahertz (MHz) radiation.
- Prausnitz and Susskind (1962) mouse study of pulsed 9.270-MHz radiation,
- Spalding et al. (1971) mouse study of unmodulated 800-MHz radiation.
- Szmigielski et al. (1982) mouse study of 2450-MHz radiation in three specialized mouse assays: growth of lung cancer explant tissue; growth of spontaneous breast tumors; and growth of benzo[a]pyrene-induced skin cancer.
- Baum et al. (1976) rat study of high-intensity pulsed radiation spanning the frequency range from 0 to 50 MHz.

No reports of lifetime animal exposures to extremely low frequency (ELF) fields have been published.

A detailed analysis of unpublished histopathological records from the Guy et al. (1985) rat study is described here. There is a greater emphasis on this study than on the other studies reviewed in this section because it has not yet been published in any other form. The main features of the study are described in Section 4.1.1 and its subsections, 4.1.2.6.1, 4.1.2.7, and 4.7.

4.1. UNIVERSITY OF WASHINGTON LONG-TERM RAT STUDY

This study was published as a series of nine reports dated from September 1983 through August 1985 (Guy et al., 1983a, b, 1985; Chou et al., 1983; Johnson et al., 1983, 1984; Kunz et al., 1983, 1984, 1985). In a summary of these reports, Dr. Robert McGaughy of EPA's Office of Health and Environmental Assessment (OHEA) concluded that there was a need to have a more complete animal-by-animal description of the survival and histopathologic findings than was provided by the published reports (McGaughy, 1987). Consequently, he asked Dr. Lawrence Kunz, the pathologist in the University of Washington study, to provide a description of the histopathologic findings for each animal along with tables summarizing these findings. His report (Kunz, 1988) formed the basis for the analysis of the survival and histopathologic

data given in this document. The data were analyzed by Dr. Robert McGaughy and Sharon O'Boyle of the Computer Sciences Corporation (CSC).

The University of Washington study was designed to simulate, in experimental animals, the maximum absorbed power (0.4 watts per kilogram body weight) of 450-MHz radiation which is permitted by the 1982 American National Standards Institute (ANSI) 95.1 standard under the worst-case conditions when people with the body weight of children are being continuously exposed (Guy et al., 1983b). The frequency of 450 MHz was chosen by the U.S. Air Force, which sponsored the study, to represent a typical midrange radar system. For this purpose, a frequency of 2450 MHz was chosen for the rat exposure. The rationale for this choice was that the ratio of wavelength to maximum body dimension is about the same for these two forms of radiation.

4.1.1. Description of Study

4.1.1.1. Animal Facility

An animal exposure facility was designed and built especially for this study (Guy et al., 1983a). It consisted of two rooms, each capable of housing 100 rats. The animals were housed individually in waveguide chambers which allowed unrestrained movement during irradiation. Radiofrequency power was delivered to one-half of the chambers. The location within each room of the exposed and nonexposed chambers (or animals) was random. In each room, there were 50 exposed and 50 nonexposed animals. People could enter the room only from clean hallways which in turn could be entered only through a shower after donning autoclaved garments. Soiled cages and waste collectors were taken out of the room into a common "dirty" hallway adjacent to both rooms. An air pressure gradient was maintained in which air flowed from the clean hallways to the ceiling of the exposure rooms into the dirty hallway. The air flow rate in the exposure rooms was approximately 22 exchanges per hour and the ambient temperature was held constant at 21 ± 1°C. Microwave power was delivered continuously for 21.5 hours per day, allowing the remaining time for daily maintenance procedures.

4.1.1.2. Animals

Sprague-Dawley rats were chosen for the experiment for several reasons according to the authors: (a) Since it is an outbred strain, its genetic heterogeneity would mimic the genetic variation in human populations; (b) Males grow rapidly-to their adult weight, lessening the

trauma of drawing blood samples; (c) They are docile and easily handled in the laboratory. The rats were Cesarean-born and barrier-reared animals ordered in the summer of 1980 from Camm Research Institute in Wayne, New Jersey. The colony was serologically tested at Yale University and found to be free of specific pathogens. They were fed Purina Certified Autoclavable Rodent Chow which was checked for acceptable levels of required nutrients after being autoclaved.

4.1.1.3. Microwave Exposure

The delivery of RF power to the animals was carefully calculated to simulate human exposure conditions. The details are given in two reports (Guy et al., 1983b; Chou et al., 1983). Scale models of the human body with synthetic fluids simulating the RF power absorption of tissues were constructed. The power absorbed by these models was measured, and the results were scaled to full-sized humans. The spatial distribution of the absorbed power in the models was also measured with a computerized thermographic system. This system generated maps of the distribution of absorbed power in different regions of the body. These maps reveal inhomogeneities in the absorbed dose with complicated patterns that depend on body posture and polarization of the radiation. Similar measurements were made on models simulating rat exposure, and the parameters of the rat waveguide exposure chamber radiation were adjusted to give average and peak-to-average ratios analogous to the human exposure. The authors found that, because the human shape is more irregular than the rat shape, the peak-to-average ratios in humans can approach 13, whereas with rats the ratio is typically only 2 to 3. The parameters of the animal irradiation chosen after the analysis of these measurements were as follows (Guy et al., 1983b): input power to each waveguide: 0.14 watts (W); average power density in the chamber: 0.48 milliwatts per square centimeter (mW/cm^2); average specific absorption rate (SAR): 0.4 watts per kilogram (W/kg) body weight for 200-gram (g) rats and 0.1 W/kg for 800-g rats; predicted range of hot-spot power for a 330-g rat: 0.63 to 1.33 W/kg; frequency: 2450 MHz.

The 2450-MHz microwave power was modulated with the pattern shown in Figure 4-1 (Guy et al., 1983a, page 41). It was first modulated with 10 microsecond-wide pulses occurring at a rate of one pulse per 1.25 milliseconds. Then a train of 50 such pulses, each train lasting 62.5 milliseconds, was switched on and off every 0.125 seconds, so that there were eight of these pulse trains occurring each second. Therefore, in terms of frequency, this signal has three predominant frequencies: (1) the microwave component at 2450 MHz; (2) the pulse repetition rate of 50/(0.0625 seconds) = 800 pulses per second (pps); and (3) the square wave

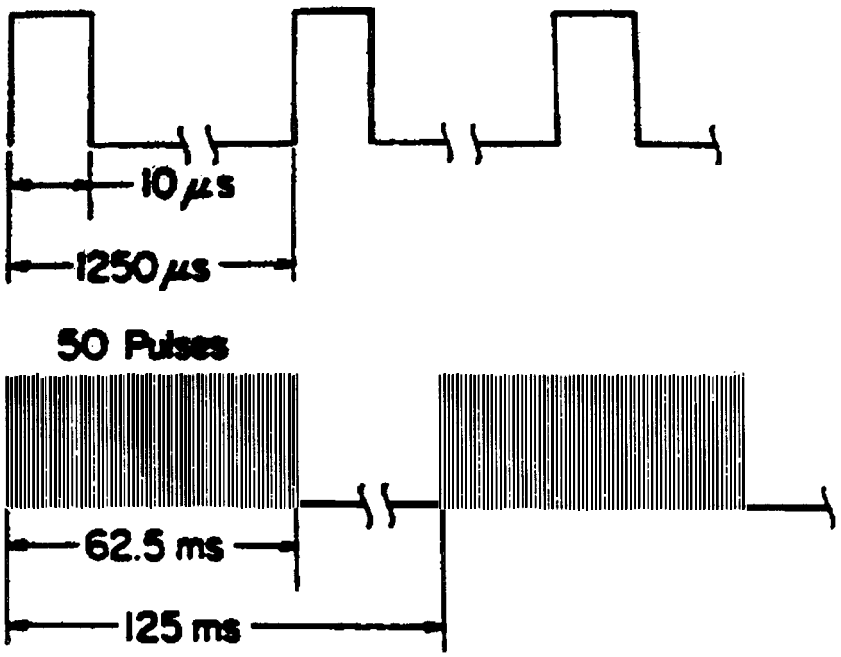

Figure 4-1. Modulation characteristics of the pulsed microwave source: fifty 10-microsecond-wide pulses per group, with a repetition rate of 800 pulses per second during the burst of 50 pulses.

modulation of 1/(0.125 seconds) = 8 pps. This radiation was delivered to the animal exposure chambers continuously for 21.5 hours per day. Starting at 8:00 a.m. each morning, 7 days per week, the microwave power was turned off for 2.5 hours while the animals were taken out of their cages, the required measurements on the animals were made, the cages were cleaned, the water and food supply were replenished, and the animals were returned to their cages. These operations were completed for the entire colony of 200 animals between the hours of 8:00 a.m. and 12:15 p.m. each day. One could say that the animals were experiencing another diurnal frequency component in the radiation of 1/(24 hours) or 1.2×10^{-5} Hz as well as the three components listed above.

Since a specific absorption rate of 0.4 W/kg is as high as 25% of the resting and 15% of the average metabolic rate of an old lethargic 600-g rat, and about 10% of the resting and 5% of the average metabolic rate of a young 200-g rat, the experiment included several measurements of thermoregulation, energy metabolism, and growth (Guy et al., 1983a).

However, body temperature was not measured.. The cage temperature was kept at 21°C, which is below the "thermoneutrality" temperature range (28° C to 33° C) in which the metabolic rate is a minimum. The lower ambient temperatures were necessary to avoid placing an extra metabolic load on the animals receiving the radiation.

This description of the microwave exposure obviously involves several parameters and, as we have stated in Chapters 1 and 7, the parameter, or the combination of parameters which is relevant to potential carcinogenicity, is not known.

4.1.1.4. Protocol of the Experiment

The following quote from Johnson et al. (1984) succinctly describes the protocol.

> Two hundred male rats at 3 weeks of age were obtained from a commercial, barrier-reared colony and randomly assigned to exposed and sham-exposed treatment conditions. Throughout this [exposure] period all surviving animals were bled at regular intervals, and blood samples were analyzed for a panel of serum chemistries, hematological values, protein electrophoresis patterns, and thyroxine (T_4) and serum corticosterone levels. In addition to daily measures of body mass and food and water consumption, oxygen consumption and carbon dioxide production were periodically measured on a subpopulation of the exposed and sham-exposed groups. At regular intervals throughout the study, activity was assessed in an open-field apparatus. After 13 months, 10 rats from each treatment group were killed for immunological competence testing, whole-body analysis, and gross and histopathological examinations. [The histopathologic examinations were done on all grossly evident lesions and on 36 tissues of each animal.] The surviving 23 rats were killed at the end of 25 months [following the beginning of exposure], and similar analyses were made of 10 from each group.

4.1.2. Results of the Study

During the study, measurements were made on a variety of physiologic functions. We state here the conclusions of these measurements without describing the results in detail. The separate volumes describing the results are as follows: Volume 4, Open-field behavior corticosterone; Volume 5, Evaluation of the immune system's response; Volume 6, Hematological, serum chemistry, thyroxine, and protein electrophoresis evaluations; Volume 7, Metabolism, growth, and development; Volume 8, Evaluation of longevity, cause of death, and histopathological findings.

4.1.2.1. Behavior and Corticosterone

Observation of the degree of activity in whole body movements was made every 6 weeks during the first year and every 12 weeks during the second year. No differences in the exposed vs. control groups were observed except in the first session. Plasma corticosterone was measured every 12 weeks during the first year and just before the termination of the

experiment. No significant differences were found, indicating no cumulative effects of the exposure on anxiety, fear, or stress.

4.1.2.2. Immune Competence

At the 13-month interim kill and following the end of the experiment, the following three tests were performed: (1) numbers of B- and T-cell antigen-positive lymphocytes and complement-bearing lymphocytes; (2) in vitro test of the proliferation of spleen lymphocytes induced by five mitogenic agents; and (3) the ability of spleen cells to form antibodies and lyse cells in response to immunization with sheep red blood cells, which are T-cell dependent antigens.

The first test showed that at 13 months the exposed group had a significantly larger number of B- and T-cells than did controls, but no difference was seen at 25 months. There were no differences at either time in the percentage or total number of cells with complement receptors in the spleen, which the authors interpret as an indication that the exposure does not alter the maturation of lymphocytes.

In the second test, the exposure significantly enhanced the effectiveness of three mitogens and significantly decreased the effectiveness of a different mitogen at the 13-month test.

In the third test, the exposure had no significant effect on the response to the antigen.

4.1.2.3. Blood Chemistry and Hematologic Measurements

A group of 11 hematologic measurements and 21 serum chemical measurements and serum protein electrophoresis patterns were performed every 6 weeks during the first year and every 12 weeks during the second year. There were no significant differences between the exposed and control group for any of the measurements. Thyroxine levels were determined every 12 weeks, and no effect of exposure was detected, although the expected age-related decrease in thyroxine was observed in both groups. The authors interpret this finding as an indication that the functioning of the entire hypothalamic-pituitary-thyroid endocrine system which regulates tissue metabolism was not adversely affected by the exposure.

4.1.2.4. Metabolism

Daily measurements of body weight and food and water consumption showed no difference between exposed and control groups. Food intake in these animals was almost twice that of animals kept under ambient temperature conditions; this difference is similar to

earlier results in the laboratory and can be attributed to the lower temperature of the cages (21° C) as compared to "thermoneutral" conditions (25° C to 33º C) under which the metabolic rate vs. temperature is at a minimum.

Weight measurements of heart, brain, liver, kidney, testicles, and adrenal organs were made on 10 animals in each exposure group at 13 months and on 12 animals in the exposed group and 11 animals in the control group at the termination of the experiment. No exposure-related differences in any organ occurred at 13 months. At the end of the experiment, only the adrenal weights showed differences between treatment groups. Data for the mean adrenal weight were as follows (Johnson et al., 1984):

The authors observed that at the end of the experiment there was a statistically significant

	Control		Exposed	
	Adrenal Weight, grams (mean ± SE)	Number of Animals	Adrenal Weight, grams (mean ± SE)	Number of Animals
Animals with adrenal tumors	0.069 ± 0.004	4	0.132 ± 0.016	7
Animals without adrenal tumors	0.068 ± 0.005	7	0.092 ± 0.017	5
Ail animals	0.068 ± 0.004	11	0.116 ± 0.014	12

increase in adrenal weight in all animals. However, when animals with benign adrenal tumors were separated from the remainder in the analysis, there was no statistically significant difference in weights in animals without tumors. Therefore, the authors concluded that the increased adrenal weight was related to the tumors and irrelevant to metabolic processes. The slightly higher weight in exposed animals without tumors (compared to control animals without tumors) was attributed to one animal with a hyperplastic adrenal cortex that was secondary to a pituitary tumor.

Several chemical measurements of the body carcass were made on animals at 13 months and at the end of the experiment. These were total moisture, total ash, total crude fat, protein-bound nitrogen, nonprotein-bound nitrogen, six fatty acids, and 27 minerals. No exposure-related differences occurred in any of these measurements. The authors interpreted this to mean that there is no evidence that the RF treatment irreversibly altered the body's metabolic processes.

Oxygen consumption and carbon dioxide production were measured under the same waveguide conditions as in the long-term study but after termination of the experimentwith a

separate set of 36 animals obtained from the same suppliers. Measurements were performed daily for 30 days encompassing both daytime and nighttime hours. No exposure effect was observed in mature rats for either daytime or nighttime period. However, in young animals the nighttime CO_2 production, O_2 consumption, and the ratio of CO_2 production to O_2 consumption were lower in the exposed group than the control group. The authors explained this finding with the postulate that: (a) under the slightly lowered temperature conditions of the experiment, the absorbed radiation in the exposed group contributes to the maintenance of the core temperature, whereas in the control group, increased metabolism supplies the heat necessary to maintain the core temperature; and (b) in young smaller animals, the specific absorption rate (W/kg) is larger than in older, larger animals.

4.1.2.5. Survival

The times of death in the new pathology report (Kunz, 1988) were analyzed using the "LIFETEST" procedure of the SAS set of statistical analysis programs (SAS, 1985). The results of this test showed that the exposed group had a slightly longer time to 50% survival (669 days) than did the control group (653 days). However, the difference in mean survival time for the exposed group (649 ± 17 days) compared to that of the control group (623 ± 19 days) was not statistically significant. At the end of the 25-month exposure period, 12 animals of the exposed group and 11 animals of the control group were still alive (Figure 4-2). The original report (Kunz et al., 1985) came to the same conclusions qualitatively but did not give the actual mean time to death or note the slightly longer survival time in exposed animals,

The most frequent cause of death in both groups was kidney disease and urinary tract blockage (Table 4-1). Benign and malignant neoplasms were not frequent as a cause of death, but pituitary adenomas (4 in exposed vs. 9 in controls), lymphosarcomas (4 vs. 2) and pituitary carcinomas (2 vs. 0) each were the cause of more than two deaths, and eight other types of benign or malignant neoplasms were the cause of one death each. There were no statistically significant differences between the groups for any of the causes of death.

4.1.2.6. Histopathologic Findings

The Kunz et al. (1985) report tabulated, for each animal in the study, the cage location, age at death, mode of death (spontaneous or killed), number of nonneoplastic lesions, and number of neoplastic lesions, classed separately as benign, primary, or metastatic. It also listed the total number of nonneoplastic and neoplastic lesions by type for the exposed and

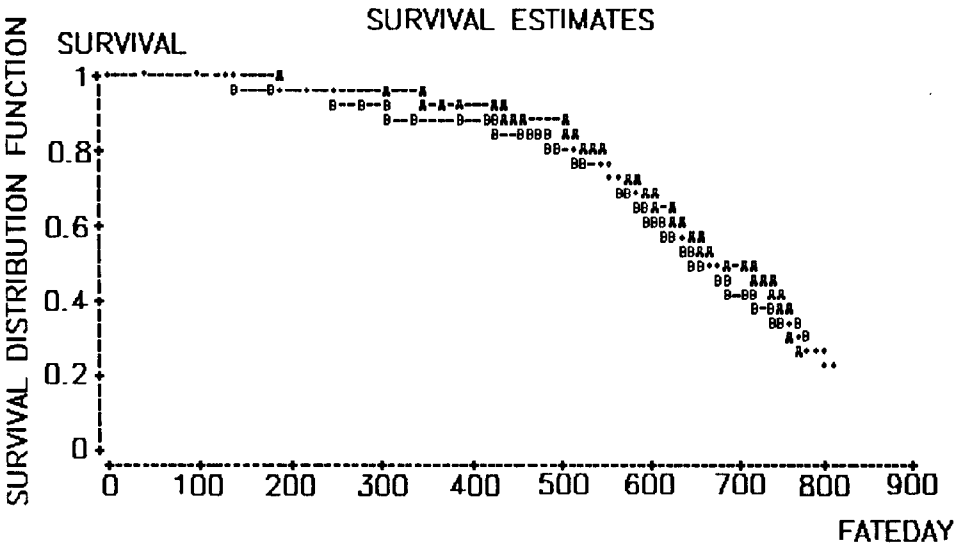

Figure 4-2. Kaplan-Meier analysis of survival: exposed (A) vs. control (B).

control groups separately. However, it did not have the information necessary to specify the number of animals with any particular tumor type or combination of types or the times of death for these animals.

The new report (Kunz, 1988) has a complete description of histopathologic findings for each of the 200 animals. A description of the findings for a typical animal is given in Table 4-2. It shows the animal number, time of death, cause of death, and the histopathologic diagnosis for each tissue.

At the EPA, Dr. Robert McGaughy (OHEA) and Sharon O'Boyle (CSC), converted these descriptions to a computer database coded so that the animals with any arbitrary specified attribute or combination of attributes could be selected and examined for any other attribute.

This database was the source for the analysis presented below.

4.1.2.6.1. Tumor incidence. Table 4-3 shows the number of animals with tumors of various organ sites and tumor types, the time of appearance of the first tumor at each site, and the crude incidence of combined benign and malignant tumors of each site.

TABLE 4-1. FREQUENCY TABLE FOR CAUSE OF DEATH: ALL ANIMALS

Cause of Death	Group	
	Control	Exposed
Chronic progressive nephropathy	15	16
Urinary tract blockage	17	9
Final sacrifice	11	12
interim sacrifice	10	10
Atrial thrombosis	9	7
Anesthetic/bleeding	9	5
Pituitary adenoma	9	4
Indeterminable	4	5
Lymphosarcoma	2	4
Cardiomyopathy	2	4
Degenerative vacuolar encephalopathy	1	3
Asphyxiation	--	3
Pituitary carcinoma	--	2
Gastric squamous papilloma	1	1
Congestive heart failure	1	1
Nephroblastoma	1	1
Auditory sebaceous carcinoma	--	1
Gastric hyperkeratosis	--	1
Squamous cell carcinoma	--	1
Myocardial hypertrophy	1	--
Pyelonephritis	--	1
Liposarcoma	--	1
Hemangiosarcoma	--	1
Adrenal carcinoma	1	--
Pancreatic islet cell adenoma	1	--
Encephalopathy	1	--
Urinary tract blockage (calculus)	1	--
Adrenal cortical carcinoma	--	1
Hemopericardium	--	1
Glomerulonephropathy	--	1
Hemorrhagic cystitis	1	--
Transitional cell carcinoma	--	1
Cardiac neurinoma	1	--
Enteroliathisis	--	1
Chronic suppurative nephritis	1	--
Cerebral hemorrhage	--	1
Cerebral thrombosis	--	1

SOURCE: Kunz, 1988.

TABLE 4-2. SINGLE ANIMAL, MICROSCOPIC OBSERVATIONS

Animal number: E6 Sex: Male Group: (1) Exposed Fate: (Day = 661) Spontaneous death

Cause of death	-Chronic progressive nephropathy
Bone marrow	-Within normal limits
Adrenal	-Adenoma, cortical, focal, moderate
Thyroid	-Perifollicular cell adenoma, focal, moderate
	Atrophy, diffuse, moderate
Parathyroid	-Within normal limits
Trachea	-Within normal limits
Esophagus	-Within normal limits
Brain	-Within normal limits
Heart	-Cardiomyopathy, ventricle, L., multifocal, moderate
	Cartilage at heart base, focal, mild
Skeletal muscle	-Within normal limits
Spleen	-Hemosiderosis, diffuse, mild
Liver	-Inflammation, chronic, perilobular, multifocal, minimal
	Hepatocellular adenoma, focal, moderate
Lung	-Hyperplasia, lymphoid, peribronchial, multifocal, minimal
	Congestion, diffuse, moderate
Salivary gland, parotid	-Within normal limits
Salivary gland, sublingual	-Within normal limits
Salivary gland, mandibular	-Within normal limits
Lymph node, cervical	-Histiocytosis, diffuse, moderate
	Hemosiderosis, diffuse, moderate
Thymus	-Within normal limits
Lymph node	-Within normal limits
Kidney	-Chronic progressive nephropathy, diffuse, moderate
Urinary bladder	-Within normal limits
Testis	-Within normal limits
Epididymis	-Within normal limits
Prostate	-Within normal limits
Seminal vesicle	-Within normal limits
Stomach	-Within normal limits
Duodenum	-Within normal limits
Jejunum	-Within normal limits
Ileum	-Within normal limits
Cecum	-Within normal limits
Colon	-Within normal limits
Pancreas	-Within normal limits
Skin	-Within normal limits
Eye	-Within normal limits
Harderian gland	-Within normal limits
Ear, middle	-Within normal limits
Nasal tissues	-Within normal limits
Spinal cord	-Within normal limits
Stifle joint	-Within normal limits
Pituitary	-Cyst, focal, moderate
Zymbal's gland	-Inflammation, chronic, periductal, multifocal, mild
Preputial gland	-Within normal limits

SOURCE: Kunz, 1988.

TABLE 4-3. CRUDE INCIDENCE AND TIME OF APPEARANCE OF NEOPLASTIC LESIONS

Site/Type	Number of Animals with Tumors		Time of First Tumors[a] (days)		Crude Tumor Incidence[b]	
	Control	Exposed	Control	Exposed	Control	Exposed
Adrenal cortex	12	12	619	589	12/85	12/76
adenoma	11	9			(14%)	(16%)
carcinoma		3				
Adrenal medulla		7	811	673	1/73	7/67
benign pheochromocytoma	1	7			(1.4%)[c]	(10%)[c]
Thyroid	9	12	448	661	9/85	12/76
parafollicular cell adenoma	9	10			(11%)	(16%)
parafollicular cell carcinoma	0	2				
Liver		3	791	590	1/85	3/76
hepatocellular adenoma	0	3			(1.2%)	(3.9%)
hepatocellular carcinoma		0				
Pituitary	21	19	457	540	21/85	19/76
adenoma	21	17			(25%)	(25%)
carcinoma	0	2				
Testes	0	2	--	626	0/85	2/76
interstitial cell tumor	0				(0%)	(2.6%)
squamous cell carcinoma	0					
Epididymis	0	1	--	650	0/85	1/76
squamous cell carcioma	0				(0%)	(1.3%)
Pancreas	2	2	781	650	2/85	2/76
islet cell adenoma	2				(2.4%)	(2.6%)
squamous cell carcinoma	0					
Urinary bladder	0	2	-	590	0/85	2/76
benign transitional cell	0				(0%)	(2.6%)
malignant transitional cell	0	1				
Stomach	4	4	248	639	4/85	4/76
gastric squamous papilloma	4	3			(4.7%)	(5.3%)
squamous cell carcinoma	0					
Duodenum	0		--	569	0/85	1/76
squamous cell carcinoma	0				(0%)	(1.3%)
Lymph node	0	1	--	590	0/85	1/76
transitional cell carcinoma	0	1			(0%)	(1.3%)
Soft tissues, thorax	0	2	--	505	0/85	2/76
fibroma	0				(0%)	(2.6%)
hemangiosarcoma	0					
Mesentery	0	2	--	552	0/85	2/76
liposarcoma	0				(0%)	(2.6%)
transitional cell carcinoma	0					
Lymphosarcoma[d]	3	4	448	438	3/85	4/76
					(3.5%)	(5.3%)

TABLE 4-3. CRUDE INCIDENCE AND TIME OF APPEARANCE OF NEOPLASTIC LESIONS (continued))

Site/Type	Number of Animals with Tumors		Time of First Tumor[a] (days)		Crude Tumor Incidence[b]	
	Control	Exposed	Control	Exposed	Control	Exposed
Skin						
benign			615	656		
sebaceous adenomas	0	2				
basal cell tumor	0	1				
keratoacanthoma	1	1				
lipoma	0	1				
pilomatricoma	0					
neurilemoma, hypodermis	1	0				
malignant						
auditory sebaceous carcinoma	0	1				
basal cell tumor	0	1				
fibrosarcoma, dermis	0	1				

[a]Adenomas occurred before carcinomas at every site.
[b]Crude tumor incidence is defined as the number of animals with tumors divided by the number alive at the time of the first tumor in each treatment group minus the number of killed animals.
[c]The incidence of adrenal medulla tumors is presented in Table 4-4 and accompanying text.
[d]In the control group, the three animals had lymphosarcomas in 15 different tissues, and in the exposed group, the four animals had lymphosarcomas in 21 different tissues.

For organ sites where adenomas are considered to progress to malignant tumors, which is true for most of the sites in the table, the total number of animals is given in a separate column, For skin tumors, however, these totals are not given because there is no clear justification for considering these very different tumors a single entity. The animals with lymphosarcoma had widespread metastases, and the separate tissues in which this occurred are not listed.

Table 4-3 shows the time of death of the animal which had the first tumor at each organ site. In all cases adenomas occurred before carcinomas. The crude incidence is defined here as the number of animals with a tumor at a site divided by the number of animals alive at the time of the first tumor and at risk for the development of tumors for the rest of the natural lifespan. It is called “crude” because it is unadjusted for mortality and it represents only an approximation of the number of animals at risk to the tumor. Ten animals in each group were intentionally killed at day 448. The first tumor in the control group was a stomach papilloma at day 248, when 95 animals were alive, and the first tumor in the exposed group was a lymphosarcoma, appearing at day 438 when 86 animals were alive. The number of animals considered to be at risk for the development of lifetime tumors is 10 less than this, or 85

control animals and 76 exposed animals. These latter numbers were used as the denominators for the crude incidence column.

In a more detailed examination of the adrenal tissues, Dr. Kunz noted, in a letter to Dr. Robert McGaughy (July 5, 1990), that although the adrenal glands of all 200 animals in the experiment were examined, the adrenal medulla tissue of some animals was missing from the histopathological section. He also noted that for other animals the adrenal medulla tissue from both left and right glands was present, whereas for some animals only one of the two adrenal medullas was present. Table 4-4 shows the number of animals in each of these four categories (exposed or control and one medulla or two medullas present) and the frequency of animals with tumors in these categories.

For the exposed group, the number of animals at risk for the detection of adrenal medulla tumors is equal to the number of animals with medulla tissue (90), minus the number with medulla tissue that died before day 438 (13), minus the number of serial sacrificed animals with medullas present (10), which is equal to 67 animals. In this calculation we noted that, although 14 animals died before day 438, one of them had no medulla present. Similarly, for the control group, the number of animals at risk for the detection of adrenal medulla tumors is 88 - 5 - 10 = 73 animals, Therefore, the crude incidence of these tumors is 7/67 = 10% in the exposed group versus 1/73 = 1.4% in the control group; p = 0.023 using the Fisher's exact one-tailed test. These incidence figures are listed in Table 4-3.

In the interpretation of adrenal medulla tumors (Table 4-4) one should check whether the presence of a variable number of adrenal medulla tissues per animal (0, 1, and 2) has appreciable effect on the tumor incidence. This is not likely to be a problem for the following reasons: (a) there is no appreciable difference in the number of animals with no adrenal medulla between the exposed group (10 animals) and the control group (12 animals), and (b)

TABLE 4-4. FREQUENCY OF BENIGN ADRENAL MEDULLA TUMORS

Category	Treatment Group	No. of Medullas Present	Animals in Category	Animals with Benign Tumors
1	Exposed	2	70	6
2	Exposed	1	20	1
3	Control	2	60	1
4	Control	1	28	0

SOURCE: Adapted from information provided by Kunz in a letter to McGaughy (July 5, 1990).

in the exposed group, the incidence of tumors among animals with two tissues present (6/70 = 8.5%) is not significantly different than among animals with one tissue present (1/20 = 5%).

Several observations about the data in Tables 4-3 and 4-4 can be made.

4.1.2.6.1.1. Adrenal medulla tumors. Benign pheochromocytoma of the adrenal medulla is the only lesion in Table 4-3 that has a statistically significant elevation in the crude incidence of tumors in the exposed group compared to the control group (7/67 in the exposed group vs. 1/73 in the control group; p=0.023 using the Fisher's exact one-tailed test). This site has the largest group difference in the number of animals with tumors (seven animals in exposed versus one animal in control), and it has a relatively large difference in the time of appearance of the first tumor (138 days earlier in the exposed group than in the control group). The single tumor in the control group was detected at terminal sacrifice.

In view of the steadily decreasing survival of the animals in both the control and exposed groups as the experiment progresses, a late appearing tumor inevitably is detectable with less sensitivity because fewer animals are at risk late in the experiment. Therefore, the smaller incidence in controls could be considered another aspect of the late occurrence in controls. To emphasize this point, another definition of "crude" incidence of tumors could be constructed, called the site-specific crude incidence rate: the number of animals with tumors of a particular site divided by the number of animals alive at the time of the first tumor at that site. With this definition, the crude incidence of adrenal medullary tumors is as follows: (a) control group: 1/9=0.011, since only nine animals with adrenal medulla tissue were alive at the terminal sacrifice time of 811 days, and (b) exposed group: 7/38 = 0.184. This difference in proportions is not significant using the Fisher's exact test at a probability level of $p<0.05$. If the "site-specific crude incidence" is calculated for the other tumor sites, thyroid tumors (but no other sites) become statistically significant (9/76 = 0.125 in control animals versus 12/44 = 0.279 in exposed animals; p=0.031). The first thyroid tumor appears later in the exposed group than in controls (as opposed to earlier with the adrenal medulla) and the difference in the times of first appearance (213 days) is larger than with the adrenal medulla.

Therefore, we are faced with a contradiction because the large difference in the time to first death with adrenal medulla tumors in the two treatment groups causes two apparently reasonable definitions of crude incidence to lead to different conclusions. One solution to this dilemma is to disregard the concept of site-specific crude incidence rate because we are not

sure that the underlying assumption (namely, that tumors at various sites in the body occur independently of each other) is correct. The crude incidence in Table 4-3 assumes that animals in each of the separate experimental groups are at risk to all tumors after the first tumor at any site.

Another solution to this dilemma is to use time-adjusted statistical significance tests, both on single tumor sites (which assumes independence of the sites) and on relevant combinations of sites (which assumes that the selected combination of sites acts with a common mechanism). This approach is preferable because it avoids the use of a statistically extreme event (the time of appearance of the first of several tumors) as a measure of when the animals are at risk and at the same time adjusts for any differing mortality patterns between experimental groups. The latter problem does not exist in this case, since the control and exposed groups have similar mortality patterns (see Figure 4-2).

The time adjusted tests employed here are the Cox tests for homogeneity of the two groups and for dose-related trend. They are calculated with the use of the microcomputer version 2.1 of the program described by Thomas et. al. (1977). Version 2.1 and its documentation were kindly supplied to the author R.E. McGaughy by D. G. Thomas of the National Cancer Institute.

The results of these statistical significance tests for the adrenal medulla pheochromocytomas and the combined thyroid adenomas and carcinomas are given in Table 4-5. For the adrenal pheochromocytomas both the Fisher exact test of the crude incidence and the time-adjusted trend tests are significant (p=0.023 and p=0.045, respectively), whereas the incidence of thyroid tumors is not significant in either test. These results indicate that the crude incidence metric is not giving a misleading index of tumor incidence and the "site-specific crude incidence" is not appropriate for this data set. It also shows that the excess incidence of pheochromocytomas is not likely due to chance and is therefore likely to be an effect of the microwave exposure.

4.1.2.6.1.2. <u>Malignant tumors of all sites</u>. Another observation that can be made about the data in Table 4-3 is that malignant tumors (carcinomas and sarcomas) of all sites occur in more animals in the exposed than in the control group. This includes endocrine and exocrine glands, gastrointestinal tract, skin and soft tissues, urinary bladder, and mesenchymal tissue. The crude incidence, the Fisher exact test for significance of the crude incidence, and the time-adjusted tests of significance of all sites listed in Table 4-3 are given in Table 4-5. For carcinomas of all sites combined as well as for carcinomas and sarcomas of all sites.

TABLE 4-5. STATISTICAL SIGNIFICANCE OF SELECTED TUMOR TYPES AND SITES

Site	Lesion	Crude Tumor Incidence		Statistical Significance[b]		
				Fisher Exact Test	Time-adjusted Tests[c]	
		Control	Exposed	of Crude Incidence	Homogeneity	Trend
Adrenal Medulla	Pheochromocytoma (Benign)	1/73	7/67	0.023	0.091	0.045
Thyroid	Adenomas & Carcinomas	9/85	12/76	0.23	0.71	0.35
All Sites	Malignant Tumors	5/85	18/76	0.0012	0.014	0.0068
	Carcinomas	2/85	11/76	0.0049	0.026	0.013
	Sarcomas	3/85	7/76	0.12	0.38	0.19
Glandular Organs[a]	Adenomas & Carcinomas	31/85	35/76	0.14	0.81	0.40
	Carcinomas	1/85	8/76	0.018	0.048	0.024
	Adenomas	31/85	34/76	0.18	---	---

[a]Adrenal cortex, adrenal medulla, thyroid, liver, pituitary, testes, epididymis, and pancreas.
[b]One-tailed p-values.
[c]Cox tests, calculated with Thomas et al. (1977) computer program.

combined, all three tests are significant at a level of $p<0.05$, but sarcomas of all sites combined are not statistically significant. The rationale for combining malignant tumors of all sites is that all tissues are exposed to the radiofrequency and the ELF fields to approximately the same intensity and there is no a priori reason why one individual site should be either singled out or excluded from this combination.

4.1.2.6.1.3. Glandular tumors. Several endocrine and exocrine glands in Table 4-3 have a slightly larger incidence of malignant tumors in the exposed group than in controls, although none of them is individually statistically significant. These are adrenal cortex, adrenal medulla, thyroid, liver, pituitary, testes, epididymis, and pancreas. This group of sites is obviously a subset of the group of tumors at all sites, which was discussed in the previous section. They are discussed separately here because of the possibility that, being sensitive to circulating hormones, the functioning of these tissues might be altered by the interaction between plasma membrane hormone receptors and electromagnetic fields or field-induced currents. In Section 5.5 of this document, this interaction is discussed for ELF fields, and the pulse modulation in this experiment (at 8 pps and 800 pps) might supply the requisite energy to induce such an interaction.

If animals with tumors of these glands are combined, the count shown in Table 4-5 is obtained. Note that the incidence of carcinomas of these sites is statistically significant, whereas the incidence of benign endocrine tumors is not statistically significant.

Many of the animals with carcinomas in one organ also had adenomas in another organ in each treatment group. If Tables 4-3 and 4-5 are compared, one can see that some animals have multiple tumors of these organs. For example, in the control group there are 44 animals that have adenomas of one of the glandular organs mentioned above (Table 4-3), whereas Table 4-5 shows that there are only 31 animals with adenomas in one or more of these organs. Table 4-6 compares incidence data for the separate organs (from Table 4-3) with those for the combined organs (from Table 4-5).

The difference between the sum of animals with separate tumors and the number of animals with combined tumors is the number with multiple tumors. This is shown in Table 4-7. It shows that multiple adenomas occur more frequently than multiple carcinomas in both treatment groups but that the microwave exposure does not appreciably change the multiplicity of either carcinomas or adenomas. An increase in multiplicity would be expected in the exposed group if the field exposure effectively removed a hormonal factor like melatonin which normally inhibits the growth of several different glandular tumors.

TABLE 4-6. MULTIPLICITY OF TUMORS IN GLANDULAR ORGANS

	Control		Exposed	
	Sum of Animals with Separate Tumors (Table 4-3)	Animals with Combined Tumors (Table 4-5)	Sum of Animals with Separate Tumors (Table 4-3)	Animals with Combined Tumors (Table 4-5)
Adenomas	44	31	48	34
Carcinomas	2	1	10	8

TABLE 4-7. NUMBER OF ANIMALS WITH MULTIPLE TUMORS (Derived from Table 4-6)

	Control	Exposed
Adenomas	13	14
Carcinomas	1	2

Another issue that needs to be explored is whether there are associations between tumor sites, such that the appearance of a tumor in one organ (e.g., pituitary) predisposes the animal to an increased risk of tumors in another organ. This could be explored by calculating a matrix of pairwise coefficients and examining the significance of these correlations.

4.1.2.6.1.4. Exposure-induced changes in progression of tumors. Since Dr. Kunz evaluated the severity of benign and malignant lesions, it is possible to explore whether the exposure affects the severity of the tumors. For this purpose, the rank-sum test recommended by Gart et al. (1986, p. 163) and Snedecor and Cochran (1980) was used. In this test, ranks are assigned to the various degrees of severity. In order to assign these ranks, a listing was made of the terms used by Dr. Kunz in describing hyperplasia, benign tumors, and malignant tumors. This list showed that he used the terms minimal, mild, moderate, and severe for hyperplasia and for adenoma but only the terms moderate and severe for carcinomas. In view of this, it is logical to rank the progression of neoplastic lesions from minimal hyperplasia to severe carcinoma as shown in Table 4-8.

This test was done for the adrenal medulla, adrenal cortex, thyroid, and pituitary. One example of the data set for a rank test is given in Table 4-9 for adrenal cortical tumors. For these data, the test statistic was not significant (p=0.31), indicating that the severity of the tumors was not significantly different in the exposed group than in the controls. The result of these tests (Table 4-10) is that the difference in severity is not statistically significant between the exposed group and the control group for any of the individual glandular tumors except for the adrenal medulla. Therefore, the microwave treatment is increasing the severity of adrenal medulla pheochromocytomas but not any other individual site. Of greater interest is whether the exposure is increasing the severity of the glandular tumors as a group. However, an index

TABLE 4-8. ASSIGNMENT OF RANKS TO STAGES OF PROGRESSION

Stage	Assigned Rank	Stage	Assigned Rank
No tumor	0	Benign, minimal	5
Hyperplasia, minimal	1	Benign, mild	6
Hyperplasia, mild	2	Benign, moderate	7
Hyperplasia, moderate	3	Benign, severe	8
Hyperplasia, severe	4	Malignant, mild	9
		Malignant, severe	10

TABLE 4-9. SEVERITY RANKINGS OF ADRENAL CORTICAL PRENEOPLASTIC AND NEOPIASTIC LESIONS

Description of Lesion	Assigned Rank	Number of Animals	
		Exposed	Control
No lesions	0	2	2
Cellular alterations			
minimal	1	14	15
mild	2	21	28
moderate	3	14	9
severe	4	1	0
Benign tumors			
minimal	5	0	0
mild	6	1	6
moderate	7	8	4
severe	8	0	1
Malignant tumors			
moderate	9	1	0
severe	10	2	1

TABLE 4-10. RESULTS OF TESTS FOR THE STATISTICAL SIGNIFICANCE OF GRADED TUMOR RESPONSE

Gland	Significance Level (p-value)
Adrenal medulla	0.012
Adrenal cortex	0.31
Thyroid	0.111
Pituitary	0.641

of composite severity of a whole group of tumors is difficult to define, so this question will remain unanswered.

4.1.2.6.2. Historical Controls. In order to find out if the stock of animals in this study has a different or unusual response pattern compared to endocrine tumors from other Sprague-Dawley rat colonies, it is useful to compare the incidence of primary neoplastic lesions in the endocrine organs in the control group of the University of Washington study with the corresponding incidence in other published studies in this strain. This comparison is summarized in Table 4-11.

TABLE 4-11. COMPARISON OF SPONTANEOUS ENDOCRINE TUMORS IN SPRAGUE-DAWLEY RAT STOCKS

Tumor Site/Type	University of Washington Control	University of Washington Exposed	Hap[a]	CD[a]	Charles River SD[b]	Diablo SD[b]	Holtzman SD[b]	Sprague Dawley[b]	Sprague Dawley[c]
Adrenal									
cortical adenoma	11/85 (13%)	9/76 (12%)	15/70 (21%)	18/88 (21%)	--	--	--	--	2/216 (0.93%)
cortical carcinoma	1/85 (1.2%)	3/76 (3.9%)	3/70 (4.3%)	0/88 (0%)	--	--	--	--	1/216 (0.46%)
combined cortical tumors	12/85 (14%)	12/76 (16%)	--	--	0/448 (0%)	7/209 (3.3%)	2/229 (0.87%)	16/226 (7.1%)	--
pheochromocytomas	1/73 (1.4%)	7/67 (10%)	16/70 (23%)	13/88 (15%)	9/448 (2%)	1/209 (0.5%)	7/229 (3.1%)	13/134[d] (10%)	--
Pituitary									
adenocarcinoma	0/85	2/76 (2.7%)	0/56 (0%)	2/93 (2.2%)	--	--	--	--	1/216 (0.46%)
Thyroid									
C-cell carcinoma	--	--	--	--	--	--	--	--	1/216 (0.46%)
medullary tumor	--	--	6/71 (8.5%)	5/98 (5.1%)	--	--	--	--	--
parafollicular (light cell)	--	--	--	--	12/466 (2.6%)	8/196 (4.1%)	9/200 (4.5%)	15/223 (6.7%)	--
parafollicular cell adenoma	9/85 (11%)	10/76 (13%)	--	--	--	--	--	--	--
parafollicular cell carcinoma	0/85 (0%)	2/76 (2.6%)	--	--	--	--	--	--	--

[a]Anver et al. (1982)
[b]MacKenzie and Garner (1973)
[c]Altman et al. (1985)
[d]A second laboratory had significantly smaller incidence (values not given).

The most direct comparison possible is with the Anver et al. (1982) report. They examined two particular stocks of barrier-bred Sprague-Dawley rats housed under standard laboratory (not barrier) conditions for neoplastic, inflammatory, and degenerative diseases. The Hap stock, bred originally at NIH and raised at Harlan Laboratories, Indianapolis, Indiana, was observed between 6 and 29 months of age, and the longer-lived Crl:COBS[R] CD[R] SD stock or CD rats from Charles River Breeding Laboratories, Wilmington, Massachusetts, was observed from 12 to 38 months of age. The authors found that, although the life expectancy of the two stocks was different, the cumulative incidence of the diseases was about the same on a lifetime basis.

MacKenzie and Garner (1973) in an earlier study compared the spontaneous tumor occurrence in Sprague-Dawley rats from four different suppliers. This information was generated in the course of a large series of studies on irradiated foods.

The Altman et al. (1985) report is a summary tabulation of the historical control incidence in seven different laboratories. It came from the beginnings of the Laboratory Animal Data Base Program of the National Library of Medicine. It is judged less useful than the other two studies because the animals and pathologic diagnoses came from more heterogeneous sources.

For adrenal cortical tumors, Table 4-11 shows no consistent pattern. The adenomas in the University of Washington study control group are less frequent than those in the two stocks reported by Anver et al. (1982) but much more frequent than the less-reliable data compiled by Altman et al. (1985). The combined adenoma and carcinoma reflect the same pattern. The carcinoma incidence in the University of Washington controls is midway between that in the two strains reported by Anver and somewhat higher than that reported by Altman et al. (1985). Clearly, the University of Washington controls are not inconsistent with the wide variation reported in this literature.

For pheochromocytomas, the control incidence in the University of Washington study control group is much smaller than the Anver et al. (1982) data and within the wide range of the stocks reported by MacKenzie and Garner (1973).

For pituitary adenocarcinomas, the University of Washington control incidence matches the CD and not the Hap stock of Anver's report and is somewhat higher than Altman's data.

For the thyroid, follicular tumors have been deleted from this comparison and the parafollicular, medullary, and c-cell tumors are assumed to represent the same entity. The zero incidence of carcinomas in the University of Washington controls is consistent with Altman's data but decidedly lower than that in the other two reports. This discrepancy may be due to the inclusion of benign tumors along with carcinomas in the other two studies.

The conclusion that can be derived from examination of historical control data is that the control animals used in the University of Washington study are not demonstrably different than in other similar rat strains. Therefore there is no firm basis for attributing the statistical significance of the adrenal pheochromocytomas or the combined endocrine carcinoma response to an abnormally low control incidence. Although Kunz et al. (1985) pointed out that the incidence of malignant endocrine tumors was not appreciably greater than the range reported in the literature, we hesitate to draw conclusions about the effect of the microwave exposure from a comparison of incidence in the exposed group with historical control data reported in the literature. However, we agree with Kunz et al. (1985) that the incidence of

tumors at any one site is not remarkably larger than commonly observed in other animal colonies of this strain.

4.1.2.7. Summary of Results

This was a carefully designed, well executed study in rats of pulsed radiofrequency radiation at power levels calibrated to simulate human exposure at the upper limit allowed by current standards. The applied power was at most only 25% of the resting metabolic rate and was apparently well tolerated by the animals. The number of animals (100 control and 100 exposed) was moderately large and the histopathologic examination of the tissues was extensive. In retrospect, the chief drawback of the study is that only one treatment level was investigated. A room temperature control group and the addition of females to the experimental design would have helped to assess the role of temperature and sex-related hormonal factors.

The data analysis has developed the following conclusions:

- The incidence of benign pheochromocytomas of the adrenal medulla was significantly higher in the microwave-exposed group than in controls, but the incidence was not remarkably higher than that in control groups of other Sprague-Dawley rat colonies.
- No other single type of tumor was significantly increased by the pulsed microwave treatment.
- The incidence of carcinomas alone and combined carcinomas and sarcomas of all sites combined is statistically significant and higher in the treated group than in controls. The rationale for combining all sites is discussed in the next section.
- The incidence of malignant tumors in the endocrine and exocrine glands as a group was significantly higher in the microwave-exposed group than in controls. However, the incidence of benign tumors of these organs and the incidence of total benign and malignant tumors were not elevated in the exposed group. Glandular tumors here consist of adrenal cortex, adrenal medulla, thyroid, liver, pituitary, testes, epididymis, and pancreas. The rationale for this combination of tumor types is discussed in the next section.

- Multiple adenomas occur more frequently than multiple carcinomas in both treatment groups, but microwave exposure does not appreciably change the multiplicity of either carcinomas or adenomas.
- There is no exposure-related difference in the severity of adrenal cortical, adrenal medulla, thyroid, and pituitary tumors when ranked according to a scale of progression from minimal hyperplasia to severe carcinoma.

4.1.2.8. Discussion of Results

4.1.2.8.1. Benign Adrenal Pheochromocytomas. The significance to humans of the adrenal pheochromocytomas induced by the microwave exposure can be discussed in relation to two issues. One issue is whether there is a difference between humans and animals in the "functionality," or the endocrine activity of the gland with tumors. In human adrenal pheochromocytoma, plasma and urinary catecholamine levels are elevated (Bravo et al., 1979), whereas there is typically no evidence of secretory granules or hypertension in rats with these tumors. Bosland and Bar (1984) have measured blood pressure and urinary catecholamine metabolites in aged Wistar rats with spontaneous adrenal medullary hyperplasia and pheochromocytomas. They found that the correlation between blood pressure and urinary catecholamine metabolites in animals with hyperplasia or tumors is not appreciably different than for animals without these lesions, They also found that most of the hyperplastic lesions and tumor cells show little or nonexistent staining for chromatin granules, in contrast to the heavy staining of normal adrenal medullary cells. Presence of these granules indicates secretory activity. They conclude that spontaneous tumors do not produce excess catecholamines in the Wistar rats as is the case with humans. They also review other animal studies where adrenal medullary tumors induced by radiation, chronic nicotine, chronic thiouracil, chronic estrogen, and growth hormone, and acute alloxan exposures have been correlated with endocrine function. The results are inconsistent, with radiation and nicotine inducing tumors with no chromaffin staining or weak chromatin staining and thiouracil and alloxan inducing chromatin-containing tumors, With growth hormone, the results are conflicting, with one study showing an increase in blood pressure and the other study showing no blood pressure effect.

On the other hand, there are several chemical agents that induce adrenal pheochromocytomas. Gopinath et al. (1987) list the following agents as inducers of

proliferative lesions in the medulla: nicotine, reserpine, synthetic retinoids, thiouracil, neuroleptics, growth hormone, 4-chloro-m-phenylenediamine, 1,1,2-trichloroethane, Zomepirac (an analgesic), Blocadren (a beta-androgenic blocker), lactose, and sugar alcohols such as mannitol, sorbitol, xylitol, and lactitol. Several different mechanisms have been postulated. Roe and Bar (1985) point out that medullary tumors are correlated with high food intake and increasing weight gain, and that they are commonly associated with pituitary adenomas, thyroid tumors, adrenal cortical tumors, islet cell tumors of the pancreas, and interstitial cell tumors of the testis. They indicate that the sugar alcohols could induce adrenal medullary proliferative disease by increasing the absorption of calcium from the gut, and discuss several facts that indicate a link between increased calcium absorption and catecholamine release by the medulla. They also stress that the induction of medulla neoplasia in response to carbohydrate intake is restricted to the rat and does not occur in humans.

In the University of Washington study, no blood pressure or urinary catecholamine measurements were made, and no chromaffin staining was carried out. Therefore, the endocrine activity of the induced tumors is not known. However, the absence of any effect of exposure on corticosterone levels, whole-body activity, blood serum chemistry, and thyroxine levels indicates that if increased catecholamine levels are being induced by the radiation, the hormone balance is not seriously disrupted.

One could postulate that the pheochromocytomas induced in the University of Washington study have some relationship to the abnormally high food intake in these animals due to the lower than normal ambient temperature of both the control and microwave exposed groups. If such a relationship does exist, it has some indirect causation since both control and exposed groups had double the normal food intake but the pheochromocytomas affected the exposed group preferentially.

The second issue is whether the presence of benign pheochromocytomas in the animals indicates that humans may be susceptible to malignant tumors. Tischler and DeLillis (1988) point out that nodules from proliferating adrenal medullary tissue can be transplanted into syngeneic rats and develop into metastasizing tumors. Also a cell line has been cultured from the medulla of an irradiated rat which develops tumors upon transplantation into rats and which secretes norepinephrine. Therefore these lesions undoubtedly have the capacity to metastasize. Tischler and DeLillis quote figures of 2% (4 of 213) lung metastasis in one large study of F344 rats and state that it is comparable to the less than 5% frequency of metastasis from human adrenal medullary lesions. They conclude that most medium and large sized medullary nodules in rats are neoplasms but that they are probably not malignant as judged

by the criteria applied to human tumors. Hollander and Snell (1976) similarly regard them to be of at least low-grade malignancy. The National Toxicology Program (NTP) has used the adrenal pheochromocytoma response in male F344 rats as an indication of carcinogenicity for at least two agents, reserpine and 4-chloro-m-phenylenediamine. However, in the absence of ancillary evidence of endocrine dysfunction, this lesion is generally regarded as relatively innocuous and relatively unlikely to result in malignancy.

4.1.2.8.2. Combinations of Separate Tumor Sites. The biological significance of an excess of malignant tumors of all sites and an excess of malignant tumors in endocrine and exocrine glands as a particular subset of sites is uncertain. Most chemical carcinogens affect only one or a few tissues, and this generalization is broadly-enough recognized to be reflected in EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) in which the following statement appears: "A statistically significant excess of tumors of all types in the aggregate, in the absence of a statistically significant increase of any individual type, should be regarded as minimal evidence of carcinogenic action unless there are persuasive reasons to the contrary." In this discussion, we will present reasons for combining tumors and assess whether they are persuasive, starting first with tumors of all sites.

There are two reasons for combining tumors of all sites in this study. First, the distribution of the "toxic agent" to the various tissues with EM radiation is likely to be more homogeneous than for chemicals, so that all tissues are exposed more or less equally by EM fields. There are two components to this toxic agent, radiofrequency fields and pulse modulation at 800 pps and 8 pps. The authors have shown with thermograms (Chou et al., 1983) that the radiofrequency energy deposition is uniform within a factor of 2 or 3, with the peak fields being located at the nose and tail. The lower frequency components would be completely uniform in distribution if magnetic fields were to be shown as the biologically effective agent, but would be as variable as the tissue electric conductivity if the biologically effective agent were field-induced currents. By contrast, the tissue distribution of chemical agents depends upon blood flow rates, tissue partition coefficients, and tissue clearance rates which are expected to be more variable than the electrical parameters. In the absence of a quantitative evaluation of these factors, which could be done with some effort, our judgment is that the tissue distribution of the EM field "toxic agent" is more uniform than that of a "typical" chemical agent. However, due to the uncertain outcome of a quantitative analysis that has not yet been

performed, there are currently no firm persuasive reasons for asserting that the distribution of the toxic agent is significantly more homogeneous for EM radiation than for chemicals.

Other reasons for the variability of tissue responses are biochemical differences (presence of enzymes) and differences in cell proliferation rates. For both of these factors, the effects of EM fields and chemicals are expected to be the same, since EM field effects are probably ultimately mediated by the same cellular mechanisms as chemicals.

Therefore, we find no compelling persuasive reason, given the current state of knowledge of these factors, for deviating from the Guidelines for Carcinogen Risk Assessment with respect to combining carcinomas of all sites. The conclusion is that the finding of a statistically significant excess of malignant tumors of all sites furnishes only minimal evidence of carcinogenic action.

For the finding of excess malignant tumors in the endocrine and exocrine glands as a group, a different rationale was used for the combination. It is based on the hypothetical similarity of effects induced by the low-frequency component of the pulsed microwave exposure (which was 8 pulse trains per second and 800 individual pulses per second during each pulse train, see Figure 4-1) and effects induced by power frequency (50-Hz or 60-Hz) electric and magnetic fields, reviewed in Chapter 5. The rationale consists of a generalized argument and a more specific one. The generalized argument is that all tissues in the body are potentially affected by low-frequency EM fields and that either ion currents induced by these fields or the direct action of magnetic fields alter chemical reactions associated with plasma membranes. It has been shown (Section 5.5) that low-frequency pulsed magnetic fields inhibit the function of parathyroid hormone at its cell membrane receptor. If this happens with other hormone receptors, then one can postulate that other endocrine and exocrine glands, whose secretory activity is regulated by small concentrations of circulating hormones interacting with plasma membrane receptors, would be especially sensitive to fields or ion currents that can alter receptor function. The more specific rationale for combining the same tumor types is that nocturnal pineal melatonin activity is known to be inhibited by ELF electric fields (Wilson et al., 1986) and that pineal gland function is closely coupled to the function of other glands (see Section 5.7.1). Melatonin is known to inhibit tumor growth-enhancing hormones like prolactin and estrogen. The postulate has been made that when the blood melatonin concentration decreases because of the action of EM fields on the pineal gland, a tumor growth inhibitor has been reduced or effectively removed, thereby causing a stimulation of tumor growth. Although only breast and prostate tumors have been discussed in this

connection, the same regulation by melatonin might hold for other hormonally-regulated endocrine organs as well.

This rationale for combining endocrine tumors is consistent with the information in Chapter 5 and is therefore a reasonable hypothesis, but it obviously contains several untested assumptions. It could be extended to include other hormonally sensitive tissues besides the endocrine glands, One aspect of the experimental findings is inconsistent with the proposed mechanism. If hormonally-stimulated growth of tumors were occurring in this experiment, one would expect the treated animals to have more frequent and more severe benign tumors than the control group. This was examined and found not to be the case. The effect seems to be the induction of malignant tumors without the appearance of precursor benign tumors. We expect that informed opinions will differ about how persuasive this argument is for combining endocrine gland tumors. Indeed, more than one reviewer of previous drafts of this document has found it to be excessively speculative. In view of these opinions, we conclude that with our current knowledge there is no persuasive reason, based on established laboratory findings, to combine the tumors of three glands into a single group. The conclusion is that the finding of a statistically significant excess of malignant tumors in all endocrine and exocrine glands as a group furnishes only minimal evidence of carcinogenicity. It is possible that future research on mechanisms of action will supply enough information to strengthen this rationale.

In this connection, it should be noted that the human observations supply some support for the postulate that ELF fields induce tumors in a variety of sites. Leukemias and central nervous system tumors have been observed in several studies with residential power frequency exposures. However, in male telephone workers, breast tumors were observed in one study with a different type of electromagnetic field exposure than power frequency. In some occupational studies, malignant melanoma occurred.

4.2. PRAUSNITZ AND SUSSKIND (1962) STUDY

In the first report of a long-term microwave irradiation study in experimental animals, the authors exposed male Swiss albino mice to microwave power for 59 weeks (14 months), 5 days per week for 4.5 minutes per day. The power source was a radar transmitter with a frequency of 9270 MHz (3.2 cm wavelength) modulated with 2 microsecond pulses at a pulse repetition frequency of 500 pulses per second. The irradiation was carried out in a walk-in anechoic chamber via a horn antenna. Doses in the initial dose finding experiments were adjusted by varying the distance between cages and the horn antenna. The power density was calibrated with a precision 1/2 dipole antenna connected to a thermistor.

To establish what power levels to use for the long-term experiment, individual animals with rectal thermometers were exposed to fixed power densities, and the rectal temperature was measured as a function of time. It was found that over a power density range of 0.068 to 0.20 mW/cm^2, half of the animals died when the temperature reached 6.7° C above normal and that the duration of exposure required to reach the LD_{50} temperature varied from 16 to 3 minutes over the power density range. Over this range the total LD_{50} dose (proportional to power density x duration) is approximately 1.1 $(mW)/cm^2$-minutes. For the long-term experiment, the authors chose a power level of 0.1 mW/cm^2 for 4.5 minutes, which amounts to a total dose of a little less than one-half the LD_{50}. They found that this pattern (0.1 mW/cm^2 for 4.5 minutes) causes an average temperature rise of 3.3° C.

In the long-term experiment, the groups of 10 mice were placed in special plastic cages for the irradiation, and they were housed 10 to a cage for the rest of the time. A total of 300 mice were used; 100 were sham-exposed, and 200 were irradiated for 4.5 minutes per day, 5 days per week for 59 weeks (14 months). During the experiment, the following measurements were made: blood counts; spot checks of urine for glucose; weekly weighing of all mice; and periodic recording of body temperature. When dead animals were found, a histologic analysis was made of all tissues that had not undergone extensive postmortem autolysis. Histologic examinations were done on all animals at three kill times: (1) 10 irradiated and 5 control animals at 7 months, (2) 20 irradiated and 10 control animals at 16 months, and (3) the remaining 67 irradiated and 19 control animals at 19 months.

The authors found that the irradiated animals had better survival (65%) than controls (50%). The difference was especially pronounced at 10 months and later. There was no trend in body temperature throughout the experiment. The body weights in the two exposure groups were not significantly different. The red and white blood cell counts were the same in both groups at 4 months.

In the 60 irradiated and 40 control mice that died spontaneously during the experiment, there were two adverse effects that were more severe in the irradiated than control animals: (1) testicular degeneration (atrophy with no sperm) occurred in 23/57 (40%) of irradiated animals and in only 3/37 (8.1%) of control animals, and (2) cancer of the white cells or leucosis was seen in 21/60 (35%) of irradiated animals and 4/40 (10%) of control animals. This condition was described as either monocytic or lymphatic organ tumors or myeloid leukemia in the circulating blood.

At the 7-month interim kill, which was half-way through the exposure period, both exposed and untreated groups had the same histologic findings with respect to blood cell counts,

kidney congestion, seminiferous tubules, and lymphoid infiltration in the brain, kidney, and duodenum. At the 16-month interim kill, which was 1 month after cessation of the exposure, 6/20 (30%) of the irradiated animals had leucosis vs. 1/10 of the controls. At the final 19-month interim kill, which was 4 months after cessation of the exposure, testicular atrophy was seen in 14/67 (21%) of the irradiated animals vs. 1/19 (5%) of the control animals, and testicular weights were less in the irradiated group. However at that time, leucosis, as measured by abdominal lymphoma, had no higher incidence in irradiated animals (12/67, 18%) than in controls (4/19, 21%).

The authors did not comment on their inconsistent findings of leukosis. It occurred in animals dying spontaneously, which could occur at any time in the experiment. It did not occur midway through the exposure or 4 months after cessation of exposure, but it did occur one month after cessation of exposure. Therefore, it might be a transient phenomenon which takes longer than 7 months of irradiation to induce but which regresses after cessation of exposure. The testicular atrophy, on the other hand, is apparently permanent and does not regress after exposure.

4.3. SPALDING ET AL. (1971) STUDY

The authors exposed female RFM mice to 800 MHz (wavelength of 37.5 cm) microwave radiation placed in the center portion of a rectangular 10-foot long wave guide. There were 24 animals in both the exposed and the control groups, The exposures took place 2 hours per day, 5 days per week for 35 weeks (8.1 months) and the power level at the mice's location was 43 mW/cm^2. They measured red and white blood cell counts, hemoglobin, hematocrit, voluntary activity (with an exercise device), body weight, and survival. These measurements were done periodically (approximately 23 times in 100 weeks) and analyzed by pair-wise differences between exposed and control groups, No histopathologic observations were made. The authors found no statistically significant differences in any of these observations between the exposed and control groups at any time during the study, with one exception: the body weight of animals older than 86 weeks in the exposed group was larger than that in controls. The mean survival time was 655 days (93 weeks).

4.4. SZMIGIELSKI ET AL. (1982) STUDY

These authors measured the effects of 2450-MHz microwave radiation at power density levels of 5 and 15 mW/cm^2 in an anechoic chamber in three different mouse bioassays:

- Lung cancer colony assay in Balb/C mice, in which lung sarcoma cells from donor mice are injected intravenously into recipient mice, and the number of lung cancer colonies was measured after 1, 2, and 3 months of irradiation (2 hours per day, 6 times per week in the morning hours from 8:00 a.m. to 12 p.m.). Induction of lung tumor colonies in this assay has been interpreted in earlier work by these authors as a lowering of cell-mediated immune reactions.

- Observation of the time of appearance of spontaneous breast tumors in C3H/HeA mice during irradiation periods up to 12 months.

- Induction of skin cancer in Balb/C mice in various protocols combining microwave radiation (1, 3, and 5 months), painting with benzo[a]pyrene (BaP), and stress from solitary confinement for 1 to 8 months. The skin painting was carried out with a concentration that causes histologically proven skin cancer in 7 to 10 months in more than 85% of the mice. A 7-grade scale of severity was used to measure the progress of the skin tumors. Another report by Szudzinski et al. (1982) describes the skin tumor assay in greater detail.

The radiation resulted in a specific absorption rate in the animal of 2 to 3 milliwatts per g (mW/g) for the 5 mW/cm^2 power level and 6 to 8 mW/g for the 15 mW/cm^2 power level. At both power levels, the animals were able to maintain the body temperature within normal limits.

The results of the experiment, briefly summarized, are as follows:

- The number of lung nodules (and the standard deviation) in an unspecified number of animals observed after 3 months of irradiation in the control, chronic stress, 5 mW/cm^2, and 15 mW/cm^2 groups were 3.6 ± 2.2, 7.7 ± 2.0, 6.1 ± 1.8 and 10.8 ± 2.1. Similar numbers were observed after 2 months of irradiation. The authors concluded that lung modules were induced in a dose-dependent manner, and the magnitude of the effect induced by the lower power level was comparable to the effect induced by chronic stress confinement,

- For the control, chronic stress, 5 mW/cm^2 and 15 mW/cm^2 group, the times when 50% of the initial 40 mice developed breast tumors were 322, 255, 261, and 219 days, respectively. The times for all three treatment groups are significantly less than controls. The authors concluded that both the time of breast tumor occurrence and the

survival time is reduced in a field-strength dependent manner and, as with the lung nodule growth, the effect at 5 mW/cm^2 power level is similar to the chronic stress confinement treatment.

- The time of appearance of skin tumors induced by BaP was shortened when radiation for 1 or 3 months preceded the BaP application and when the radiation and BaP were given at the same time. In both protocols, the higher power density resulted in earlier tumors than the lower power density. In another protocol where chronic confinement stress preceded or was concurrent with BaP administration, the stress closely duplicated the effect of the 5 mW/cm^2 level of irradiation noted earlier.

In conclusion, the authors state that microwave radiation is a risk factor in the development of neoplasms, since it enhances the development of tumors in all systems tested.

4.5. BAUM ET AL. (1976) STUDY

This study examined the effects of long-term electromagnetic pulse (EMP) irradiation on Sprague-Dawley rats. The EMP irradiation consisted of high-intensity pulses of electromagnetic energy at a repetition rate of 5 pulses per second. Each pulse had an electric field intensity of 447 kV/m with rise and decay times of 5 nanoseconds and 550 nanoseconds, respectively. Irradiation was carried out continuously, except for 1 hour per day for sampling and animal care, for 94 weeks (22 months), for a total of 2.5 x 10^8 pulses.

Several different experiments were done:

- Bone marrow cellularity was measured weekly for 94 weeks in 300 irradiated males and an equal number of non-irradiated males. One-half of these animals underwent necropsy; representative specimens of 22 tissues were saved for histologic evaluation; and tissues were selectively screened for microscopic lesions;

- Peripheral arterial blood was collected from 20 irradiated and 20 non-irradiated males on alternate weeks throughout the 94-week period;

- Twenty females were exposed for 94 weeks and observed grossly for mammary tumors and other lesions;

- Five pairs of rats were irradiated for 13 weeks and their progeny were examined for abnormalities;

- The fertility of males irradiated for 94 weeks paired with females irradiated for 9 weeks was measured.

The results of all of these tests showed no statistically significant differences between irradiated and control groups. An earlier report (Skidmore and Baum, 1974) of male AKR/J mice exposure to the same fields for 38 weeks showed no leukemia induction, but these results were not discussed in the later (1976) report.

The conclusion that EMP irradiation has no apparent adverse effect in rodents is apparently valid, but the carcinogenicity evaluation does not meet current standards of complete histopathologic evaluation of all tissues and careful reporting of tumor incidence in each tissue. In addition, it is likely that the animals absorbed very little of the microwave radiation, since the maximum frequency (20 to 50 MHz) was very much less than the resonant frequency of the rats (letter from H. Bassen, Walter Reed Army Institute of Research, Washington, DC, to R. E. McGaughy, 1989). Unfortunately, Baum et al. (1976) did not measure the specific absorption in their experiment.

This study is reported here only for completeness, and no attempt is being made in this document to evaluate more recent literature on high-energy pulse radiation.

4.6. STUDIES IN PROGRESS OR PLANNED

4.6.1. Ontario Hydroelectric Power Company

As part of its program for assessing the human health effects of 60-Hz fields, the Ontario Hydroelectric Power Company is currently planning a lifetime animal cancer bioassay. It is being planned jointly with the Health and Welfare Agency of the Canadian Government. The study is being designed to test whether 60-Hz magnetic fields can induce brain cancer and leukemia in experimental animals with an 80% power for detecting doubling of the background rate. Magnetic flux densities up to 2000 microtesla μT) will be used, and the exposure duration is to be 10 hours per day for 80 weeks. Both cancer-initiated and noninitiated animals will be tested. As of December 1988, a principal investigator had not been selected.

4.6.2. U.S. Air Force

The U.S. Air Force is sponsoring a study of chronic microwave exposure of C3H/HJ mice, which have a high spontaneous mammary tumor incidence. The irradiation is being carried out continuously for 18 months, and the field has a frequency of 435 MHz (wavelength of 6.9 meters) modulated to simulate radar signals with an estimated specific absorption rate of 0.32

W/kg body weight. A special facility was constructed at Georgia Tech to carry out the study. The actual microwave exposures began in February 1988, and no interim reports are contemplated (letter from J. H. Merritt, Radiation Sciences Division, U.S. Air Force School of Aerospace Medicine, to R.E. McGaughy, December 10, 1987).

4.6.3. The University of Rochester

Under contract with the Electric Power Research Institute, the University of Rochester is undertaking a series of experiments to see what factors influence the growth rate of tumor cells in rats and in cultures of a breast tumor cell line. They will be investigating magnetic field effects on the mitotic activity of various human malignant cell lines, the repair of x-ray damage, and the timing of the cell cycle. They are also planning to measure the effect of electric fields on the growth rate of transplanted mammary carcinoma in rats and on hormonal levels (letter from Shin-Tsu Lu, Biophysics Department, Univ. of Rochester, to R.E. McGaughy, May 26, 1989).

4.6.4. Additional Studies

As a follow-up to the peer review workshop for this document held on June 28, 1990, several additional planned studies were brought to the attention of the authors of this document.

A study of leukemia in C57BL/6 mice induced by an initial gamma ray dose and a daily treatment with circularly polarized 60-Hz magnetic fields for 15 to 24 months at an intensity of 0, 0.1, and 10 gauss (G) is being carried out by T. Makinodan at UCLA. (Submitted by Richard Phillips and Richard Griesemer.)

The following information on EM-field animal experiments currently in progress or planned was submitted by Richard Griesemer:

- USA UCLA: Mouse Leukemia Promotional model using 60-Hz fields up to 10 G. Model uses C57BL/6 mice with or without ionizing radiation to determine initiating or promotion by magnetic fields. Sponsor: EPRI (P.I. Makinodan).

- France: 460-Hz pulsed magnetic fields on C3H/Bi mammary tumors, uses spontaneous viral-induced mammary tumors (P.I. Bellossi).

- Canada, Ontario: 60-Hz magnetic field skin tumor promotion in Sencar mice using DMBA and TPA (P.I. Brinkmann).

- Germany, Hannover: 50-Hz magnetic fields arid DMBA in Sprague-Dawley rat breast model. Negative study, but milligram quantities of DMBA (P.I. Brinkmann).

- Canada, Ontario: Rat (F344) Brain cancer promotion using ENU as an initiator. Sponsor: Ontario Hydro. Initial studies to start this summer. NPT will provide some animals for these experiments.

- Canada, Nova Scotia: Multigeneration mouse study and lymphoma, 250-G exposure. Experiment suffers from pathology quality and engineering problems. At 250-G there should be significant noise, vibration, and heating.

- Sweden: 500 and 5μT magnetic fields in enzyme-altered rat liver foci model. P.I. Holmberg started in November 1988.

- Sweden: 500 and 5μT skin study in NMRI mice, 19 hours per day for 12 and 24 months. P.I. Holmberg started January 1989.

- Sweden: 500, 50, and 5μT in NMRI mice initiated with NMU. Planned 2-year study to start this year (P.I. Holmberg).

- Japan: study supposedly underway. No details available.

- USA, National Toxicology Program (NTP): Long-term study of magnetic field in mice and rats in final design stages, to begin in 1991 (P.I. Boorman).

4.7. SUMMARY OF LONG-TERM ANIMAL STUDIES

Of the five long-term animal exposures to electromagnetic radiation reviewed in this document and summarized in Table 4-12, none were done using ELF frequencies alone. Two studies (Spalding et al., 1971; Szmigielski et al., 1982) were done using unmodulated microwaves, but the other three used pulsed microwaves consisting of a range of frequencies.

The study using the lowest frequencies (Baum et al., 1976) resulted in no effect even though the intensity of the fields was much greater than that seen in the other studies. Only one of these studies (Szmigielski et al., 1982) had more than one power level so that the information on “dose-response” is limited. Neither the Spalding et al. (1971) nor the Baum et al. (1976) studies reported the incidence of histopathological lesions, so that one has difficulty drawing conclusions about their apparent lack of an observed response.

In the Prausnitz and Susskind (1962) study in Swiss albino mice, lymphoma and leukemia occurred more frequently in exposed animals that died spontaneously than in controls dying spontaneously. These tumors were also more frequent in the exposed group than in the control group of animals killed one month after the end of the exposure, but the excess was not observed in animals killed 5 months after the end of exposure.

In the Szmigielski et al. (1982) study in Balb/c and C3H/HeA mice, a more clear-cut effect was observed than in any of the other studies. The effect observed was a dose-dependent

TABLE 4-12. SUMMARY OF CHRONIC ANIMAL EXPERIMENTS WITH ELECTROMAGNETIC-FIELD EXPOSURE

Study	Exposure			Study Duration	Animal Species (Number)	Results of Exposure
	Frequencies	Intensity	Duration			
University of Washington	2450-MHz, 800 pps. 8 pps. Individual animal waveguides.	0 mW/cm^2 0.48 mW/cm^2 (0.4 W/kg BW) (0.4 W/kg BW)	21.5 hr/day, 7 days/wk, 25 mo	25 mo	Sprague-Dawley Rats (200)	Benign adrenal medulla pheochromocytomas are increased. Carcinomas at all sites are increased. Malignant tumors of endocrine and exocrine organs as a group are increased. No affect on survival. No acceleration of glandular tumors. No increase in severity of tumors except in adrenal medulla. No increase in benign tumors except in adrenal medulla. No change in the multiplicity of adenomas or carcinomas.
Prausnitz and Susskind (1962)	9270-MHz, 500 pps.	0 mW/cm^2 0.1 mW/cm^2	4.5 min/day, 5 days/wk, 59 wk, (14 mo)	19 mo	Swiss-Albino Mice (300)	Better survival in exposed group. Testicular atrophy persisting after exposure. Lymphoma and leukemia occurring late during exposure period but not persisting after exposure.
Spalding et al. (1971)	800-MHz. Animals in waveguide.	0 mW/cm^2 43 mW/cm^2	2 hr/day, 5 days/wk, 35 wk	100 wk (23 mo)	RFM Mice	No effect on blood counts, voluntary activity or survival. Histopathology not examined.
Szmigielski et al. (1982)	2450-MHz. Horn antenna in anechoic chamber.	0 mW/cm^2 5 mW/cm^2 (2-3 W/kg BW) 15 mW/cm^2 (6-8 W/kg BW)	2 hr/day 6 days/wk	3 mo	Balb c Mice	Lung cancer colonies induced with positive dose trend.
				12 mo	C3H/HeA Mice	Time for development of spontaneous breast tumors is shortened in a dose-dependent manner.
				5 mo	Balb/c Mice	Time for development of BaP-induced skin tumors is shortened both when exposure precedes or is concurrent with BaP skin painting.
Baum et al. (1976)	0-20 MHz, 5 pps.	447 kV/m	22 hr/day	22 mo	Sprague-Dawley Rats	No mammary tumors in females. No bone marrow proliferation. No blood cell alterations. No developmental abnormalities. No fertility effects.

shortening of the development time of tumors already present, rather than an induction of tumors de novo. This occurred for spontaneous mammary tumors in C3H/HeA mice as well as for the development of skin tumors induced by benzo[a]pyrene in Balb/c mice. It is interesting that microwave exposure before BaP skin painting as well as microwave exposure concurrently with BaP treatment accelerated the induction time of these tumors. This suggests that the exposure is producing some factor or change in the tissues that interacts with BaP when it is given later.

There is a possibility that heating of the tissue produces one of these factors, but the mechanism of this effect is not known. At the higher intensity of the Szmigielski et al. studies, the absorbed microwave power (6-8 mW/g body weight) is about one-half of the basal metabolic rate of 30-g mice (about 15 mW/g body weight). This is a larger heat load for the animals to dissipate than in the University of Washington study, where the absorbed power was only 5% of the active metabolic rate of young 200-g rats.

The clear positive findings of Szmigielski et al. (1982) show that radiofrequency fields without low-frequency components stimulate the growth of tumors and indicate that they may act as a tumor promoter, or a modifying factor in the development of tumors. The role of tissue heating as a mechanism for this effect is not clear.

The University of Washington study, done at a power level carefully calibrated to simulate human exposure at the maximum continuous level allowed by the ANSI standard, showed the induction of benign adrenal pheochromocytomas in the exposed group and no statistically significant elevation at any other site. There was a statistically significant elevation in the incidence of carcinomas, but not sarcomas, at all sites combined. There was also an elevation of carcinomas in each of several glandular organs (pituitary, thyroid, adrenal cortex, pancreas, testes, and liver), which was statistically significant if they are all considered as a single group. This apparent induction of malignant tumors occurred without an increase in benign tumors of those sites. Benign adrenal pheochromocytomas in rats are not hormonally active as they are in humans, and they are generally regarded as innocuous and unlikely to result in malignancy.

The combining of carcinomas of all sites is based on the rationale that all tissues are about equally exposed to the same magnitude of fields and induced currents. On closer examination, this is not a persuasive argument because a difference in exposure to various tissues is only one of many factors responsible for differences in tissue response and because even tissue exposure is not clearly more uniform for EM fields than for chemical agents. Therefore, there is no clear reason to depart from the convention for chemical agents that, in

the absence of a significant response at any one site, a finding of statistical significance at all sites combined furnishes only minimal evidence of carcinogenicity.

Combining tumors across these glandular organs is based on the generalized hypothesis that electromagnetic fields affect all tissues in the body and that these glands, being specialized to respond to small amounts of specific circulating hormones, have cell membrane-bound receptors whose function could be affected by ion currents induced by the external fields. Although this concept is consistent with recent research on the mechanism of tissue interaction with low-frequency fields, there are at least two reasons why the combining of glandular organ tumors of all sites may not be appropriate. These are:

1. The proposed mechanism is based on extremely low-frequency (ELF) field phenomena, and there is some uncertainty whether the low-frequency pulse component of the radiation can induce the same effects as ELF fields.

2. This proposed mechanism, though plausible, has not been empirically established.

Therefore, with the current lack of empirical facts to confirm this proposed mechanism of cancer induction, the rationale for combining endocrine tumors of all sites is not persuasive. The study can be said to suggest, but not to demonstrate, a carcinogenic effect of pulsed RF radiation.

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5. SUPPORTING EVIDENCE OF CARCINOGENICITY

The objective of this chapter is to supplement the discussion of direct carcinogenicity observations in humans and in rodent experiments with ancillary evidence that has some bearing on the interpretation of those studies or gives some insight about the mechanisms of carcinogenesis. For chemical agents, the U.S. EPA carcinogen risk assessment guidelines suggests that physical and chemical properties of the agent, structure-activity relationships, metabolic and pharmacokinetic properties, toxicologic effects and short-term tests of genotoxic activity and promotion potential should be included in a hazard identification document. For electromagnetic (EM) fields, this chapter will discuss biological phenomena that have some relationship to the mechanisms of carcinogenesis. These are genetic effects, including DNA interactions, chromosome effects and mitosis and meiosis, tissue growth and differentiation, chemical signaling of growth induction stimuli across the cell membrane, and the influence of EM fields on hormones, growth factors, cell transformation, the immune system, and the central nervous system (CNS).

The effects of EM fields on the various systems and cellular functions, such as calcium transport, hormone receptor activation, protein kinase and ornithine decarboxylase induction, melatonin synthesis, and certain immunologic and CNS parameters, are indicative of effects on cellular signal transduction processes. Also, it is likely that many cell growth and differentiation processes in vivo represent an interaction between the genetic complement of the cells and the effects of hormones, cytokines, and/or growth regulatory factors on signal transduction processes (Luben, 1990). Although many of these findings do not deal directly with cancer, they do indicate that regulation of cellular growth and differentiation may be directly modulated by EM fields (Luben, 1990). In addition, the processes of signal transduction and oncogenesis are apparently closely linked, as discussed by Druker et al. (1989).

5.1. GENOTOXICITY OR NONGENOTOXICITY

5.1.1. Introduction

Genetic alterations are critical events in the carcinogenesis process. Thus, evidence on the ability to produce a heritable genetic lesion (e.g., gene mutation, chromosomal aberration, aneuploidy) can potentially provide useful mechanistic information for induced carcinogenesis

and is regarded as important qualitative information that reinforces the cancer concern for a particular agent. It should be emphasized, however, that genetic alterations inducing gene mutations are only one component of carcinogenesis. Thus, the observations of the National Toxicology Program that there are mutagens that are not carcinogens and carcinogens that are not mutagens are to be expected. The use of results from short-term genotoxicity tests as supporting evidence for or against carcinogenicity of an agent must be used with caution.

This review addresses the biological effects of EM fields caused by direct action of the field as opposed to secondary thermal effects. Genotoxicity studies in which thermal effects were clearly involved are not included; however, it is virtually impossible to state with certainty that the results observed following exposure to EM fields in the radiofrequency (RF) range were not due to thermal effects. The following sections consider separately extremely low frequency (ELF) electromagnetic fields (either magnetic fields alone, electric fields alone or both together) and RF electromagnetic fields (predominantly in the microwave region). The genotoxicity sections are organized by end point; therefore, a given paper may be discussed in more than one section if more than one end point was examined and the demonstration of no effect on one end point does not imply no effect on all end points.

Because this review is intended to provide support for or against the carcinogenicity of EM fields, studies on induction of dominant lethal mutations were not included as this assay system is not a useful prescreen for carcinogenicity (Green et al., 1985).

5.1.2. Effects on Nucleic Acids

Effects discussed in this section include DNA damage and repair, DNA synthesis and related topics.

5.1.2.1. Extremely Low Frequency Electromagnetic Fields

Strekova and Spitkovskii (1971), in an attempt to study a possible mechanism of action of magnetic fields on mitosis, examined the effect of a constant heterogeneous 12,000-oersted (Oe) [1,200 millitesla (mT)] magnetic field on the rheological properties of deoxyribonucleoprotein (DNP) strands. A graduated cylinder containing physiological saline solution was placed between the poles of a permanent magnet and a drop of DNP solution from calf thymus was placed on top of the saline solution. Strands of DNP formed as the drop fell. After a period of time the strands started to contract and the contraction of the strand and

the strand diameter were measured. The diameter of the strand was significantly greater than control values after 15- or 60-minute exposures to the magnetic field ($p<0.05$). There were also significant differences in kinetics of relative changes in length of DNP strands. Reaction to the field was apparent during the first 15 seconds of exposure and was dependent on protein content of the DNP. At high protein content (nitrogen/phosphorous ratio=4.6-4.9) the relative contraction of the DNP in the magnetic field was lower than the control, while at a more standard protein content (nitrogen/phosphorous ratio=3.7-4.2) it was higher ($0.01<p<0.05$). The authors feel the data support the hypothesis that magnetic fields can modify or cause structural damage within the nucleoprotein complex of chromosomes and thereby effect mitosis.

Chinese hamster ovary (CHO) cells were exposed for 1 hour to 60-hertz (Hz) magnetic fields (0.1 or 2 mT), 60-Hz electric fields [1 or 38 volts per meter (V/m)], or to combined 60-Hz electric and magnetic fields (38 V/m and 2 mT) and analyzed for DNA single-strand breaks (Reese et al., 1988). Cells were exposed to the electric field in calcium- and magnesium-free phosphate buffered saline at ice temperature with the graphite electrodes isolated by agar bridges. Magnetic fields were generated with a Helmholtz coil system. The alkaline elution technique used detects both actual single-strand breaks and alkaline-sensitive sites in the DNA. No significant difference in the number of single-strand breaks (or alkaline-sensitive sites) was found between exposed cells and sham-exposed control cells for any exposure ($p<0.05$). Appropriate controls were run to ensure that DNA-DNA or DNA-protein crosslinks were not interfering with the results and the cells were exposed at ice-bath temperature to prevent normal strand break repair.

Whitson et al. (1986) took another approach to detect DNA damage induced by electric fields in cultured cells. They exposed human skin fibroblasts in culture to 60 Hz, 1,000 V/cm [100 kilovolts per meter (kV/m)] electric fields between two parallel aluminum plates and found no significant effects on cell growth or survival after exposures up to 96 hours. Using the 5-bromodeoxyuridine photolysis assay they found no significant effect on excision repair of ultraviolet (UV) induced pyrimidine dimers after exposures up to 48 hours and no DNA damage that was repairable by the excision repair pathway after exposures up to 48 hours.

Several reports have shown an effect of electric or magnetic fields on DNA synthesis in cultured cells. Panchuk et al. (1981) exposed human embryo fibroblastoid cells in culture in glass tubes to “commercial frequency” (presumably 50 Hz), 50 kV/m electric fields between

parallel metal plates for various times. Delayed entry into the S phase was apparent by 3 hours after starting exposure and became significant by 24 hours ($p<0.001$). The delay remained relatively constant during 7 days of exposure. The authors also reported a shortening of S phase and a stimulated incorporation of labeled thymidine during DNA synthesis as compared to controls. Liboff et al. (1984) exposed human foreskin fibroblasts in culture to sinusoidally varying magnetic fields with frequencies of 15 Hz to 4 kilohertz (kHz) and amplitudes of 2.3×10^{-3} to 5.6×10^{-1} mT generated by modified Helmholtz coils. They found an enhancement of DNA synthesis with a threshold between 5×10^{-3} and 25×10^{-3} mT/second. The enhancement was maximum during the middle of S phase and was independent of the time derivative of the magnetic field. Takahashi et al. (1986) looked at DNA synthesis in Chinese hamster V79 cells in culture after exposure between Helmholtz coils to pulsed magnetic fields. The effect of pulse width (pulse shape not given) was examined with a 100 Hz, 2×10^{-2} mT field (pulse width 6, 10, 25, 50, 75, or 125 microsecond). DNA synthesis was significantly enhanced (about 30%, $p<0.001$) with a 25 microsecond pulse width but no significant effects on DNA synthesis were found with the other pulse widths. The second experiment held the pulse width constant at 25 microseconds and the magnitude constant at 2×10^{-2} mT and varied the frequency (5, 10, 30, 100, or 300 Hz). DNA synthesis was enhanced about 13% at 10 Hz ($p<0.01$) and about 30% at 100 Hz ($p<0.001$) with no significant effect at other frequencies. The final experiment held the frequency and pulse width constant at 100 Hz and 25 microseconds and varied the intensity. DNA synthesis was significantly enhanced in the range of 2 to 8×10^{-2} mT ($p<0.01$ - $p<0.001$) but was significantly inhibited at intensities greater than 2×10^{-1} mT (80% of control level at 4×10^{-1} mT, $p<0.01$). The presence of windows of activity as demonstrated in this study obviously complicates evaluation of biological effects of pulsed magnetic fields, particularly if the active windows vary with cell type. The previous study (Liboff et al., 1984) using human fibroblasts found no evidence for a window of activity for either frequency or amplitude.

5.1.2.2. Radiofrequency Electromagnetic Fields

DNA in aqueous solutions has been shown to absorb microwaves (Swicord et al., 1983, and other reports cited in this reference). Swicord et al. (1983) measured the absorption of 8 to 12 gigahertz (GHz) microwaves by DNA in saline solution following treatment of the DNA for increasing times with DNase *Escherichia coli.* Temperature during measurements was

maintained at 25 ± 0.2° C. They found that absorption increased with increasing DNase treatment time, implying that absorption increased with decreasing DNA chain-length. Absorption also increased with frequency. It remains to be determined whether this resonant absorption is relevant to any biological effects in vivo. Additional data on absorption of microwaves in this frequency range by *Escherichia coli* DNA are given in Swicord and Davis (1983).

An inhibitory effect of 1 GHz continuous wave (CW) and 1 GHz pulsed wave (PW) microwaves on DNA synthesis in cultured mouse L1210 leukemia cells was reported by Chang et al. (1980). This study was done to determine if low-power-density microwave radiation could enhance the antitumor activity of methotrexate. The authors used incorporation of tritiated deoxyuridine into DNA as a measure of DNA synthesis because methotrexate interferes with the conversion of deoxyuridine to thymidine which must occur before incorporation in DNA. The power density of CW microwaves ranged from 5 to 50 milliwatts per square centimeter (mW/cm^2) with an exposure time of 20 minutes. A peak inhibition of incorporation of tritiated deoxyuridine of about 25% occurred between 15 and 25 mW/cm^2 of CW but no inhibition was seen at 50 mW/cm^2. A similar inhibition of incorporation resulted from a PW exposure at an average power density of 10 mW/cm^2. The temperature of the culture increased from 23.5 ± 1° C before irradiation to 30.7 ± 3.5° C at 25 mW/cm^2 CW and 37.4 ± 0.9° C at 50 mW/cm^2 CW, the highest temperature reached being the normal growth temperature for these cells. CW exposure up to 25 mW/cm^2 increased the cellular uptake of methotrexate about 80% compared to unirradiated controls while 50 mW/cm^2 CW and 10 mW/cm^2 PW actually reduced uptake to below control level. Combined microwave exposure (15 mW/cm^2) and methotrexate [0.2 molar (M)] reduced DNA synthesis slightly more than either alone. Thus microwave exposures as described above can, by themselves, inhibit DNA synthesis and can enhance the inhibition of DNA synthesis due to methotrexate exposure.

Differential killing assays were employed in several investigations to determine if microwaves caused DNA damage. This assay compares the survival of wild type DNA repair-proficient cells to the survival of DNA repair-deficient cells following exposure to the agent of interest. If an agent causes DNA damage, survival of the repair-deficient cells should be lower than that of wild type cells. Averbec et al. (1976) reported in abstract form that no differential killing occurred between wild type and excision and/or recombinational repair defective strains of the bacteria or the yeast *Saccharomyces cerevisiae.* Exposures were for

30 minutes to 70- to 75-GHz microwaves with power densities up to 60 mW/cm^2. Cells were irradiated on Millipore filters on agar plates to try to avoid thermal effects. The temperatures are not reported but the results were negative in any case.

Dardalhon et al. (1981) used a number of repair competent and deficient strains of *E. coli,* including uvrA-, recA-, and multiple deficiency strains (uvrA- recA-) and (recA- recB- recC-), and *S. cerevisiae* wild type and (rad 2-20 rad 9-4) strains. No significant effects were seen on survival after exposures to 9.4, 17, and 70-75 GHz microwaves. Power densities were varied from 1 to 50 mW/cm^2 at the two lower frequencies and from 1 to 60 mW/cm2 at the 70-75 GHz range. Cells were irradiated on Millipore filter discs on solid agar plates for 30 minutes. Heating the bacterial cells above 50° C conventionally for 30 or 60 minutes decreased survival, particularly of the (uvrA- recA-) cells, indicating that these repair pathways are involved in repairing heat-induced DNA damage. The conclusion reached is that microwave exposure as reported here does not cause lethal DNA damage or DNA lesions repaired by the uvr or rec pathways in bacteria or the rad 2 or rad 9 pathways in yeast.

5.1.3. Gene Mutations

With few exceptions, attempts to induce gene mutations by exposure to EM fields have been unsuccessful. The experiments have covered a range of frequencies and intensities and have used as test objects bacteria, yeast, plants, insects, and mammalian cells in culture. Because most studies were negative, this section will be presented in tabular form (Table 5-1) with some comments on the positive reports.

5.1.3.1. Extremely Low Frequency Electromagnetic Fields

One publication available for this review reported a positive response in the *Drosophila melanogaster* sex-linked recessive lethal (SLRL) test after exposure to static electric fields (Portnov et al., 1975). SLRL can result from gene mutations, small deletions, or chromosome aberrations (Lee et al., 1983), depending on the nature of the chemical or physical insult. The mechanism of action in this case is unknown. Female Canton-S flies were exposed for 24 hours to static electric fields of either 1500 or 3300 volts per centimeter (V/cm) (150 or 330 kV/m) and mated to Muller-5 males immediately after exposure. SLRLs, determined in the F2 generation, were significantly more frequent in the exposed populations than in controls at

TABLE 5-1. NEGATIVE GENE MUTATION REPORTS

Test Object	Genetic End Point	Exposure			Reference
		Frequency	Intensity or SAR	Time	
Bacteria					
Salmonella typhimurium: TA98, TA100	Reverse mutation to histidine auxotrophy	100 Hz sinusoidal magnetic field	1.26×10^{-4} mT 1.26×10^{-3} mT 1.26×10^{-2} mT 1.26×10^{-1} mT	48 hours 40 hours 40 hours 40 hours	Juutilainen and Liimatalnen, 1986
S. typhimurium: TA86, TA100	Reverse mutation to histidine auxotrophy	0.3 Hz triangular waveform magnetic field	15mT 30 mT	Up to 24 hours	Moore. 1979
S. typhimurium: TA100, TA1530,	Reverse mutation to histidine autotrophy				
LSV3, SV19, SV21	Forward mutation to arabinose resistance				
Escherichia coli					
WP2(UVRA), WP_2(UVRA ExrA)	Reverse mutation to tryptophane auxotrophy	2.45 GHz CW 3.07 GHz pulsed 27 MHz magnetic field 27 MHz electric field	35-80 W/kg 85-100 W/kg 20 A/m 3 W/kg	3 to 7 hours 2 to 2.5 hours 2.5 to 4.5 hours 2.5 to 5.5 hours	Anderstam et al., 1983
WU 36-10-89	Reverse mutation to tyrosine auxotrophy				
sd-4	Forward mutation to streptomycin independence				
KMBL 1853	Forward mutation to rifampicin resistance				
E. coli, K12	Reverse mutation to tryptophan auxotrophy	70-75 GHz	5-100 mW/cm^2	30 minutes	Averbeck et al., 1976 (abstract)
E. coli, WWU	Reverse mutation to arginine auxotrophy	1.7 GHz CW 2.45 GHz CW	88 V/m (SAR 3W/kg) 10 mW/cm^2 (SAR 15W/kg) 50 mW/cm^2 (SAR 70W/kg)	3 to 4 hours	Blackman et al, 1976
E. coli, WP2	Reverse mutation to tryptophane auxotrophy	17 GHz 70-75 GHz	? very low 9 mW/g	Up to 20 hours 30 minutes	Dardalhon et al., 1981

TABLE 5-1. NEGATIVE GENE MUTATION REPORTS (continued)

Test Object or SAR	Genetic End Point Time	Exposure Frequency Reference	Exposure Intensity		
Fungus					
Aspergillus amstelodami A9	Forward mutation 8-azaguanine R. Forward mutation conidial color	8.7175 GHz	2.09 mW/cm^2	3 to 6 hours	Dahahi et al., 1982
Aspergillus nidulans	Forward mutation morphological	2450 MHz	< 10 mW/cm^2	10 to 240 minutes (abstract)	Baranski et al., 1976
Insect					
Drosophila melanogaster embryo	Eye pigmentation	2450 MHz	100 W/kg	6 hours	Hamnerius et al., 1979
D. melanogaster/male, Canton-S	SLRL (spermatozoa, spermatids, spermatocytes)	Homogeneous static magnetic field	1300 mT 3700 mT	10 days 7 days	Kale and Baum, 1979
D. melanogaster/male, Canton-S	SLRL (spermatozoa)	Static electric field Homogeneous static	30 kV.m - polarity 926.6 mT	24 hours 24 hours	Diebolt, 1978
D. melanogaster/male Oregon-R	SLRL (spermatozoa)	2375 MHz CW	15 W/cm^2 20 W/cm^2 25 W/cm^2	60 min./day/5 days 10 min/day/5 days 5 min/day/5 days	Marec et al., 1985
D. melanogaster/male, Oregon-R	SLRL (spermatozoa, spermatids)	146.34 MHz 29.00 MHz	62.5 V/m 600 V/m	12 hours 12 hours	Mittler, 1976
D. melanogaster/male, Oregon-R	SLRL (spermatozoa)	Homogeneous static	1110 mT	15 minutes	Mittler, 1971
D. melanogaster/females	SLRL	98.5 MHz	0.3 V/m	134 hours/wk/32 wks	Mittler, 1977
D. melanogaster/male, Oregon-R	SLRL (spermatozoa)	2450 MHz	6.5 W/cm^2 5.9 W/cm estimated	45 minutes	Pay et al., 1972
Tradescantia Clone 4430 Clone 02	Stamen hair test	Electromagnet Permanent magnet	770 mT 160 mT	6 days 0 to 11 days	Baum and Nauman, 1984
Chinese hamster ovary CHO-K1-BH_4 cells	HGPRT locus 6-thioguanine resistant	60 Hz electric field	3.5 V/m 10.9 Vm	24 hours	Frazier et al., 1987

both exposure levels ($p<0.05$) and more frequent at the lower field level than at the higher level but not significantly so ($p>0.05$).

5.1.3.2. Radiofrequency Electromagnetic Fields

A number of positive results were reported after exposures to radiofrequencies. Danilenko et al. (1974) reported an increase in the number of histidine revertants and morphological variants following irradiation of an histidine-dependent strain of *Candida tropicalis* D-2 with a 37-GHz electromagnetic field. This study also reported a synergistic interaction of the ultra-high frequency (UHF) field with N-nitroso-N-methylurea and 1-methyl-3-nitro-1-nitrosoguanidine. The data in this paper are incomplete or unclear. The exposure was given as 20 minutes at 1 milliwatt (mw) for the combined chemical and irradiation studies but no data were given for irradiation alone. The same exposure must be assumed. Chemical treatment alone was for 3 hours; however, in combined treatments the cells were treated for 1.5 hours, then irradiated, then treated again with chemical for “up to 3 hours.” It may be incorrect to conclude synergism when the exposure times are different. The authors say that no significant temperature change occurred during the course of the experiments, but they provide no data.

A number of studies by Harte (1972, 1973, and others cited therein) reported the induction of embryo lethal and morphological mutants in *Oenothera hookeri* (evening primrose) by 1.5- or 3-meter (m) radio waves [200 or 100 megahertz (MHz)]. In Harte (1973) the plants were grown for an entire growth cycle in the vicinity of an antenna radiating at 3 m (100 MHz) with electric field intensities of 250, 235, and 145 millivolts per meter (mV/m) at 1, 0.5, and 0.1 m above the ground, respectively. M1 and M2 generations were analyzed. In Harte (1972) pollen was irradiated with 1.5 m (200 MHz) radio waves at 1.4 or 1.8 mV/m for 4 or 12 hours and the M1 and M2 generations were analyzed. Harte (1975) performed the same type of experiments with *Antirrhinum majus* (snapdragon). Pollen was irradiated with 1.5 m (200 MHz) radio waves (field strength 1.5 V/m) for 4, 12 or 43.75 hours. Again, both embryo lethal and morphological variants were reported; however, serious infections occurred in all groups and control data from the literature had to be used, making the results unreliable. Both embryo lethal and morphological variants can be caused by gene mutations or by various chromosomal effects. *Oenothera* has quite atypical cytogenetic behavior (Steiner, 1975) so the effects observed in these studies are most likely not due to gene mutations.

A study by Blevins et al. (1980) reported induction of gene mutations in Salmonella *typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 by 2450-MHz microwaves. This study is difficult to evaluate because no attempt was made to keep temperature constant and at 23 seconds of exposure the temperature reached 100° C. The control was heating by conventional oven and any difference between mutation induction at a given temperature by the two heating methods (much greater in all strains with microwave heating) was attributed to non-thermal effects of the microwaves. No mutation induction occurred below about 70° C by either heating method. This conclusion assumes equivalency of the two heating methods, which because of possible effects such as differential absorption and thermal gradients, may not be a valid assumption.

A discussion of the Fröhlich (1968) model in Biological Effects of Radiofrequency Radiation (U.S. EPA, 1984) may be pertinent (see Section 2.4.3. for a discussion of the Fröhlich model). Fröhlich's proposed mechanism ". . . is a possible mechanism for grouping individual photons or phonons with energies< < kT (the average thermal energy per molecule at body temperatures). This process results in the application of energy in a significant amount (>kT) at a single locus. Effects resulting from this process could not be duplicated by addition of the same amount of energy to the system by a different process." In any event, the relevance of the results with respect to carcinogenicity in humans is questionable since mutation induction occurred only at 70° C and above. In conclusion, there is no unequivocal evidence for induction of gene mutations by EM fields.

5.1.4. Chromosome Effects

5.1.4.1. Extremely Low Frequency Electromagnetic Fields

Two studies reported on induction of chromosomal aberrations in plant roots following exposure to electric fields. Dubrov et al. (1968) grew onion seedlings on filter paper for 43 hours, then placed the filter paper on a polymer film electrode in a Petri dish, placed the dish on top of another electrode charged oppositely and allowed the seedlings to grow an additional 24 hours. The electrodes "were connected to an alternating static potential of 4.5 kW [kilowatts] of industrial frequency" [sic], probably 50 Hz. The authors reported a chromosomal aberration frequency in root tip cells that was more than twice the control frequency when the seedlings were grown on a positively charged electrode and about 60%

above control levels when grown on a negatively charged electrode. No data were provided on types of chromosomal aberrations. Miller et al. (1976) exposed broad bean roots to 75-Hz electric fields at 10 V/m for 1 to 6 days and found no significant effects on chromosome aberration induction in root tip cells. The raw data are not given.

The ability of magnetic fields to induce chromosomal aberrations in plants was also examined. Miller et al. (1976) exposed broad bean root to 75-Hz magnetic fields of 0.5, 5, or 17 gauss (G) (0.05, 0.5, or 1.7 mT) for up to 6 days and found no induction of chromosomal aberrations in root tip cells, but, as in their electric field exposure studies above, no raw data are presented. A higher frequency of chromosome breaks occurred in pea root tip cells exposed between the poles of an electromagnet to 8000 Oe (800 mT) than in control cells (Goswami and Dave, 1975). Other chromosomal anomalies were also observed. The time of exposure was not given. Shevchenko et al. (1978) found no induction of chromosomal aberrations in root tip cells of *Crepis capillaris* following exposure to constant magnetic fields. In one experiment, germinating seeds were exposed for 1 or 2 days to a constant magnetic field of average field strength 9000 Oe (900 mT) [gradient about 200 oersted per centimeter (Oe/cm), 20 millitesla per centimeter (mT/cm)] or average field strength of 12,000 Oe (1,200 mT) (gradient of 300-400 Oe/cm, 30-40 mT). In the second experiment, dry seeds were exposed to 9000 Oe (900 mT) as above for 2 months and then germinated in the same field for 2 days. No increase in chromosomal aberrations frequency was induced by any exposure condition.

Magnetic fields were shown to cause premature decondensation (despiralization) of chromosomes in pea and garlic root tips (Goswami, 1977). It is not clear if the exposures were for 10 or 15 minutes or were two 15-minute exposures separated by 30 minutes in distilled water. Field strength was 7400 Oe (740 mT). Decondensation of chromosomes was also seen in onion root tip cells after exposure to 6000 G (600 mT) for 140 hours starting from the time dry seeds were placed on moist filter paper (Herich, 1976). Goswami (1977) speculated that removal of proteins from the chromosome and/or chelation of divalent cations was responsible for the decondensation.

The final plant paper considered in this section reported no induction of micronuclei in *Tradescantia* pollen mother cells after exposure of inflorescences to magnetic field intensities of 160, 760, or 780 mT for 6 or 7 days (Baum and Nauman, 1984). Both *Tradescantia* clone 02 and 4430 were used with similar results.

The remaining papers discussed in this section used rodent or human cells (in vivo and cell culture) as test objects.

Two papers examined the effects of magnetic fields on chromosomal aberration induction in mice. Strzhizhovskii et al. (1979) found no increase in frequency of chromosome aberrations in corneal epithelial cells in mice exposed to 3 to 127 kOe (300 to 12,700 mT) for one hour. The magnetic field, produced by a water-cooled electromagnet with a cylindrical active zone, had one constant component and one saw-tooth component with a period of 30 seconds. The authors state that “the intensity of the constant component coincided with the amplitude of the saw-toothed component.” Additional data were not given. No numerical data were provided on aberrations.

Mastryukova and Rudneva (1978) exposed C57BL and CBA mice to a static magnetic field of 1000 Oe (100 mT) for one day (presumably 24 hours) and examined the duodenal epithelium at 0, 1, 3, and 24 hours and 6, 10, 12, 20, 24, and 30 days postexposure. The authors report an increase in percent of pathological mitoses immediately after exposure [13.0 (0.78%) compared to 6.3 (0.86%) in controls] due mostly to chromosome damage, but they do not give specifics of the damage. The peak time of chromosome damage was 24-hour postexposure with the percent decreasing to control levels between 10 and 30 days. Eberle and May (1982) found no effect on the rate of structural chromosome or chromatid aberrations or micronuclei formation in bone marrow cells of Chinese hamsters exposed to 1000 mT for 3 or 24 hours, 7000 mT for 3 hours or 14,000 mT for 15 minutes and killed 26 hours later. There were increases in hypo- and hyperploid cells, indicating a possible effect on chromosome segregation.

El Nahas and Oraby (1989) reported the induction of micronuclei in bone marrow polychromatic erythrocytes (PCE) of male Swiss mice exposed to uniform 50-Hz electric fields of 170, 220, and 290 kV/m for 24 hours. No statistically significant increase in micronuclei occurred at a field intensity of 100 kV/m. The number of micronuclei found increased with field intensity and was dependent on time of the postexposure that elapsed before the animal was killed, reaching a maximum at 72 hours after exposure began. The mean number of micronuclei per 500 PCE at 72 hours was 12.4 ± 4.67, 19.6 ± 4.16, and 23.2 ± 12.27 at 170, 220, and 290 kV/m, respectively. The micronuclei frequency decreased at 96 hours after beginning exposure but was still significantly above control levels. Control levels varied in different experiments from a mean of 3.3 ± 1.53 to 4.4 ± 1.52 per 500 cells.

A number of studies in which human lymphocytes were examined following exposure to ELF fields are available in the literature. Mileva et al. (1985) exposed human lymphocytes to a magnetic field (permanent magnetic field of 3 kilooersted (kOe), 300 mT, for 30 minutes to 6 hours) and found no significant difference in chromosomal aberrations between exposed and control cells ($p>0.05$).

Cohen et al. (1986a, b) exposed human lymphocytes to 60-Hz electromagnetic fields (0.25 V/m and 1 or 2 G, 0.1 or 0.2 mT) or to just the electric or magnetic field alone for 69 hours. Cohen et al. (1986b) also treated human lymphoid cell lines from patients with various chromosomal instability syndromes. No significant increase in chromosome breaks in any of the cell lines or in normal lymphocytes resulted from these exposures ($p>0.05$).

Rosenthal and Obe (1989) exposed human peripheral lymphocytes to 50 Hz, 5 mT magnetic fields for 48 hours and also found no effect on the number of chromosome breaks compared to unexposed controls. Tsoneva et al. (1975) had reported induction of chromosome and chromatid breaks in cultured human lymphocytes after exposure to 1750, 3910, or 6000 G (175,391, or 600 mT) for 30 seconds or to 1750 G (175 mT) for 30 or 60 minutes. The cells were exposed before cultivation.

Nordenson et al. (1984) found no increase in chromosomal aberrations in human lymphocytes following exposure of whole blood to a 50-Hz electric field, current density of 1 milliampere per square centimeter (mA/cm^2), for 3 hours; however, an exposure to ten 3-microsecond-long spark discharge pulses (peak field strength 350 kV/m, about 5 seconds between pulses) did cause a significant increase in chromosome breaks to a level comparable to 0.75 Gray (Gy) of ionizing radiation ($p<0.001$). Other abnormalities, including polyploidy, endoploidy, and premature chromosome condensation, were also seen in exposed cells. In the same publication, these authors examined 72-hour cultures of peripheral lymphocytes from men who had worked at a 400-kilovolt (kV) switchyard for 1 to 8 weeks immediately preceding blood sampling. Significant increases in chromosomal aberrations were found compared to unexposed controls ($p<0.0005$).

In contrast to the in vivo results of Nordenson et al. (1984), Bauchinger et al. (1981) reported no increase in chromosomal aberrations in 48-hours cultures of lymphocytes from workers exposed for more than 20 years to 50-Hz electric and magnetic fields in 380 kV switchyards ($p>0.05$). This difference may be explained by the comment in the discussion of Nordenson et al. (1984) that all except one worker in their study had acute exposure to high

strength electric fields and to spark discharges immediately before donating blood. Lymphocytes from the one exception showed no chromosome or chromatid breaks.

The sister chromatid exchange (SCE) assay is a method considered to be more sensitive than analysis of chromosome breaks for detecting damage to DNA in chromosomes. The actual mechanism of SCE formation is not fully understood but apparently involves DNA breakage and reunion (Latt et al., 1981). Five of the six papers to be considered in this section reported no effect of ELF fields on SCE induction. Four of the negative papers, using human lymphocytes and lymphoblastoid cells, were discussed above in the paragraph on chromosomal aberrations and details of exposure are given there (Cohen et al., 1986a, b; Bauchinger, 1981; Rosenthal and Obe, 1989). Rosenthal and Obe (1989) used a 72-hour culture for SCE analysis in addition to the 48-hour culture mentioned in the previous section on chromosome aberrations. The fifth negative paper (Benz and Carsten, 1986) reported in abstract form that exposure of male and female mice to 60-Hz, 15-kV/m - 3 G (0.3 mT) or 50 kV/m - 10 G (1 mT) fields for 1 to 28 weeks did not produce significant effects on SCE levels in bone marrow cells.

The only positive report, also discussed above in the section on chromosomal aberrations (Eberle and May, 1982), found an increase in SCE induction in Chinese hamster bone marrow cells after in vivo exposure to homogeneous static magnetic fields (1000 mT for 3 or 24 hours, 7080 mT for 3 hours or 14,000 mT for 15 minutes and killed 26 hours later). Increased SCE levels were seen at all exposures with a maximum increase about twice the control level after 3 hours at 7000 mT.

5.1.4.2. Radiofrequency Electromagnetic Fields

Radiofrequency EM fields have been shown to induce chromosomal aberrations in a number of test systems; however, it is very difficult to state unequivocally that the effects are nonthermal. A typical control for possible thermal effects is either to maintain the culture at the starting temperature (a few tenths of a degree) or to compare the results with microwave heating to those with conventional heating. Neither approach may be acceptable because all that can be measured is average culture temperature. Resonant absorption inside the cell may cause local hot spots not representative of the average culture temperature. This caveat will not be repeated with each experiment but should be kept in mind.

Chen et al. (1974) exposed Chinese hamster cells in culture (unspecified tissue or cell line) to 2450-MHz microwaves of various intensities for various times. From a starting temperature of 22° C, the cells were exposed for 10 minutes to 50 mW/cm^2 or for 4, 8, or 10 minutes to 85 mW/cm^2. The culture temperature after irradiation was 37 to 41° C. A similar experiment was done with a starting temperature of 37° C and exposures for 8 or 10 minutes to 20 mW/cm^2, 4 minutes to 50 mW/cm^2, or 2 or 3 minutes to 85 mW/cm^2. With a 37° C starting temperature, culture temperatures following irradiation were 40° to 43° C. Conventional heating to 45° C did not induce chromosomal aberrations. Data were presented separately for 10 types of chromosomal damage plus polyploidy. The authors state that "the difference in aberrations observed between the control and the irradiated samples were not significant at the 5% level" and then try to make a point that in some cases they are. The data are so varied with no consistent pattern that conclusions are not really justified. Similar data are presented for human amnion cells and the same comments apply.

Alam et al. (1978) used Chinese hamster CHO-K1 cells in a study of chromosome aberration induction by 2450 ± 25 MHz-microwaves under temperature controlled and uncontrolled conditions, Exposures were given as 30 minutes at 25-watt (W) incident power without temperature control (temperature of the culture reached 49° C) and 30 minutes at 75-, 125-, and 200-W incident power with the temperature maintained at 29° C. At the three higher powers the power density at the surface of the culture medium exceeded 200 mW/cm^2. The culture without temperature control had significant increases in chromosome breaks compared to control cells, and nuclear vacuoles and pycnotic and decondensed chromosomes were seen. Under temperature controlled conditions, none of these effects were seen.

A long-term exposure study was done by Yao (1982). He cultured rat kangaroo RH5 and RH16 cells for 50 passages (320 days) in incubators with the cell culture temperature maintained at 37° C by either 2450-MHz microwave heating or by conventional heating. The power density necessary to maintain this temperature by microwave heating is not given; however, the author states that the magnetron was operated at "about 10 volts" and that "the energy absorption dose rate of the medium and cell culture was tested and estimated to be 15.2 ± 1.82 mW per gram." A synthetic rubber cylinder at the center of the incubator absorbed "most of the microwave radiation and was heated- by it." Heat released by the cylinder was exhausted by a fan through an opening in the top of the incubator. An

equilibrium was reached in 2 hours between the heat from the rubber cylinder and the culture medium and the heat exhausted through the top air opening. The RH16 cell line has a normal 2n = 12 chromosome complement, but the RH5 line lost the number 5 chromosome and has a 2n = 11 chromosome complement. Cells were examined for chromosomal aberrations at 10, 20, 30, 40, and 50 passages. The microwave-exposed cells showed retarded growth, and after 20 passages chromosome aberrations and polyploid cells appeared. By passage 50, 43% of the irradiated RH5 cells had at least one aberration and 35% were polyploid. Also, there was a significant increase in number of chromosome breaks per cell in this cell line. Many of the irradiated RH5 cells lost a chromosome (usually chromosome 4) during irradiation, and after 30 passages, 41% of the cells had 10 chromosomes. Only 6% of the irradiated RH16 cells were aberrant after 40 passages, and no aberrant cells were found after 50 passages. About 31% of the RH16 cells were polyploid after 30 passages. Following return to a conventional incubator, the number of chromosome breaks and polyploid cells decreased. Because the RH5 line was hypoploid before irradiation it might have been more sensitive to microwave irradiation than the RH16 line.

Yao had previously reported induction of chromosomal aberrations in corneal epithelium of female Chinese hamsters after in vivo exposure to 2450-MHz microwaves (Yao, 1978). The right eye of each animal was irradiated at 100 mW/cm^2 for 5, 10, 20, or 30 minutes or at 25 mW/cm^2 for 10 or 20 minutes. The percent of abnormal cells and the number of chromosome breaks per cell were significantly higher than control values ($p=0.05$) at 100 mW/cm^2 for 30 minutes. Dicentrics were the-most common anomaly. There was no mention of temperature increases in this 1978 report.

Chromosomal aberrations, polyploidy, and aneuploidy were found in rat bone marrow cells after in vivo exposure to 12-centimeter (cm) (about 2450 MHz) microwaves for 7 hours daily for 10 days at power densities of 50 or 500 W/cm^2 (Kapustin et al., 1976). The types of aberrations included chromatid deletions, acentric fragments, and chromatid breaks. Bone marrow was examined after 18 hours, 2 weeks, or 2 weeks with hypoxia following the end of exposure. At the lower exposure, the percent of abnormal cells increased from about 19% at 18 hours to about 34% at 2 weeks, while at the higher exposure the percent of abnormal cells decreased from about 40% at 18 hours to 23% at 2 weeks. This decrease probably reflects elimination of cells severely damaged at the high exposure level. Control animals had about 4% abnormal cells in the bone marrow. Postexposure hypoxia led to a lower percent of

abnormal ceils at 2 weeks but still well above control levels. No increase in chromosomal aberrations was seen in bone marrow cells of male (CBA x C57BL)F1 mice after exposure to 2400-MHz microwaves (Ramaiya et al., 1980). Mice were irradiated at 800 mW/cm^2 for 21 seconds daily for 10 days. The percent of aberrant bone marrow metaphases was given as 1.37% in controls and 1.62% in irradiated mice. Beechey et al. (1986) irradiated male (C3H/HeH x 101/H)F1 mice with 2450-MHz microwaves amplitude modulated at 100 Hz and examined spermatocytes for chromosome aberrations. Exposures were to 0.1, 1.0, or 40 mW/cm^2 for 30 minutes/day, 6 days/week, for 2 weeks. Spermatocytes were isolated 2 to 3 days postexposure, when sampled germ cells were treated as spermatocytes and at 30 days postexposure, when treated spermatogonia were sampled. The rise in rectal temperature did not exceed 1° C in sham-exposed and the two lower exposure mice and did not exceed 3° C in the high dose mice. There were no significant differences in chromosomal aberrations or univalents at any exposure level compared to sham-exposed mice, although the highest percent of cells with aberrations occurred at the highest dose level in cells treated as spermatocytes.

Human lymphocytes were irradiated with 2950-MHz [sic] pulsed microwaves (1200 Hz, 1 microsecond pulse width) following 66 hours of culture at 37° C (Stodolnik-Baranska, 1974). Exposure was to 20 mW/cm^2 for 5, 10, 15, or 20 minutes with 0.5° C rise in temperature at 15 minutes and 1° C rise after 20 minutes. Various abnormalities were seen, including chromosome stickiness, aneuploidy, dicentrics, chromatid breaks, and possibly changes in chromosome spiralization. The general trend was towards greater effects at longer exposure times. The increases appear to be significant, but statistical data are not presented.

Wolff et al. (1985) exposed human lymphocytes and Chinese hamster ovary (CHO) cells for 12.5 hours to the emissions of a magnetic resonance imaging instrument with a magnetic field strength of 2350 mT. The 100-MHz signal was pulsed at 100 pulses of 330 microsecond duration per minute. Both mitogen-stimulated (with phytohemagglutinin) and unstimulated lymphocytes were used. Unstimulated lymphocytes are in the G_0 phase of the cell cycle and do not leave this resting stage and progress through the cell cycle until stimulated. No increase in chromosome aberrations occurred in any of the cultures.

No significant increase in SCE levels was detected in any paper considered in this section. Wolff et al. (1985) used human lymphocytes and CHO cells under exposure conditions just described above. Ciaravino et al. (1987b) exposed CHO cells for 2 hours to 2450-MHz

microwaves pulsed at 25,000 pulses per second, 10 microsecond pulse width. The specific absorption rate was given as 33.8 watts per kilogram (W/kg) resulting in a maximum culture temperature of 39.2° C. There were no interactive effects when cells were treated simultaneously with microwaves and mitomycin C, a chemical agent that causes SCEs in CHO cells. Ciaravino et al. (1987a) reported in abstract form an identical study except adriamycin, another SCE inducer, replaced mitomycin C. There were no interactive effects. Finally, McRee et al. (1981) exposed female CD-l mice to 2450-MHz CW microwaves at 20 mW/cm^2 for 8 hours/day (two 4-hour periods separated by 1 hours) for 28 days. Deep colonic temperature was maintained at 0.7(to 1(C above the initial value during the 4-hour irradiation periods. There was no difference in SCE frequency in bone marrow cells compared to sham-exposed or normal controls.

5.1.4.3. Summary

Chromosome aberrations have been reported in a number of test objects following exposure to static and varying electric and magnetic fields as well as RF fields, but results are not consistent. Chromosome breaks are most commonly seen. Chromosome decondensation occurred after exposure to static magnetic fields. Other abnormalities such as polyploidy, aneuploidy, chromosome stickiness, and dicentrics have been seen in some experiments with no consistent pattern. One study reported the induction of SCEs by static magnetic fields; however, all other studies with either ELF or RF fields were negative.

Table 5-2a summarizes the chromosome effects of static and ELF fields while Table 5-2b summarizes the chromosome effects of RF fields.

5.1.5. Summary of Genetic Effects

It is very difficult to draw general conclusions about the genetic activity (toxicity) of EM fields. Because of the variables involved, there are virtually unlimited numbers of exposure scenarios possible. Some of the variables are:

- Frequency - 0 to many GHz
- Continuous wave or pulsed
- Pulse width
- Pulse shape

TABLE 5-2a. CHROMOSOME EFFECTS[a], EXTREMELY LOW FREQUENCY FIELDS

Test System	Exposure	End Point[b]	Results	Reference
ELF Fields (electric and/or magnetic)				
Plants				
Onion root tips	4.5 kW; 50 Hz; 24 hr	CA	+	Dubrov et al., 1968
Broad bean root tips	10 V/m; 75 Hz; 1-6 days	CA	–	Miller et al., 1976
Broad bean root tips	0.05, 0.5, 1.7 mT; 75 Hz; 1-6 days	CA	–	Miller et al., 1976
Pea root tips	800 mT static field; time not given	C breaks	+	Goswami and Dave, 1975
Crepis capillaris root tips germinating seeds exposed	900 mT static field (20 mT/cm gradient) 1 or 2 days	CA	–	Shevchenko et al., 1978
	1200 mT static field (30-40 mT/cm gradient) 1 or 2 days	CA	–	0.7 V/m
Crepis capillaris root tips dry seeds exposed	900 mT static field; 2 months	CA	–	
Pea root tips	740 mT static fields; two 15 min exposures	C uncoiling	+	Goswami, 1977
Garlic root tips	740 mT static fields; two 15 min exposures	C uncoiling	+	Goswami, 1977
Onion root tips germinating seeds exposed	600 mT static fields; 140 hr	C uncoiling	+	Herich, 1976
Tradescantia pollen mother cells	160, 760, 780 mT static fields; 6 or 7 days	Micronuclei	–	Baum and Nauman, 1984

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TABLE 5-2a. CHROMOSOME EFFECTS[a], EXTREMELY LOW FREQUENCY FIELDS (continued)

Test System	Exposure	End Point[b]	Results	Reference
Mammal, mammal cell culture				
Mouse strain H, in vivo bone marrow	309 mT static field; 30 min - 6 hr	CA	–	Mileva et al., 1985
Mouse, in vivo corneal epithelium	300 - 12700 mT static field: 1 hr	CA	–	Strzhizhovskii et al., 1979
Mouse, in vivo duodenal epithelium	100 mT static field; 1 day	CA	+	Mastryukova and Rudneva, 1978
Mouse, in vivo bone marrow	15 kV/m; 0.3 mT static field; 1-28 wk 50 kV/m; 1 mT; 1-28 wk	SCE	–	Benz and Carsten, 1986
Chinese hamster, in vivo bone marrow	1000 mT static field; 3 or 24 hr	CA	–	Eberle and May, 1982
		numerical aberrations	+	
		SCE		
	7000 mT static field; 3 hr	CA	–	
		numerical aberrations	+	
		SCE	+	
	14000 mT static field; 15 min	CA	–	
		numerical aberrations	+	
		SCE	+	
Mouse, Swiss, in vivo	50 Hz; 100, 170, 220, 290 kV/m; 24 hour	Micronuclei	+	El Nahas and Oraby, 1989
Human lymphocytes, in vitro	300 mT static field; 30 min - 6 hr	CA	–	Mileva et al., 1985
Human lymphocytes, exposed before cultivation	175, 391, 600 mT static fields; 30 sec 175 mT; 30 or 60 min	C breaks	+	Tsoneva et al., 1975
		C breaks	+	
Human lymphocytes, in vitro or human lyhmphoid cell lines in vitro	0.25 V/m; 0.1 or 0.2 mT; 60 Hz; 69 hr	C breaks	–	Cohen et al., 1986a, b
	69 hr	SCE		
	0.25 V/m; 60 Hz; 69 hr	C breaks	–	
		SCE		
	0.1 or 0.2 mT; 60 Hz; 69 hr	C breaks	–	
		SCE	–	

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TABLE 5-2a. CHROMOSOME EFFECTS[a], EXTREMELY LOW FREQUENCY FIELDS (continued)

Test System	Exposure	End Point[b]	Results	Reference
Human lymphocytes, in vitro	5 mT; 50 Hz; 48 or 72 hr	C breaks	–	Rosenthal and Obe, 1989
		SCE	–	
Human lymphocytes, whole blood	1 mA/cm^2; 50 Hz; 3 hr	CA	–	Nordenson et al., 1984
	350 kV/m peak spark discharges, ten 3-µsec long sparks, 5 sec between	C breaks		
		numerical aberrations	+	
		PCC	+	
Human, in vivo, switchyard workers; lymphocytes	400 kV; 1-8 wk	CA	+	
Human, in vivo, switchyard workers; lymphocytes	380 kV; 59 Hz; > 20 years	CA	–	Bauchinger et al., 1981
		SCE	–	

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TABLE 5-2b. CHROMOSOME EFFECTS[a], RADIOFREQUENCY FIELDS

Test System	Exposure	End Point[b]	Results	Reference
RF Fields				
Mammal, mammal cell culture				
Chinese hamster, in vitro CHO-K1 cells	2450 +/- 25 MHz; 25 W incident power; 30 min; no temp. control	C breaks C uncoiling	+ +	Alam et al., 1978
	2450 +/- 25 MHz; 75, 125, 200 W incident power; 30 min; temp. controlled at 29 degrees C	C breaks C uncoiling	" "	
Rat kangaroo, in vitro RH5 cells	2450 MHz MW heated incubator; 320 days; temp. at 37 degrees C	CA numerical aberrations	+ +	Yao, 1982
RH16 cells		CA numerical aberrations	" +	
Chinese hamster, in vivo corneal epithelium	2450 MHz; 100 mW/cm^2; 5, 10, 20 30 min	C breaks dicentrics	+ +	Yao, 1978
	2450 MHz; 25 mW/cm^2; 10, 20 min	C break dicentrics	" "	
Rat, in vivo bone marrow	2450 MHz; 0.05, 0.5 mW/cm^2; 7 hr/day; 10 days	CA numerical aberrations	+ +	Kapustin, et al., 1976
Mouse (CBA x C57BL)F1, in vivo. bone marrow	2400 MHz; 800 mW/cm^2; 21 sec/day, 10 days	CA	"	Ramaiya et al., 1980
Mouse, CD-l, in vivo, bone marrow	2450 MHz; 20 mW/cm^2; 8 hr/day; 28 days	SCE	"	McRee et al., 1981
Mouse (C3H/HeH x 101/H)F1, in vivo, spermatocytes	2450 MHz; amplitude modulated at 100 HZ; 0.1, 1.0, 40 mW/cm^2; 30 min/day; 6 days/wk; 2 wk	CA univalents	"	Beechey et al., 1986
Human lymphocytes, in vitro	2950 MHz; pulsed at 1200 Hz; 1 µsec pulse width; 20 mW/cm^2 5, 10, 15, 20 min	C stickiness numerical aberrations dicentrics C breaks	+ + +	Stodolnik-Baranska, 1974

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TABLE 5-2b. CHROMOSOME EFFECTS[a], RADIOFREQUENCY FIELDS (continued)

Test System	Exposure	End Point[b]	Results	Reference
Human lymphocytes, in vitro	MRI device; 2350 mT; 100 MHz; 1.67 pulses/sec; 330 µsec pulse width	CA SCE	" "	Wolff et al., 1985
Chinese hamster, in vitro CHO cells		CA SCE	" "	
Chinese hamster, in vitro CHO cells	2450 MHz; 25000 pulses/sec; 10 µsec pulse width; 2 hr	SCE	"	Ciaravino et al., 1987a, b

[a]Summary only - the result is given as positive if any exposure scenario gave positive results - see text for details.

[b]CA = chromosome aberrations - includes all structural aberrations. Usually used if the types of aberrations were not specified. Numerical aberrations are not included in CA but are given separately where appropriate.

C breaks = chromosome or chromatid breaks
SCE = sister chromatid exchange
Numerical aberrations = polyploidy or aneuploidy
PCC = premature chromosome condensation

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- Pulse amplitude
- Field intensity, flux density, etc.
- Field orientation
- Magnetic, electric, or combined fields
- Time of exposure
- Temperature
- Test object (whole animal, plant, cell culture, bacteria, etc.)

The biological effects can depend on any or all of the above variables, and in some cases very narrow “windows of activity” are seen, making extrapolation from one scenario to another impossible. Although the sections on genetic activity do not constitute an exhaustive review, the inclusion of all related papers would be unlikely to increase the reliability of any conclusions drawn. Also, this review was to consider nonthermal effects only, but as described previously, it is not always possible to eliminate thermal effects with exposures in the microwave region.

In spite of the problems mentioned, some conclusions (none of which are absolute) follow:

- In the absence of thermal effects, nonionizing EM fields do not cause DNA damage measurable by DNA breaks, DNA repair or differential killing of repair defective organisms.
- DNA can, under some exposure scenarios, absorb energy from EM fields.
- DNA synthesis can be affected by electric, magnetic, and EM fields and both enhancement and inhibition have been shown with no obvious pattern.
- Chromosomal aberrations have been reported in a number of test objects following exposure to static and varying electric and magnetic fields as well as RF fields, but results are not consistent. Chromosome breaks are most commonly seen. Chromosome decondensation occurred after exposure to static magnetic fields. Other abnormalities such as polyploidy, aneuploidy, chromosome stickiness, and dicentrics have been seen in some experiments with no consistent pattern.
- Sister chromatid exchanges are probably not induced by EM fields.
- Gene mutations are not induced by EM fields.

In summary, EM fields clearly interact with genetic material, as detected by chromosomal aberrations. Effects on transcription (gene induction) have also been reported (see Section 5.3.1). However, no obvious relationship between exposure parameters and effect is apparent, and it is premature to conclude from the genetic evidence available that EM fields are or are not likely to be carcinogenic.

5.2. EFFECTS ON MITOSIS AND MEIOSIS

Many of the publications considered in this section report an effect of EM fields, particularly the magnetic component, on cell cycle progression and/or mitotic index. Although these end points are not genetic end points in the sense that gene mutations, DNA damage, and chromosomal aberrations are, they clearly demonstrate that EM fields affect DNA function.

5.2.1. Extremely Low Frequency Electromagnetic Fields

Plants have been commonly used in studies on the biological effect of ELF fields because the root meristem provides an easy to work with population of actively growing cells. Robertson et al. (1981) studied long-term exposure of pea roots in an aqueous inorganic nutrient medium [conductivity about 0.08 siemens/meter (S/m)] to 60-Hz electric fields of 140 or 430 V/m and examined growth rate and mitotic index in the root tip cells. Mitotic index in this paper was defined as the number of cells in mitosis per 1,000 nuclei. No significant effects were found at 140 V/m; however, at 430 V/m both growth rate and mitotic index were reduced. The peak reduction in mitotic index, about 55% of control, occurred at 4 hours of exposure with gradual recovery at 6 and 8 hours of exposure. Reduction of growth rate was immediate and constant after exposure started and was about 40% at 2 days of exposure to 430 V/m. Growth rate had almost returned to normal 5 days after exposure stopped. It is likely that the changes observed in this study and in the following two studies are due to membrane effects. The induced membrane potentials reported in these studies of 3 to 7 mV in a 300-V/m field (which is considered the threshold for growth effects) and 6 to 12 mV in a 490-V/m field “represent a significant fraction of the normal resting potential of most cells.”

Another report from the same laboratory (Brulfert et al., 1985) examined pea root growth and mitotic index as described previously as well as cell cycle duration. Exposure in an aqueous inorganic nutrient medium (conductivity about 0.08 S/m) for 48 hours to 60-Hz electric fields of 430 V/m produced a reduction in root growth to 44% that of control roots,

comparable to the reduction observed in the previous experiment. The mitotic index, determined after a 25-hour exposure, did not differ significantly from the control value. This result is not inconsistent with the previous study, where the reduction in mitotic index was maximum at 4 hours with recovery by 8 hours. Duration of the cell cycle was determined after a 25-hour exposure and found to be about 10% longer than that of control cells. The conclusion reached was that reduced root growth was due to reduced cell elongation, probably resulting from altered cell membrane function.

A third report from this laboratory (Inoue et al., 1985) examined growth and mitotic index in broad bean *(Vicia faba)* roots after exposure to 60-Hz electric fields of 200, 290, and 360 V/m. As above, exposure was in an aqueous inorganic nutrient medium (conductivity 0.07 - 0.09 S/m) and lasted 4 days for root growth determinations and up to 30 hours for mitotic index studies. *Vicia faba* roots were used because the cell size is greater than that of pea roots and, for a comparable electric field exposure, a larger cell should have a larger induced transmembrane potential and resulting greater sensitivity to electric fields. There was a significantly reduced rate of root growth proportional to field strength, and the rate of reduction was significantly greater than that observed in pea roots. (A three-way analysis of variance was performed on the data). Growth rate was almost back to normal by 4 days after exposure stopped. There was no significant difference in mitotic index ($p>0.05$) between exposed and control roots at any exposure, including an exposure that reduced root growth to 35% of control. The authors say the results support the hypothesis that the cell membrane is the site of action of electric fields.

One of the few studies that considered effects produced by the geomagnetic field was done by Nemirovich-Danchenko and Chastokolenko (1976). They determined the mitotic activity of *Allium fistulosum* root meristems as a function of orientation of the seeds in the geomagnetic field, morphological isomerism of the seeds, and age of the radicles when a 2000 Oe (200 mT) magnetic field from a permanent magnet was applied. Seeds of this onion were characterized as right-hand or left-hand based on position of the embryonic radicle in the seed and positioned with the embryonic radicle in the direction of geographic north or south. There were therefore four possible experimental orientations. Age was represented by radicle length which was 0.5, 1.0, or 4.0 millimeters (mm) when the magnetic field was applied. The magnetic field lines were perpendicular to the axis of the radicle and to the surface of the earth. Without regard to morphological isomerism, the highest mitotic activity was seen when

the radicle was oriented to the north and no increase occurred upon exposure to the 2000 Oe (200 mT) magnetic field for 3 hours. Activity was significantly lower with a southern orientation ($p<0.01$ was considered significant), but it increased to that of the northern orientation after a 3- hour exposure to the 2000 Oe (200 mT) magnetic field. The authors' conclusion is that with a northern orientation the maximum possible number of root tip cells are dividing, and the additional magnetic field cannot increase the activity, whereas with a southern orientation, not all possible cells are dividing, and the additional magnetic field induces these cells to divide. There was no significant difference in mitotic index with respect to isomerism. Apparently the magnetic field effect occurs before the genetically determined time of mass cell division in the meristem, and if the field is applied after that time, there is no effect on mitotic activity.

Herich (1976) germinated onion seeds *(Allium cepa)* on wet filter paper in a 6000-G (600 mT) static homogeneous magnetic field for 140 hours, then examined the root tips for mitotic activity and cell cycle progression. The mitotic index of exposed cells was reduced to 73.3% of control cells due to an inhibiting effect of the magnetic field on transition of cells from interphase to prophase.

Greene (1983) grew onion bulbs *(Allium cepa)* in flats placed at various distances from an experimental 60-Hz high voltage (normally 895 kV line-to-ground, no further data given) transmission line. Flats were either on the ground, on 1 -meter redwood posts or on 1 -meter insulators. The unperturbed electric fields measured at the exposure sites varied from 0 (grounded Faraday cage) to 15.5 kV/m and were about 50% higher than this on top of the posts. Exposures lasted 5, 10, or 15 days at which time root tips were examined and mitotic index reported as percent of cells in mitosis per 1000 cells. One-way analysis of variance was performed on all data. The author stated that there were many statistically significant differences between exposure stations; however, when the Duncan's multiple comparison test was run on the data, there were no significant differences at the 5% level with respect to exposure level.

Gemishev (1976) studied the effects of constant magnetic fields on root growth and mitotic index in sunflower *(Hellianthus annus)* roots. (This paper is in Russian with an English summary and English headings for tables.) Seeds presoaked in distilled water were exposed to a magnetic field of 450, 1000, or 2000 G (45, 100, or 200 mT) for 1 hour and the roots were examined at 24 and 96 hours for root and hypocotyl growth and at 48 hours for mitotic activity. Growth of roots and hypocotyls was stimulated by the magnetic field, particularly at 459 G (45

mT). At 24 hours, the length of control roots averaged 8.55 ± 14 mm, while at 450 G (45 mT) the average length was 10.07 ± 0.16 mm. At 96 hours, the respective lengths were 177.78 ± 1.56 mm and 195.99 ± 0.89 mm. Differences were less at higher field strengths. Results were similar with hypocotyl growth. The mitotic index was about 2.4 times the control level at 450 G (45 mT) and only about 0.3 times higher at 2000 G (200 mT).

The effect of magnetic fields on meiosis in lily *(Lilium henryi)* pollen mother cells was reported by Linskens and Smeets (1978). They exposed anthers for 4 hours to a "homogeneous magnetic field of 5000 G" (500 mT) (no additional information on the magnetic field given) and found a significant number of abnormalities at anaphases I and telophases I immediately after exposure (X^2 = 6.38 and 4.39, respectively) and at anaphases II and telophases II at 18 to 24 hours after exposure (X^2 = 12.61 and 4.12, respectively). Aberrations observed included bridges, fragments and chromosomes left at the equatorial plane. Also normal synchrony of the meiotic divisions was reduced. At 48 to 50 hours after exposure, the number of abnormalities at telophases II was no longer significant (X^2 = 3.71).

Effects of ELF fields have been seen in test objects other than plants. Mitotic delay was induced in the slime mold *Physarum polycephalum* by 60- and 75-Hz electromagnetic fields (Marron et al., 1975). The fields were produced by application of crossed electric and magnetic fields alternating in phase at 60 or 75 Hz at levels of 0.7 V/m and 2.0 G (0.2 mT). Timing of the cell cycle can be done quite accurately in *Physarum polycephalum* because mitosis is naturally synchronized in stationary cultures. Mitotic delay became significant (95% confidence level) after 80 to 100 days exposure to the 60-Hz field and after 100 to 120 days exposure to the 75-Hz field. The mitotic interval returned to the control interval during 30 to 60 days after the culture was removed from the field. No significant delay occurred in cultures exposed for 200 days to 75-Hz fields of 0.15 V/m and 0.4 G (0.04 mT). The same group of authors also examined the effect of intermittent field exposure on cell cycle duration in *Physarum polycephalum* (Goodman et al., 1984). A 76-Hz [sic] sinusoidal field of 1.0 V/m and 1.0 G (0.1 mT) was applied to the cultures for 16 hours/day, 5 days/week, but the total exposure time was not given. The number of hours to metaphase II increased from 15.97 in unexposed cultures to 16.40 in exposed cultures, an average difference of 0.43 % 0.03 hours ($p<0.01$ for this difference and all others given for this paper). In comparison, continuous exposure to a 75-Hz field of 0.7 V/m and 2.0 G (0.2 mT) increased the duration of the mitotic

cycle by 0.64 ± 0.03 hours. Continuous exposure to a 75-Hz 2.0 G (0.2 mT) magnetic field alone increased the duration by 0.46 ± 0.03 hours, while continuous exposure to a 75-Hz 0.7 V/m electric field alone increased the duration by 0.39 ± 0.03 hours.

The ability of static electric fields to induce nondisjunction of the X chromosome in *Drosophila melanogaster* Canton-S flies was examined by Portnov et al. (1975). Exposure of females to 150 or 330 kV/m fields for 24 hours did not result in detectable X chromosome nondisjunction in F1 offspring ($p>0.05$).

Barnothy and Sumegi (1969) kept male Swiss mice for 13 days in a vertical, homogeneous magnetic field of 9000 Oe (900 mT) with a gradient of less than 200 Oe/cm (20 mT/cm). Measurements were made to ensure that no high-pitched noise, which can be a stressor to mice, was present. Mitotic index determined in the liver was, per 400 cells, 11.84 ± 0.80 in the exposed mice and 5.17 ± 0.35 in sham-exposed mice ($p=0.0001$).

Mastryukova and Rudneva (1978) also found an effect of magnetic fields on mice as described in the section on chromosomal aberrations. They looked at duodenal epithelial cells and in addition to chromosome damage they also reported changes in the mitotic index. C57BL and CBA mice were exposed for 1 day to a 1000 Oe (100 mT) static magnetic field between the poles of an electromagnet, and the mice were killed 0, 1, 3, and 24 hours and 6, 10, 12, 20, 24, and 30 days postexposure. The mitotic index was slightly but significantly reduced in exposed animals at 0, 1, and 3 hours ($p<0.001$, 0.05, and 0.05, respectively) and significantly increased at 6, 10, and 12 days ($p<0.01$, 0.02, and 0.001, respectively). The mitotic index of corneal epithelial cells of mice exposed for 1 hour to magnetic fields of 3 to 127 kOe (300 to 12,700 mT) was determined by Strzhizhovskii et al. (1979). The electromagnet had a cylindrical active zone and produced a two-component magnetic field. One component was constant and one had a saw-tooth waveform with a period of 30 seconds. The authors state that “the intensity of the constant component coincided with the amplitude of the saw-toothed component.” No other information on the magnetic field was given in the paper. The mitotic index decreased with field intensity, reaching 50% of the control level at 8 kOe (800 mT). The greatest rate of decrease (14.3% per kOe, 100 mT) occurred between 3 and 8 kOe (300 and 800 mT), while the rate of decrease between 8 and 127 kOe (800 and 12,700 mT) was only 0.24% per kOe (100 mT), reaching 20% of normal at 127 kOe (12,700 mT). One day following cessation of exposure to either 3 or 127 kOe (300 or

12,700 mT) the mitotic activity returned almost to normal and by 2 days had overshot to almost twice normal. Return to normal from this point was somewhat different for the two exposures. After 3 kOe (300 mT), the mitotic index declined to 10% above normal by day three and to normal on day four. After the 127-kOe (12,700 mT) exposure, the mitotic index declined to about 75% above normal by day three, about 15% above normal by day four with a slow decline to normal by day 15. The authors conclude that the magnetic field "causes a reversible retardation of the cells at late stages of the mitotic cycle, in particular, in the premitotic G2 period." Part of the rise of mitotic activity above control levels is due to the synchronous entry into mitosis of those cells blocked in G2.

The effect of 50-Hz electric fields of 50 kV/m on the mitotic index of cultured human embryo fibroblastoid cells was determined by Dyshlovoi et al. (1981). The mitotic index of the exposed cultures decreased with exposure time until at 24 hours the decrease was statistically significant ($p<0.001$). In another series of experiments, the cultures were exposed to the same intensity field for 48 hours at which time the mitotic index was reduced by about 30% ($p<0.01$). Twelve hours following termination of exposure the difference was no longer significant ($p>0.05$). The authors felt that the mitotic index reached its lowest value after a critical time and no additional reduction occurred with longer exposure times. To prove this they maintained cultures in exponential growth in the field for 7 days and determined the mitotic index at 48, 96, 120, 144, and 168 hours. As before, at 48 hours the mitotic index was significantly reduced ($p<0.01$); however, at 96 hours the mitotic index in exposed cultures was twice that of controls ($p<0.01$) and remained significantly above control levels until after 168 hours ($p<0.05$ at 168 hours). The fields also caused degenerative changes in the cultures. The authors speculate that the degenerative changes were due to inhibition of synthetic processes in the cells.

5.2.2. Radiofrequency Electromagnetic Fields

McRee et al. (1981), as discussed in the section on SCE, exposed female CD-1 mice to 2450-MHz 20 mW/cm^2, microwaves for 8 hours/day for 28 days and examined bone marrow cells. An average specific absorption rate (SAR) was given as 21 milliwatts per gram (mW/g) and deep colonic temperature increase as 0.7° to 1° C. There was no difference in the mitotic index of bone marrow cells in control, sham-exposed or exposed mice.

An effect of 9.4-GHz pulsed (1,000 Hz pulse rate, 0.5 microsecond pulse width) microwaves on meiosis in male Balb/c mice was demonstrated by Manikowska et al. (1979). The mice were exposed for 1 hour/day, 5 days/week, during 2 weeks to intensities of 0.1, 0.5, 1.0, or 10.0 mW/cm^2, and spermatocyte and spermatogonial metaphases examined. The number of metaphases I with univalents was significantly greater than controls at all exposures at the $p<0.001$ level of significance. The number of translocations (metaphases with quadri- or hexavalents) was significantly greater than controls at all exposure levels except 0.5 mW/cm^2 ($p<0.001$). Metaphase I, metaphase II, and spermatogonial metaphase counts (number of cells in meiosis per 1,000 cells examined) were significantly lower at 0.1 mW/cm^2 exposure than in controls ($p<0.05$). Metaphase II counts were also significantly lower than controls at 0.5 mW/cm^2. Translocations occurred at random with respect to chromosome pairs, and no particular chromosome pair was more likely than another to have a translocation. The authors speculate that the microwave exposure interfered with chiasma formation and/or behavior.

Stodolnik-Baranska (1974) exposed human lymphocytes in culture to 2950-MHz [sic] pulsed microwaves (1200 Hz pulse rate, 1 microsecond pulse width). At 20 mW/cm^2 applied after the cells had been in culture for 66 hours, the mitotic index increased with exposure time to about twice the control value at 20 minutes (or after two 20-minute exposures separated by 30 minutes). Similar results were found after 3 or 5 hours exposure at 7 mW/cm^2 when applied after the 64th hour of incubation. Little effect on mitotic index was seen when cells were irradiated after 70 hours of incubation. Irradiation of unstimulated lymphocytes (no phytohemagglutinin) induced blastoid forms and macrophage-like cells.

5.2.3. Summary

Table 5-3 is a summary of the section on mitotic and meiotic effects of EM fields. As shown, both static magnetic and electric fields can alter the mitotic index and cell cycle progression of a number of cell types in a number of species. However, there is no clear pattern to the effect. Likewise ELF electric fields, at least in the 50- to 75-Hz range reported in Table 5-3, cause perturbations of mitotic activity and cell cycle progression. Apparently an inhibiting effect on mitotic activity, if it occurs, occurs early during exposure with recovery to or beyond control levels at later times. This effect was seen in plant systems and in **a** human cell culture study. Therefore, a report of no effect in a test system at 24-hour exposure may mean

TABLE 5-3. EFFECTS ON MITOSIS AND MEIOSIS

Static Fields	Exposure	End Point	Result	Reference
Static Fields				
Allium fistulosum (germinating onion seeds; root tip cells examined)	North or south orientation in geomagnetic field (0.05 mT) plus 200 mT static field	Mitotic activity	Lower activity with southern orientation 200 mT additional field raised activity of southern oriented seeds to that of northern oriented seeds	Nemirovich-Danchenko and Chastakolenko, 1976
	600 mT static magnetic field 140 hr	Mitotic activity, cell progression	Activity reduced due to inhibiting effect on transition of cells from interphase to prophase	Herich. 1976
Allium cepa (germinating onion seeds; root tip cells examined)	45, 100, 200, mT static magnetic field, 1 hr		Mitotic index 2.4 times higher at 45 mT and 1.3 times higher at 200 mT	
Hellianthus annus (germinating sunflower seeds, root tip cells examined)	500 mT static magnetic field, 4 hr	Mitotic index at 48 hr post-treatment	Chromosomal bridges and fragments, segregation errors at anaphase and telophase I and II	Gemishev, 1976
Lillium henry; (lily pollen mother cells)	900 mT static magnetic field, 13 days	Meiotic abnormalities	M.I. increased	Linskens and Smeets, 1978
Mouse (Swiss male)	100 mT static magnetic field, 1 day	Mitotic index in liver	M.I. increased at 0, 1, 3, hr post-exposure	Barnothy and Sumegi, 1969
Mouse (C57B6; CBA)		Mitotic index in duodenal epithelium	M.I. increased at 6, 10, 12 days postexposure	Mastryukova and Rudneva, 1978
Mouse	300 - 12,700 mT magnetic field, 1 hr field had one constant component and one sawtooth component with period of 30 sec	Mitotic index in corneal epithelial cells	Mitotic index decreased with increasing field intensity but not in a uniform manner	Strzhizhovkii et al.. 1979
Drosophila melanogaster canton-S females	150, 330, kV/m electric field, 24 hours	Nondisjunction of x chromosome in F, offspring	No effect	Portnov et al., 1975

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TABLE 5-3. EFFECTS ON MITOSIS AND MEIOSIS (continued)

Static Fields	Exposure	End Point	Result	Reference
Elf Fields				
Pea roots	60 Hz, 140, 430 V/m chronic	Mitotic index growth rate	Maximum decrease of M.I. at 4 hr exposure to 430 V/m recovery by 8 hr. Constant reduction in growth rate from start of exposure	Robertson, et al., 1981
Pea roots	60 Hz, 430 V/m 25-48 hr	Mitotic index cell cycle	No effect on M.I. (measured at 24 hr exposure) Boot growth reduced (measured at 48 hr) Cell cycle duration increase (measured at 24 hr)	Brulfert et al., 1985
Broad bean roots	60 Hz, 200, 290, 360 V/m up to 30 hr for M.I. 4 days for root growths	Mitotic index root growth	No effect on M.I. root growth reduced proportional to field strength	lnoue et al., 1985
Allium cepa Onion roots	60 Hz, high voltage line 15.5, 23 kV/m 5, 10, 15 days	Mitotic index	No effect	Greene, 1983
Physarum polycephalum (slime mold)	60, 75 Hz crossed electric and magnetic fields 0.7 V/m, 0.2 mT up to 120 days or 0.15 kV/m, 0.04 mT up to 200 days	Mitotic delay (cell cycle)	Significant delay after 80-100 days at 60 Hz and after 100-120 at 75 Hz; no effect at lower field	Marron et al., 1975
Physarum polycephalum (slime mold)	65 Hz 16 hr/day, 5 days/wk, 1 V/m, 1.0 mT; 0.7 V.m, 0.2 mT; 0.2 mT; 0.7 V/m	Mitotic delay cell cycle	Mitotic cycle duration increased by all treatment	Goodman et al., 1984
Human embryo fibroblastoid cells	50 Hz, 50 kV/m up to 7 days	Mitotic index	Significantly reduced at 24 and 48 hr but above control levels at 96 hr and longer exposure	Dyshlovoi et al., 1981

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TABLE 5-3. EFFECTS ON MITOSIS AND MEIOSIS (continued)

Static Fields	Exposure	End Point	Result	Reference
RF Fields				
Mouse female CD-1	2450 MHz, 20 mW/cm^2 8 hr/day for 28 days (average SAR = 21 mW/g	Mitotic index in bone marrow		No effect
Human lymphocytes	2950 MHz, 1200 Hz pulse rate, 1 µsec pulse width 20 mW/cm^2, 20 min or 7 mW/cm^2 3-5 hr	Mitotic index	Increase with both exposures	Stodolnik-Boranska, 1974
Mouse, male Balb/c	9400 MHz, 1000 Hz pulse rate, 0.5 µsec pulse with 1 hr/day, 5 days/wk, 2 wk 0.1, 0.5, 1.0, 10 mW/cm^2	Meiotic index in spermatogonia and spermatocytes metaphase I and II abnormalities	Metaphase I with univalents increased at all exposure levels; increased translocations at all but lowest exposure levels, metaphase I, II, and spermatogonial metaphase counts decreased at 0.1 mW/cm^2, metaphase II counts decreased at 0.5 mW/cm^2	Manikowska et al., 1979

only that the author(s) didn't take a sample soon enough. The three studies using RF fields are not directly comparable as seen in Table 5-3, and no general conclusion is possible.

5.3. EFFECTS ON TRANSCRIPTION, TRANSLATION, AND CELL TRANSFORMATION

5.3.1. Extremely Low Frequency Electromagnetic Fields

Goodman and her collaborators have published a number of papers in which cellular transcription was induced in gnat *(Sciara coprophila)* larval salivary glands following exposure to ELF fields. Goodman et al. (1983) exposed salivary glands to pulsed magnetic fields in 0.5 milliliters (mL) of Schneider's Drosophila medium in petri dishes between a pair of 10-cm by 10-cm Helmholtz aiding coils oriented vertically, producing a magnetic field parallel to the bottom of the petri dish. The glands (still attached to the larval bodies) were exposed to either repetitive single pulses (single 380-microsecond pulses of 15 mV amplitude repeated at 72 Hz) or to repetitive pulse trains [5millisecond pulse trains of 200-microsecond pulses (also 15 mV amplitude) repeated at 15 Hz]. The rate of change of the magnetic field was about 0.1 G/microsecond (0.01 mT/microsecond) for the pulse trains and 0.05 G/microsecond (0.005 mT/microsecond) for the single pulses. The authors measured transcription in three ways: (1) nascent RNA chains attached to specific chromosome regions were identified by autoradiography; (2) nick translation using deoxyribonuclease I to identify transcriptionally active chromatin regions; and (3) RNAs of various size classes were isolated and analyzed for changes in the pattern of tritiated uridine incorporation. At 15 and 45 minutes of exposure to the single pulse field, there was a specific increase in RNA transcription in most of the bands and interband regions of the chromosomes. At 30 minutes, exposure transcription was about at the control rate. Nick translation showed some "hot spots" of transcription at 45 minutes of exposure. The pulse-train field led to a gradual increase in transcription up to 45 minutes of exposure but not to the level reached by the single pulse exposure. Effects of both types of fields decreased after 60 minutes of exposure. Isolation of RNA on sucrose gradients showed a fourfold increase in total RNA but an 11 -fold increase in the mRNA size class at 15- and 45-minute exposures to single pulse fields. All size classes of RNA were at control levels after 15 minutes of exposure to pulse-train fields, but after 45 minutes, the levels of all RNA size classes had increased.

Goodman and Henderson (1986), using the same test system just described, compared the effect of wave shape on transcription induction. The magnetic fields were generated with 10 x 10 cm Helmholtz aiding coils orientated vertically. The authors used a 72-Hz sine wave (0.8 mV positive amplitude, 1.15 mT peak magnetic field, rate of change of field was 0.5 T/sec, induced electric field at a radius of 2 cm was 5 x 10^{-3} V/m) and a 72-Hz repeating single pulse (380-microsecond positive pulse width, 4.5 microseconds negative spike, 3.5 mT peak magnetic field, rate of change of field was 9200 mT/second, induced electric field at a radius of 2 cm was 9.2 x 10^{-2} V/m). Autoradiographs of the salivary gland chromosomes, particularly the X chromosome, showed similar induction of transcription for both EM field types. The grain patterns were consistent with induction of mRNA gene sites and suggested that enhanced transcription was occurring at sites normally active at this stage of larval development. Analysis of RNA on sucrose gradients showed increased incorporation of tritiated uridine into size classes consistent with processed and unprocessed mRNA (6-10 S and 20-25 S). When the sine wave frequency was raised to 222 Hz (0.37 mT) or 4400 Hz (0.018 mT) a similar pattern of induction resulted but to a lesser degree. The relative transcriptional activity of the 6-10 S size class was inversely correlated with frequency. Goodman et al. (1987) did a more detailed analysis of grain count distribution over the X chromosome of *Sciara* after exposures to 72-Hz single pulse, pulse train, or sinusoidal EM waves as described in the previous two papers. In addition to enhanced transcription at normally active sites, they also found transcription occurring at sites not detectably active in control cells. The response was qualitatively the same with the three different fields but the sinusoidal and single pulse fields were more effective than the pulse train field.

Goodman and Henderson (1988) again using the *S. coprophila* salivary gland system, reported altered polypeptide synthesis following exposure to ELF fields of various waveforms and frequencies. Table 5-4 summarizes the exposures used.

The polypeptide patterns obtained by two-dimensional gel electrophoresis were qualitatively and quantitatively different for each type of exposure and different from control and heat-shocked cells; however, conclusions about specific effects of the different types of exposure are not possible. Individual proteins were not identified, and it is not possible to ascribe the observed effects to either the electric field or the magnetic field. No conclusions could be made concerning any possible effect of frequency.

TABLE 5-4. CHARACTERISTICS OF ELECTROMAGNETIC FIELDS TESTED

Frequency (Hz)	Positive induced amplitude (mV)	Positive duration (µsec)	Burst width (msec)	Negative space (µsec)	Negative spike (µsec)	Peak magnetic field (mT)	Electric field (V/m)
72	15	380			4500	3.5	9×10^{-3}
15	14.5	200	5	28	24	1.9	9×10^{-3}
1.5	2.5	250	30	10	4	0.38	1.5×10^{-3}
72	0.8					1.1	5×10^{-4}
60	0.8					1.5	5×10^{-4}

An effect of magnetic fields has also been shown on the lac operon system by Aarholt et al. (1982). In this system the beta-galactosidase gene is under control of the lac operon and is normally repressed by a repressor protein. If the dynamic equilibrium between synthesis and degradation of the repressor protein is changed, changes in rate of synthesis of beta-galactosidase should be seen. The authors exposed the bacteria to a 50-Hz square wave magnetic field varying from 0 to 0.7 mT and measured beta-galactosidase synthesis. The rate of synthesis was quite dependent on field strength; it started to decrease at 0.27 mT, was less than one-third of the control rate at 0.30 mT, then increased to the control rate by 0.32 mT. The rate remained at the control level until the field intensity reached about 0.51 mT when the rate began to increase, reaching more than twice the control rate at 0.54 mT. The rate fell sharply beyond 0.56 mT and returned to the control rate again at 0.58 mT. The field strength effect on synthesis rate was strongly dependent on cell concentration. The field strength dependence was seen at 1.5×10^7 cells/mL (the lowest cell concentration reported), remained constant until about 3×10^7, increased to its greatest level between 3.6×10^7 and 5.0×10^7 cells/ml, and disappeared above 1×10^8 cells/mL. The effect is maximum when the intercellular distance is about 30 m and is no longer present when the intercellular distance is less than 20 µm. The mechanism of the observed effects in not understood; however, based on the work reported in this paper and on work by others cited in this paper, the authors speculate that the effect involves the repressor protein rather than the DNA.

The following comment is not intended as additional proof of a transcription-inducing potential of ELF fields but is intended to show that this is a rapidly developing area and additional peer-reviewed publications should soon be available. A number of meeting abstracts and presentations have appeared in the past year showing transcriptional changes

in cells (including human and other mammalian cells) exposed to ELF electromagnetic and magnetic fields. Oncogenes are among the genes induced.

5.3.2. Radiofrequency Electromagnetic Fields

Cell transformation has also been demonstrated following microwave exposure. This subject is included here on the assumption that the transformed phenotype results ultimately from altered gene expression.

Balcer-Kubiczek and Harrison (1985) presented what they considered to be evidence for microwave carcinogenesis in vitro. Their conclusion was based on an observed synergistic effect of pulsed 2.45-GHz microwaves (120 pulses/second, 83-microsecond pulse width, SAR = 4.4 W/kg) and x-rays on the frequency of malignant transformation of C3H/10T1/2 mouse embryo cells. The synergistic effect was seen only if the cells were treated with the tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA) following exposure. A similar experiment was done with benzo[a]pyrene instead of x-rays, but no TPA treatment was given. Temperature of the cell cultures during microwave exposure (37.2 ± 0.1° C) was controlled by immersing the culture flasks in a constant-temperature water bath, but as discussed previously, the effective temperature at localized intracellular sites may be higher than the average culture temperature. Cells were irradiated with microwaves for a total of 24 hours, either continuously in the presence of 2.5 to 12.5 M benzo[a]pyrene or with an interruption after 6 hours to allow for exposure to 1.5 - 6 Gy of 100 kV (peak) x-rays. Following exposure to x-rays, some cultures received 0.1 micrograms per milliliter (µg/mL) TPA. Results of the transformation studies are given in Table 5-5. No results are given on induction of cell

TABLE 5-5. EFFECT OF MW IRRADIATION ON TRANSFORMATION FREQUENCY(x 10^3) IN C3H/10T1/2 MOUSE EMBRYO FIBROBLASTS

Treatment	1.5 Gy	4.5 Gy	0 Gy
X-ray only	0.31	2.9	
X-ray + MW	0.40	2.9	
X-ray + TPA	1.80	5.1	
X-ray + MW + TPA	6.0	8.2	
BP only			10.0
BP + MW			10.3

transformation by microwaves alone or by microwaves plus TPA, obvious experiments when the authors conclude that the microwave effect is at the initiation phase. Microwave exposure alone reduced the plating efficiency by about one-half compared to sham-irradiated controls, while TPA alone increased the plating efficiency by about 40%. TPA addition to microwave-exposed cells raised the plating efficiency somewhat over that seen after microwaves alone. The authors speculate that the results were due to a membrane effect with secondary DNA damage or to an effect on DNA repair, these effects being partially reversed by TPA, allowing some cells to express the transformed phenotype that would otherwise have died.

A follow-up study was published by Balcer-Kubiczek and Harrison (1989) to further clarify the suggestion made in the 1985 study that microwaves alone may act as an initiator of neoplastic transformation in vitro or interfere with repair of damage caused by other carcinogens. Exposures of mouse C3H/10T1/2 cells in culture to 2.45-GHz microwaves pulsed at 120 pulses per second with an 83-microsecond pulse width for 24 hours, (SAR = 4.4 ± 0.8 W/kg at the cell monolayer) were as given in the previous experiment. Microwaves alone, without post-irradiation TPA, or TPA alone, produced no transformed foci in the cell cultures; however, post-irradiation treatment with 0.1 µg TPA/mL led to a significant increase in transformation frequency over the control level. Therefore, the conclusion is that microwaves, as used in this experiment, act as an initiator in a two-stage transformation assay. Unlike the previous study, there was no effect on plating efficiency by any treatment.

5.3.3. Summary

Several experiments by Goodman and colleagues have shown that pulsed and sinusoidal magnetic fields in the ELF frequency range between 1.5 and 222 Hz have the ability to affect the transcription (or gene expression) of information from DNA to mRNA in gnat *(Sciara corprophila)* larval salivary glands and the translation of the mRNA message into protein synthesis in the same system. The effect on gene expression is mainly one of enhancing the activity of genes that are already active at that stage of larval development, but new sites were also induced by the field. The protein synthesis experiments showed the induction of different patterns of molecular weight distribution for each of the waveforms used. Exposure of *Escherichia coli* bacteria to a 50-Hz square wave magnetic field resulted in a complex intensity-dependent enhancement and inhibition of the synthesis rate of a specific protein

known to be under the control of the lac operon and normally repressed by a repressor protein.

Exposure to 2.45-GHz RF radiation pulsed at 120 pulses per second followed by treatment with the phorbol ester TPA has induced the transformation to malignancy of the mouse C3H/l10T1/2 cell line (Balcer-Kubiczek and Harrison, 1989). In this system the modulated RF radiation is acting like an initiator in a traditional two-stage cancer promotion protocol in this cell line.

5.4. CALCIUM EFFLUX FROM BRAIN TISSUE

A rapid change in calcium concentration is essential in many physiologic, metabolic, and cellular processes (e.g., regulation of nerve membrane excitability, release of neurotransmitter substances from presynaptic nerve terminals, mitochondrial function, the action of cyclic nucleotides in controlling cellular activity, and the initiation of cell proliferation and tumor promotion). According to Adey (1988a), alterations in calcium efflux have been demonstrated with low frequency EM fields, with low frequency electric fields, with combined low frequency EM and static magnetic fields, and with RF fields amplitude-modulated at low frequencies,

Calcium-ion (Ca^{++})efflux from brain tissue, sensitive to electric currents applied to brain tissues in vitro, has been used as a biochemical marker to study the biological effects of EM fields.

Most studies on calcium efflux have used cerebral tissue. Blackwell and Saunders (1986) reviewed the effects of low-level RF and microwave radiation on brain tissue and animal behavior and concluded that there is some evidence for effects of low level EM radiation on Ca^{++} exchange in nervous tissue, but they noted that many experiments reporting positive effects have been criticized. Examples of calcium efflux studies are presented in the following section.

5.4.1. Extremely Low Frequency Fields

Bawin and Adey (1976) examined the effect of ELF fields on calcium efflux from chick cerebral hemispheres, chick striated muscle, and cat cerebral cortex. The tissues, maintained at 36° C during the experiment, were labelled in vitro with $^{45}Ca^{++}$. “Sets” of 10 brain tissues were exposed for 20 minutes to weak ELF sinusoidal electric fields of 1, 6, 16, 32, or 75 Hz with electric gradients at each frequency of 5, 10, 56, or 100 V/m; 50 muscle samples were

exposed to a 16-HZ, 20 V/m field. Controls consisted of sham-treated samples. The samples were assayed for radioactivity and the data were smoothed by the removal of counts more than 1.5 standard deviations away from the mean before statistical evaluation.

The results of these experiments suggested that ELF fields inhibited calcium release from cerebral tissue and the pattern of inhibition indicated the existence of frequency and amplitude "windows." In the chick brain, the maximum reduction ($p<0.01$) occurred at frequencies of 6 and 16 Hz with field gradients of 10 V/m. In the cat tissue, significant reduction in $^{45}Ca^{++}$ efflux occurred at 6 Hz ($p<0.05$) and 16 Hz ($p<0.01$) with 56 V/m gradients. Muscle tissues were unaffected by field conditions that induced changes in $^{45}Ca^{++}$ efflux from brain tissue. This study (Bawin and Adey, 1976) has been criticized, however, for the rejection of data that were more than 1.5 standard deviations away from the mean of the exposed or sham data before final analysis (Myers and Ross, 1981).

In contrast to the inhibition of Ca^{++} efflux observed at 16 Hz by Bawin and Adey (1976), Blackman et al. (1982) demonstrated an enhancement in Ca^{++} efflux at 16 Hz, but with different exposure conditions. Bawin and Adey had exposed the samples to an oscillating AC electric field with only a small magnetic component, whereas Blackman et al. (1982) used an AC electromagnetic field. Blackman et al. (1985a) tested the hypothesis that the differences in calcium efflux were due to the AC magnetic component present in the system. The exposure system consisted of a transmission line exposure chamber in which the electric and magnetic fields were perpendicular to each other and oriented in the horizontal plane. To expose samples to an AC electromagnetic field under altered local geomagnetic field (LGF) conditions, a DC magnetic field was generated by a pair of Helmholtz coils which were placed around the transmission line. The coils produced a uniform magnetic field within the exposure chamber that was parallel to the local vector of the geomagnetic field, which was inclined at 85° from the horizontal plane. One of the major findings of the study was that a 15-HZ signal, effective in inducing a change in calcium efflux when the LGF was 38 tesla (T), was rendered ineffective when the LGF was reduced to 19 T. Changes in the LGF also rendered ineffective signals effective. Blackman et al. (1985a) concluded that the AC magnetic component was essential for the efflux enhancements observed in their laboratory.

Blackman et al. (1985b, 1988b) examined frequency-dependent exposure regions that had been identified for the efflux of Ca^{++} from brain tissue of newly hatched chickens *(Gallus domesticus).* The frequency dependence of calcium efflux from the brain preparations (32

chicks/exposure) was first tested using nine different EM fields, ranging from 1 to 120 Hz [LGF: 0.38 G (0.038 mT), 85° N (inclination of the magnetic field to the horizontal plane of the AC electric and magnetic components)] (Blackman et al., 1985b). Two effective frequency regions, one at 15 and 16 Hz and the other between 45 and 105 Hz, were identified. The two frequency regions were not the same size, and the investigators decided to further characterize the frequency dependence using higher frequencies (Blackman et al., 1988b). Thirty-eight frequencies, ranging from 1 to 510 Hz (with a static magnetic field of 0.038 mT at 85° inclination), were tested using 28 to 32 chicks per exposure. The samples were exposed in a transmission line exposure chamber to crossed electric [15.9 volts root-mean-square per meter (Vrms/m)] and magnetic [73 nanotesla root-mean-square (nTrms)] fields. Cerebral hemispheres from newly hatched chickens were removed, halved, and labelled in vitro with $^{45}Ca^{++}$. Half of the halved hemispheres were exposed or sham-exposed to the field for 20 minutes. The other half (controls) were incubated for 20 minutes outside the exposure chamber. The radioactivity in the control sample was used to normalize the radioactivity in the paired-treated sample to adjust for possible influences caused by differences in sex, age, and brain mass among the animals, and in the specific activity of the labelling solutions.

When the differences in mean efflux values between exposed and sham-irradiated samples were compared, there were no discernable patterns of response as a function of frequency. However, calculation at each frequency of the p-value which combines the difference between the means of the exposed and sham-exposed groups with the variance of each group provided the investigators with a basis for hypothesizing the existence of three frequency-dependent patterns of calcium efflux in the data. One pattern occurred between 15 and 315 Hz, one occurred at 60, 90, and 180 Hz (but not at 300 Hz), and one occurred at 405 Hz. The authors speculated on mechanisms that could be responsible for EM field-induced changes in calcium-ion efflux, focusing on the initial transduction of electromagnetic energy into a small physicochemical change. Assuming that the LFG determines the frequencies that are effective in the transduction step, magnetic resonance mechanisms, either nuclear magnetic resonance or electron paramagnetic resonance, which operate through the oscillating magnetic field and require an LGF, are the leading candidates. In nuclear magnetic resonance, the oscillating magnetic field acts on nuclei with magnetic moments. The interaction between the time-varying magnetic field and nuclear magnetic moments naturally

found in biological systems provides the basis for nuclear magnetic resonance imaging (Blackman et al., 1988b).

Another mechanism, the simple Lorentz-force interaction, in which an oscillating electric field, or an electric field induced from an oscillating magnetic field, causes charged species to move in an LGF, was considered as a possible explanation for the pattern of significant results observed at 60, 90, and 180 Hz. The authors state that the usefulness of this model is hampered by the absence of a known chemical entity that would explain the specific observed frequencies and LGF field strength.

In a different type of study, Blackman et al. (1988a) tested the effects of ELF on field-induced Ca^{++} efflux in brain tissue of a developing organism. Fertilized eggs of *Gallus domesticus* were exposed in a parallel plate apparatus consisting of one ground plate between two energized plates. During their 21-day incubation period, the eggs were exposed continuously to either 50- or 60-Hz sinusoidal electric fields at an average intensity of 10 Vrms/m. The LGF in the egg exposure apparatus was 40 microtesla (μT) (0.04 mT) with an inclination of 55° N. The ambient 60-Hz magnetic field was less than 70 nanotesla (nT). The entire apparatus was mounted on a pivot which allowed the eggs to be automatically tilted through 66° once an hour.

The chickens were removed from the exposure apparatus within 1.5 days after hatching and their brains were removed, separated along the midline, and labelled for 30 minutes at 37° C with radioactive Ca^{++}. The assay consisted of a test and a control. A tube containing one of the brain halves of a pair was placed in the exposure chamber at 37° C (treated sample), and the tube containing the other brain half was placed in a water bath at 37° C for the 20-minute exposure period (control sample). The samples that had been exposed to either 50 or 60 Hz during incubation were exposed for 20 minutes to either 50- or 60-Hz EM fields at average values of 15.9 Vrms/m and 73 nTrms (in an LGF of 38 μT, 85°N to the horizontal plane of the AC electric and magnetic components). Exposure took place in a transmission line exposure chamber. Efflux of radioactive Ca^{++} from the brains of the treated and control groups was then measured by standard procedures. The ratios of counts per minute in the treated (exposed) samples were compared to those of the control samples.

The brains from chicks exposed to 50-Hz fields during incubation and exposed to 60-Hz fields in vitro exhibited increased calcium efflux (40%, $p<0.01$, Bonferroni-adjusted t-tests). The brains from chicks exposed to 60 Hz during incubation and to 60 Hz in vitro did not, The

brains from chicks exposed to 60-Hz fields during incubation were not affected by either 50- or 60-Hz fields. The investigators concluded that exposure of the developing chick to ambient power-line-frequency electric fields, at levels typically found inside homes, can alter the response of brain tissue to field-induced calcium-ion efflux, but they stated that the physiological significance of this finding for the intact organism or for other species is not clear.

5.4.2. Modulated Radiofrequency Fields

Bawin et al. (1975) demonstrated that weak VHF fields, amplitude-modulated at brain wave frequencies, increased calcium efflux from the isolated brain of the neonatal chick. Ten forebrains, preincubated with $^{45}Ca^{++}$ for 30 minutes, were used for each field condition, and each condition was tested at least three times. Fields of 147 MHz with field intensities of 1 to 2 mW/cm^2 and amplitude-modulated at 0.5 to 35 Hz (modulation depths were kept between 80% and 90%) were applied for 20 minutes. One group of tissues was irradiated with an unmodulated carrier wave, and controls were run in the absence of fields. The counts of radioactivity were normalized before statistical evaluation.

Unmodulated radiations and fields modulated at 0.5 and 3 Hz produced no significant changes in the $^{45}Ca^{++}$ efflux in comparison with the unirradiated controls. However, fields modulated at frequencies ranging from 6 to 16 Hz produced a progressive increase in the $^{45}Ca^{++}$ efflux from the brains ($p<0.05$ to $p<0.01$), then a gradual decline in efflux at higher frequencies. This is indicative of a “windowed” effect, dependent on a narrow band of slow modulation frequencies.

The Bawin et al. (1975) data evaluation has been criticized by Myers and Ross (1981) for the presentation of normalized control values, on the basis that normalization removes important information about variation of the control data between different experimental tests and between different experiments.

Albert et al. (1987) examined $^{45}Ca^{++}$ efflux from cerebral cortex tissue slices and cerebral hemispheres that were prepared from *Gallus domesticus* chicks and exposed to 147-MHz RF radiation, amplitude-modulated at 16 Hz, and applied at a power density of 0.75 mW/cm^2. The data showed that exposure had no statistically significant effect on $^{45}Ca^{++}$ efflux. These results are in contrast to the increased Ca^{++} efflux observed by Blackman et al. (1980) using the same frequencies. However, Blackman (1987) notes that Albert et al. (1987) tested a

different intensity (0.75 mW/cm^2) from that tested by Blackman et al. (1980) (0.83 mW/cm^2), suggesting the existence of an additional null effect intensity region. In a recent study, Blackman et al. (1989) confirmed the existence of narrow power density ranges for the enhancement of Ca^{++} efflux from chick forebrain tissue exposed in vitro to 50-MHz RF electromagnetic radiation (magnetic field: 0.038 mT, 60°N), amplitude-modulated at 16 Hz utilizing a series of power densities. A statistically significant ($p<0.001$ to $p<0.05$) enhancement of calcium ion efflux was observed at 1.75, 3.85, 5.57, 6.82, 7.65, 7.77, and 8.82 mW/cm^2, while no change was observed at 0.75, 2.30, 4.50, 5.85, 7.08, 8.19, 8.66, 10.6, and 14.7 mW/cm^2. In other words, six windows were observed with five being in a mathematical relationship to each other. Blackman et al. (1989) speculate that deterministic chaos is the potential cause of the multiple intensity windows observed. This probability would extend Fröhlich's model down to the ELF range.

Lin-Liu and Adey (1982) examined the effect of weak sinusoidally modulated microwave fields on $^{45}Ca^{++}$ efflux from synaptosomes undergoing continuous perfusion. Synaptosomes are isolated subcellular neuronal elements that resemble synaptic terminals in situ. Their membrane properties can be more easily manipulated than whole brain or tissue slices. The synaptosomes, prepared in duplicate from the cerebri of male Sprague-Dawley rats, were loaded with $^{45}Ca^{++}$ and applied to a millipore filter which was placed in the perfusion system and perfused with Ca-free medium for 45 minutes. One of the duplicate samples served as control and the other was exposed to the fields during perfusion. The perfusate was collected at one minute intervals and assayed for radioactivity. The temperature was maintained at 31° C to minimize synaptosomal autolysis. The 450-MHz field was either unmodulated or sinusoidally amplitude modulated at 16 or 60 Hz, the unmodulated signal had a power density of 0.5 mW/cm^2, and the modulated signals had the same peak power with a modulation depth of 75%. The electrical gradient produced by the unmodulated field was 43 V/m in air. The field intensities used were not expected to cause significant changes in calcium efflux due to thermal energy transfer. In the perfused, unirradiated samples, the rate of calcium efflux from the synaptosomes showed a biphasic response, with a fast (half-time, 5 minutes) and slow (half-time, 40 minutes) phase. The 450-MHz field modulated at 16 Hz, applied for 10 minutes during the second phase, increased the rate constant for $^{45}Ca^{++}$ by 38% ($p<0.01$, Mann-Whitney U test). Unmodulated or 60-Hz modulated signals were not effective.

These results support the experiments of Bawin et al. (1975, 1978) that 16-Hz amplitude-modulated signals can stimulate the release of preincubated $^{45}Ca^{++}$ from isolated brain tissue.

Shelton and Merritt (1981) failed to demonstrate altered $^{45}Ca^{++}$ efflux in rat cerebral tissue preloaded with $^{45}Ca^{++}$ and exposed to pulse-modulated (rather than amplitude-modulated) microwave radiation (1-GHz carrier frequency) at various power densities (16 Hz at 0.5, 1.0, 2.0, or 15 mW/cm^2 or 32 Hz at 1.0 or 2.0 mW/cm^2). Merritt et al. (1982) were also unable to alter $^{45}Ca^{++}$ binding to brain tissue with pulse-modulated microwave radiation. Rat brain tissue was loaded in vivo with $^{45}Ca^{++}$ by intraventricular injection and exposed in vitro to pulse-modulated 1-GHz radiation (SAR, 0.29 or 2.9 W/kg) or 2.45 GHz (SAR, 0.3 W/kg) and in vivo to 2.06 GHz (SAR, 0.12 to 2.4 W/kg). Merritt et al. (1982) suggest that because pulse-modulated and amplitude-modulated signals [such as those used in experiments by Bawin et al. (1975)] are quite different, the biologic effects induced by them may be different.

Dutta et al. (1984) also reported enhanced Ca^{++} efflux from human neuroblastoma cell cultures exposed to RF radiation at 915 MHz, amplitude modulated at 16 Hz at certain narrow ranges of SAR (0.05 and 1.0 mW/g). Subsequently, Dutta et al. (1989) conducted a similar study using exposure conditions analogous to those used by Bawin et al. (1975) and Blackman et al. (1980). Human neuroblastoma cells, labelled with $^{45}Ca^{++}$, were exposed for 30 minutes to EM radiation at 147 MHz, sinusoidally amplitude-modulated at 16 Hz at various SAR values (0.1, 0.05, 0.01, and 0.005 W/kg) (magnetic field: 0.016 mT, 53° inclination). Calcium-ion efflux was also measured from the human neuroblastoma cells at 147 MHz and various amplitude modulation frequencies (SAR, 0.05 W/kg) and from human neuroblastoma cells and hybrid Chinese hamster-mouse neuroblastoma cell lines at 147 MHz, amplitude-modulated at 16 Hz (SAR, 0.05 W/kg). In all cases the results for the exposed groups were compared with those for unexposed controls. The respective-findings of the three studies were as follows: significantly enhanced $^{45}Ca^{++}$ efflux was observed at SAR values of 0.05 and 0.005 W/kg ($p<0.001$ and 0.003, respectively); significant $^{45}Ca^{++}$ efflux from human cells was observed at amplitude modulation frequencies of 16 and 57.5 Hz ($p=0.008$, and $p<0.001$, respectively); and significant enhancement of $^{45}Ca^{++}$ efflux was observed in both human and nonhuman cell lines ($p<0.001$ for both). These studies show that cell lines derived from tumors of the human central nervous system respond to modulated RF fields similar to normal

nervous tissues or cell lines from nervous systems of chicks and cats. These results also confirm the findings of Bawin et al. and Blackman et al.

In addition to the in vitro effects cited above, EM field-induced alterations in calcium efflux have been observed in intact animals. Adey et al. (1982) examined the effects of weak, amplitude-modulated microwave fields on calcium efflux from the cerebral cortex of 23 awake cats. The cerebral cortex was exposed while the animals were under ether anesthesia and a plastic cylinder was inserted and placed in contact with the pial surface to make a “cortical well”; at the conclusion of surgery, ether was discontinued, and the animals were immobilized with gallium triethiodide for calcium efflux measurements. $^{45}Ca^{++}$ was placed in the wells for a 90-minute incubation, then the medium was replaced with nonradioactive solution. The solution was completely exchanged and samples were taken for scintillation counting every 10 minutes for 3 to 4 hours. Field exposure, initiated at intervals ranging from 80 to 120 minutes after incubation of the cortex with $^{45}Ca^{++}$, lasted for 60 minutes. For the efflux experiments, the 450-MHz field (3.0 mW/cm^2) modulated at 16 Hz (modulation depth of 85%) was applied in an anechoic chamber maintained at 28° C, with the cats oriented at right angles to the field. At the end of the experiment, the animals were killed with an overdose of phenobarbital, and cortical samples were taken to measure the depth of $^{45}Ca^{++}$ diffusion. Sham controls were used in this study, but sham treatment was not detailed.

The efflux of $^{45}Ca^{++}$ from preloaded cat cerebral cortex, not exposed to the experimental field, followed an exponential pattern with three phases: an initial phase of rapidly declining efflux, lasting about 10 minutes; an intermediate phase in which the slope of the efflux curve was somewhat reduced (at 20 to 80 minutes); a third phase of gentle slope starting at about 180 minutes from the beginning of sampling and extending to about 210 minutes. The efflux curve for the test group followed the control curve until field exposure was initiated 80 to 120 minutes after incubation of the cortex with $^{45}Ca^{++}$. Following field exposure, the efflux curve of the exposed group was interrupted by waves of increased $^{45}Ca^{++}$ efflux. The waves had periods of approximately 20 to 30 minutes and were irregular in amplitude, continuing into the postexposure period. A comparison of the control and field exposure data with calculated predicted curves (binomial probability analysis) indicates that the field-exposed efflux curves comprise a different population from controls at a confidence level of 0.968.

Tissue field measurements, performed in separate studies, showed a field strength of 33 V/m (0.29 W/kg) for the interhemispheric fissure. Measurement of radioactivity in cortical

samples at the end of the study demonstrated that $^{45}Ca^{++}$ penetrated the tissue at the rate of 1.7 mm/hour.

5.4.3. Unmodulated Radiofrequency Fields

Three of the studies mentioned in the preceding section under Modulated RF/microwave fields included control groups that were exposed to unmodulated fields and examined for alterations in calcium efflux or other membrane effects. No changes in calcium efflux were observed at any of the unmodulated frequencies tested. These studies with brief descriptions of field conditions are as follows: Bawin et al. (1975) - 147 MHz, 1 to 2 mW/cm^2, 20 minutes; Lin-Liu and Adey (1982) - 450 MHz, 0.5 mW/cm^2, 10 minutes; Blackman et al. (1980) - 147 MHz, 0.83 and 0 mW/cm^2, 20 minutes.

5.4.4. Summary

The preceding studies demonstrate that calcium efflux from brain tissue was increased or decreased by ELF fields, was decreased or not affected by modulated RF and microwave fields, and was not affected by unmodulated RF radiation. These responses appear to be highly dependent on specific field conditions: e.g., frequency, power density, and type of modulation, emphasizing the complexities involved in comparing one study with another. Although alterations in Ca^{++} efflux indicate some interaction of ELF at the cell membrane, the physiological significance of this effect is still not fully understood (Blackwell and Saunders, 1986; Blackman et al., 1988a), and a direct relationship between the effect of EM radiation on calcium efflux and tumor induction or promotion cannot be established at this time.

The experiments of Blackman et al. (1988a) showing frequency selectivity in the calcium efflux from brain tissue at field strengths of 16 V/m and 0.07 µT (crossed electric and magnetic fields) are the only laboratory studies showing ELF effects at levels comparable to ambient fields in residential buildings. All nonhuman effects measured in laboratory settings have occurred at field strengths much higher than ambient levels.

Adey (1988a) proposed that in the amplification stage of transductive coupling, the initial stimuli associated with EM oscillations elicit a highly cooperative modification of calcium binding to the glycoproteins that protrude from the membrane surface. Adey (1988a) suggests that the alteration in calcium binding could spread longitudinally, consistent with the

direction of flow of extracellular currents associated with physiological activity and with imposed EM fields.

5.5. INTRACELLULAR ENZYME RESPONSES

5.5.1. Protein Kinases

5.5.1.1 Modulated Radiofrequency Fields

Protein kinases are enzymes that phosphorylate proteins on serine, threonine, or tyrosine residues. These catalyzed phosphorylations have profound effects on cellular protein activity and play a major role in the regulation of a wide range of cellular functions, including signal transduction and cell proliferation.

Byus et al. (1984) examined the effects of modulated microwave fields on the endogenous activities of both cAMP-dependent and cAMP-independent protein kinases of cultured human tonsil lymphocytes. Cells were exposed in a Crawford cell exposure system to a 450-Hz field (peak intensity, 1.0 mW/cm^2), sinusoidally amplitude-modulated at various frequencies between 3 and 100 Hz for up to 60 minutes; under the exposure conditions, no temperature rise was detected in the culture medium. Calf thymus histone was used as a substrate for monitoring kinase activity.

At a modulated field of 16 Hz, no change (relative to controls) was observed in cellular cAMP-dependent protein kinase activity following 15-, 30-, and 60-minute exposures. The same exposure condition, however, caused a 50% to 55% decrease in cAMP-independent protein kinase activity after 15- and 30-minute exposure periods. After longer exposure periods, 45 and 60 minutes, no detectable change in the enzyme activity was observed, suggesting that the decrease in enzyme activity at 15 and 30 minutes was transient and returned to control values even in the presence of continued exposure.

The cAMP-independent kinase activity was also observed to decrease when the field was modulated at 60 Hz; however the decrease in activity, 15% at 15 minutes and 35% at 30 minutes, was less than that observed at 16 Hz. Again, as in the case with 16-Hz fields, a 60-minute exposure period at 60 Hz produced no decrease in activity, suggesting a transient effect.

Experiments were also carried out to determine if other modulated frequencies caused changes in lymphocyte kinase activity. Exposing lymphocytes for 30 minutes to modulated

frequencies of 3, 6, 80, and 100 Hz or unmodulated 450-Hz carrier caused no apparent decrease in cAMP-independent cellular kinase activity compared to unexposed controls. Decreases in kinase activity were observed only at 16, 40, and 60 Hz with the largest decrease occurring at 16 Hz.

This study clearly demonstrates a “windowed” effect for both time and modulation frequency in the microwave-induced decrease of lymphocyte cAMP-independent protein kinase activity. The significance of these results is unclear, however. It is not known, for example, what specific kinase (or kinases) was affected in this study. The authors of the study state that “. . .our data offer no insight into the real biological effect of these fields upon lymphocyte function in particular, or upon the general state of the immune system.” Although the significance of the results are unclear, it should be emphasized that any effect on protein kinase activity of the magnitude observed in this study would be expected to have significant effects on cellular activity because of the major role played by kinases in the control of cellular function. For example, the attenuation of cellular responsiveness (termed desensitization) following plasma membrane receptor activation is known to be controlled in some signal transduction systems through receptor phosphorylation by specific kinases. Any unwarranted decrease in the activity of one of these kinases, therefore, could cause perturbations in the signal system by allowing the receptor to be “on” for a longer period than appropriate. The B-adrenergic receptor is an example of a plasma membrane receptor which is known to be desensitized via phosphorylation by a specific cAMP-independent protein kinase (Benovic et al., 1989).

5.5.2. Ornithine Decarboxylase Activity

The enzyme ornithine decarboxylase (ODC) is the controlling enzyme in polyamine biosynthesis and is affected by a wide variety of hormones and growth factors active at the cell surface (reviewed by Byus et al., 1987); the activity of ODC can change rapidly and markedly in response to extracellular signals. ODC activity is elevated in all rapidly growing cells including transformed or cancer cells, and is increased by phorbol ester tumor-promoting compounds (reviewed by Byus et al., 1987). The following studies examined the effects of ELF and modulated RF and microwave fields on ODC activity in established cell lines.

5.5.2.1. Extremely Low Frequency Fields

Byus et al. (1987) investigated the effects of a low-energy 60-Hz field on ODC activity in human lymphoma CEM cells, mouse myeloma cells (P3), and Reuber H35 hepatoma cells. The exposure conditions were designed to allow the cell cultures to be physically isolated from any possible products of electrolysis at the carbon electrodes following field exposure. CEM and P3 cells were tested in suspension culture in a series of tissue culture flasks connected by tubing filled with agar gel. During field exposure a small current [368 microamperes(μA)] was passed through the flasks. This current produced an electric field of 10 millivolts per centimeter (mV/cm) (1 V/m) in the suspension. This field was uniform over 80% of the area of the culture flask. The cultures were exposed to the field for 1 hour, and ODC activities were compared to those of sham-exposed control cultures at time points ranging from 0 to 4 hours after exposure.

A 1-hour exposure to the 60-Hz EM field with an intensity of 10 millivolts per centimeter [mV/cm (1 V/m) produced a threefold increase in ODC activity in human lymphoma CEM cells immediately after exposure. The activity continued to increase for 1 hour after exposure to a level fivefold greater than control cultures, then returned to control levels within 2 to 4 hours of exposure. P3 cells, exposed in the same apparatus to the 60-Hz field for 1 hour, exhibited no increase in ODC activity immediately after field exposure, but did show a two- to threefold increase in activity during the 1- to 2-hour period following exposure; the activity had returned to normal by 3 hours.

Reuber H35 hepatoma cells were exposed to the 60-Hz field for one hour in monolayer culture in square Petri dishes connected by agar bridges. This system was developed to obtain greater uniformity in current distribution using low field intensities [0.1-10 mV/cm (0.01-1 V/m)]. Since the resistivity of the culture medium is 50 ohm-cm, the current densities corresponding to these electric fields are 2 to 200 $\mu A/cm^2$. ODC activity in the field-exposed cultures was compared to that of sham-exposed cultures 1, 2, and 3 hours after exposure.

The response of the H35 cells was not a typical logarithmic dose-response relationship between field strength and degree of ODC induction. Exposure of the cells at an intensity of 10 mV/cm (1 V/m), to a 60-Hz field for 1 hour elicited an increase in ODC activity of nearly 50%, which returned to control level by 1 hour after exposure. The ODC activity was only slightly increased by the 5.0-mV/cm (0.5 V/m) field, was not increased by a 1-mV/cm (0.1 V/m) field,

but was increased 30% by the much smaller field of 0.1 mV/cm (0.01 V/m). These data were not analyzed statistically. In addition, the H35 cells were exposed continuously to the 60-Hz [10 mV/cm (1.0 V/m)] field for 2 and 3 hours. The 2-hour exposure had no effect on enzyme activity and the 3-hour exposure actually decreased activity in comparison to controls. At no time during the 1- to 3-hour exposures did the temperature of the medium change by more than 0.1° C.

The authors' major conclusion from these experiments is that 60-Hz EM fields, similar in type and intensity to those found in the environment, increase the activity of the enzyme ODC inside the cell (Byus et al., 1987). The investigators could not explain the heterogeneity of response between the different cells. They also did not attempt to explain why the response induced by 0.1 mV/cm was as large as at the highest field (10 mV/cm) while only background rates were observed at 5.0 and 1.0 mV/cm.

As we have shown in Section 1.2 of this document, typical domestic 60-Hz fields of 0.1 μT and 33 V/m produce internal currents and electric fields on the order of 10^{-5} μA/cm^2 and 10^{-6} V/m. The effects produced by Byus et al. (1987) in these experiments were induced by cellular currents of 200 μA/cm^2 and electric fields in the cell medium of 1 V/m. This is at least 1 million times higher than internal currents and fields induced by ambient exposures. The authors, in stating the similarity of their experimental conditions to background fields, referred to external ambient fields rather than to the internal fields experienced by the cells.

5.5.2.2. Modulated Radiofrequency Fields

Byus et al. (1988) examined the effects of frequency-modulated microwave radiation and TPA, a phorbol ester tumor-promoting agent, on ODC activity in cell cultures. The following experiments were performed:

- Reuber H35 hepatoma cells, Chinese hamster ovary (CHO) cells, and 294T melanoma cells were exposed in circular Petri dishes in a Crawford cell exposure system, to fields of 450 MHz, 1.0 mW/cm^2, sinusoidally amplitude-modulated at 16 Hz; controls were sham exposed;

- Reuber H35 hepatoma cells were exposed to the 450-MHz fields modulated at 5, 10, 16, 20, 60, or 100 Hz; controls were sham exposed;

- Reuber H35 hepatoma cells and CHO cells, either exposed to the 450-MHz field modulated to 16 Hz or sham-exposed for 1 hour, were treated immediately with TPA.

The cultures were irradiated or sham-irradiated for 1 hour; modulation depth of the field was maintained at 75%-85%; there were no changes in the temperature of the culture medium between the beginning and end of exposure in any of the experiments. ODC activity was measured at various times ranging from 1 to 5 hours after exposure to the field or after addition of TPA. An additional experiment was performed in which DNA synthesis was determined in H35 cells that had been irradiated with a real or sham field for 1 hour and treated with TPA.

In all three cell types a 1 -hour exposure produced a notable (up to 50%) increase in ODC activity when compared with unexposed cultures. ODC activity remained elevated in the field-exposed Reuber H35 and CHO cell cultures for more than 3 hours following removal from the field, but persisted for only 1 hour in the 294T melanoma cell cultures.

In the experiment in which the Reuber H35 hepatoma cells were exposed to the various modulated 450 MHz fields, modulation frequencies of 60 and 100 Hz failed to alter ODC activity in cultures to the field for 1 hour, whereas the modulation frequency of 16 Hz caused a 50% increase in enzyme activity. ODC activity was also increased at modulation frequencies of 10 and 20 Hz, but to a lesser degree.

The effect of the modulated microwave radiation on the induction of ODC by phorbol esters (TPA) was also tested in Reuber H35 cells and CHO cells. ODC activity, which is known to be stimulated by TPA, was further stimulated in H35 and CHO cells which were previously exposed for 1 hour to the 450-MHz field modulated at 16 Hz before treatment with TPA. This effect was most evident in the H35 cells 4 and 5 hours after addition of TPA (~13% increase), and in CHO cells 3, 4, and 5 hours after addition of TPA (~50% increase). A 1-hour exposure to the same field did not alter either sham-control DNA synthesis or TPA-stimulated DNA synthesis, as measured by [^{3}H]thymidine incorporation, indicating that the increase in ODC activity is not an effect secondary to the stimulation of cell division.

Byus et al. (1988) noted that brief exposure of the cells to the EM field altered their responsiveness to TPA. TPA has been shown to have a specific cellular receptor which, when activated, becomes associated with the plasma membrane. This phorbol ester receptor has been identified as a calcium and phospholipid-dependent protein kinase and given the designation, protein kinase C. Protein kinase C, which is a cAMP-independent enzyme, has been implicated in the regulation of a variety of cellular events, including modulation of receptor functions for the major classes of hormones, adenylate cyclase activity, induction of

ornithine decarboxylase, and the induction of cell proliferation (reviewed by Byus et al., 1988). The results of this study are consistent with the idea that protein kinase C may be a target for low energy EM fields, leading sequentially to a variety of altered intracellular events (Byus et al., 1988).

5.5.3. Summary

In an examination of modulated microwave fields on cellular protein kinase activity in human lymphocytes, Byus et al. (1984) demonstrated a “windowed” effect (for both time and frequency) for the microwave-induced decrease in cAMP-independent protein kinase activity. (No effect was observed on cAMP-dependent protein kinase activity.) The maximum decrease in activity (50%-55%) was observed at 16 Hz with lesser amounts of decrease at 40 and 60 Hz; temporally, the decrease in activity was maximum after 15- to 30-minute exposures, and by 60 minutes the activity returned to normal. This microwave-mediated decrease in protein kinase activity may have important implications for hormone receptor function and the regulation of cell proliferation.

The studies of Byus et al. (1987, 1988) have also shown that ELF and low energy amplitude modulated microwave fields can increase ODC activity in various cell types. Maximum ODC induction occurred in the range of 10 to 20 Hz, corresponding to the frequency-dependent responses in brain tissue CA^{++} efflux, both for low frequency fields and for RF fields modulated at low frequencies (Bawin and Adey, 1976; Bawin et al., 1975).

Byus et al. (1988) also demonstrated a potentiation by modulated fields of TPA-stimulated ODC activity in cultured cells.

5.6. PARATHYROID HORMONE AND THE PLASMA MEMBRANE

Collagen is synthesized by osteoblasts and represents 90% of the organic matrix of bone (Rosen and Luben, 1983). Collagen synthesis in cultured rat bones can be increased by treatment with insulin and glucocorticoids, and can be decreased by parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (reviewed by Rosen and Luben, 1983). It appears that collagen may be important in the calcification of bone matrix (Bloom and Fawcett, 1969). Low energy EM fields pulsed at frequencies of 10 to 90 Hz are used to stimulate the healing of chronically ununited fractures in humans (Luben et al., 1982). The mechanisms of action of these fields, thought to be triggered at the cell membrane, have been studied in vitro with an

isolated osteoblast-like cell line (MMB-1) and whole bone, using collagen synthesis and other end points as markers (Luben et al., 1982; Rosen and Luben, 1983; Cain and Luben, 1987).

In bone cells, PTH and osteoclast-activating factor (OAF), both acting through cell membrane receptors, stimulate both the activation of adenylate cyclase to form cAMP and inhibit collagen synthesis (Cain and Luben, 1987; Rosen and Luben, 1983). Vitamin D_3 also inhibits collagen synthesis, but via a cytoplasmic rather than a membrane receptor.

5.6.1. Extremely Low Frequency Fields

Luben et al. (1982) exposed cultured cranial bone from 3-day-old mice and MMB-1 cells **(a** line developed from primary cultures of mouse cranial bone cells) to EM fields similar to those used clinically to stimulate the healing of bone fractures, and then examined the responses of the cells to PTH, OAF, or vitamin D_3 (Table 5-6). The tissues and cells were exposed, in incubators, to two pulsed fields of approximately 20 G (2.0 mT). One field, “single pulse, patient” (SPP), consisted of a continuous train of single pulses at a frequency of 72 Hz. Each pulse had an initial component 325 seconds long, with a drop of 20% between the peak of the rising phase and the onset of the falling phase. The falling phase had an overshoot of opposite polarity with a typical peak amplitude 20% of the initial deflection. The other field, “pulse train, patient” (PTP), consisted of bursts of pulses produced at a 4-kHz rate, each burst lasting 5 microseconds and being repeated at a 15-Hz rate. The initial pulse was 200 seconds long, and it was followed by a deflection of opposite polarity lasting 18.5 microseconds and limited in amplitude to 20% of the initial deflection. The magnetic fields for both SPP and PTP induced electrical gradients of ~1.0 mV/cm (0.1 V/m) around a 1 -cm loop in the spatially

TABLE 5-6. EFFECTS OF FIELDS ON cAMP ACCUMULATION IN BONE CELL MONOLAYERS

Agent	Dose ng/mL	cAMP, pmol per 106 cells (% no field, agent control) No Field	SPP Field	PTP Field
None		2.1 ± 0.3	3.1 ± 0.6	2.3 ± 0.5
PTH	10	5.7 ± 0.8[a]	3.3 ± 0.4 (58%)	2.6 ± 0.4 (46%)
PTH	30	8.3 ± 1.0[a]	4.1 ± 0.8 (49%)	3.5 ± 0.6 (42%)
PTH	100	11.6 ± 1.8[a]	5.3 ± 0.5[a] (46%)	4.9 ± 0.8[a] (42%)
OAF	1	9.3 ± 0.9[a]	4.2 ± 0.6 (45%)	3.3 ± 0.5 (35%)
OAF	10	13.8 ± 2.1[a]	5.6 ± 0.7 (41%)	4.3 ± 0.8[a] (31%)

[a] Significantly different from control (no field), $p<0.05$. Paired t tests indicated no significant differences between effects of SPP and PTP fields at any dose.

homogeneous portion of the field between the coils; the peak extracellular current density in homogeneous conducting electrolytes would be ~1.0 $\mu A/cm^2$.

The cells were exposed for 12, 72, or 90 hours in the fields, then were removed and treated with either PTH, OAF, or 1,25-dihydroxyvitamin D_3. Assays were performed for cAMP accumulation, adenylate cyclase activity, and/or collagen synthesis. In addition, total adenylate cyclase catalytic units in the membrane were assessed by activation with fluoride. (In this assay, MMB-1 cells were grown in the presence or absence of the SPP field for 72 hours and then removed; cell layers were disrupted to prepare membranes for adenylate cyclase assay and the membranes were treated in the absence of fields with either PTH or 1 millimolar (mM) sodium fluoride, and the amount of cAMP formed was determined by radioimmunoassay.) The controls were treated with (1) no agent, no field (shielded); (2) agents, but no field; (3) no agent, but fields. In the assays for cAMP accumulation, adenylate cyclase activity, and collagen synthesis, no statistically significant differences were observed between the no agent, no field controls (1) and the no agent, field exposed controls (3).

The major findings of this study are as follows:

- The production of cAMP by the bone cell monolayers was significantly increased ($p<0.05$) in the no-field controls by PTH and OAF. This increase did not occur when preparations were pretreated with each of the fields, particularly in the groups treated with 100 nanograms per milliliter (ng/mL) PTH and with 10 ng/mL OAF (Table 5-6).

- Neither basal nor fluoride-activated adenylate cyclase activity were altered in membranes from cells cultured in the fields.

- The inhibitory effects of PTH on collagen synthesis, as measured by the incorporation of [^{3}H]proline, were blocked in cells grown for 12 hours in the presence of the SPP field. The cells were exposed only to the SPP field and only for 12 hours; labelling with [^{3}H]proline took place 42 to 48 hours after field exposure.

- The fields had no effect on the inhibitory effects of 1,25-dihydroxyvitamin D_3, thought to act by a cytoplasmic, rather than by a membrane-dependent mechanism.

The investigators suggest that because the fields inhibited the activities of PTH and OAF (which have membrane receptors), but did not change the activity of 1,25-dihydroxyvitamin D_3 (which has a cytoplasmic receptor), the cell membrane is probably the primary site of interaction with the EM field. The fact that PTH-activated plasma membrane adenylate cyclase was inhibited by the field, and the fact that adenylate cyclase catalytic units in the cell membrane and basal cyclase activity were not, suggests that the fields were not acting directly

on the cyclase, but that they were interfering with the binding of hormone to receptor, the ability of the hormone-receptor complex to activate cyclase, or both. The other possible target for the fields is the coupling of the hormone-receptor complex to adenylate cyclase in the membrane. This type of effect could be mediated either directly, by effects on the intrinsic membrane coupling proteins or indirectly, by modification of other membrane functions (Luben et al., 1982).

Cain and Luben (1987) conducted further in vitro studies to elucidate the biochemical mechanisms of EM-field effects on bone healing by examining the effects of exposure to pulsed fields on PTH-stimulated cAMP accumulation and bone resorption in mouse calvaria (the superior portion of the cranium). In contrast to the study of Luben et al. (1982) in which cells were exposed to the field for 12 or more hours, the cranial bones from newborn Swiss mice in the present study were placed in culture medium and exposed to pulsed EM fields (PEMF) of extremely low frequency for only 1 hour. The exposure system consisted of a 10-cm x 10-cm Helmholtz coil kept in a humidified incubator at 37° C and 5% carbon dioxide; the generator unit remained outside the incubator. The waveform parameters used in the experiments were a positive pulse at 100 microseconds and a negative pulse of 2 microseconds, repeated at a frequency of 15 Hz. The induced magnetic field was approximately 8 G (0.8 mT) with an electric field strength of 0.6 mV/cm (60 mV/m) and a current density of 20 $\mu A/cm^2$ in the medium. The control bones were shielded during PEMF exposure.

The investigators selected this system for its usefulness in observing early and late responses to PTH which acts on the cell through plasma membrane receptors. The early response to PTH can be detected as early as 1 minute after exposure to the hormone by monitoring cellular increases in the production of cAMP. The late response, bone resorption (monitored by release of extracellular Ca^{++} from the bone matrix), can be measured 72 hours after hormone treatment.

For the cAMP assay, cranial bones were exposed to the PEMF for 1 hour and incubated for 30 minutes in medium with 5 mM theophylline, a phosphodiesterase inhibitor, which inhibits the breakdown of the accumulated cAMP. The bones were then treated with PTH and were rapidly “killed” in a microwave oven. cAMP levels were measured by radioimmunoassay.

Following a 1-hour exposure to PEMF and a subsequent 30-minute incubation with theophylline, the inhibition of PTH-stimulated cAMP accumulation was observed, similar to that

reported by Luben et al. (1982), but more subtle. The observation was complicated by the fact that exposure to PEMF accelerated the time course of cAMP response to PTH. cAMP levels in field-exposed bones peaked after 3-minutes of exposure to PTH, whereas that in the unexposed bones peaked after 5 minutes. As a result, the cAMP levels of the unexposed bones were significantly lower ($p<0.05$) than those of the field-exposed bones at 3 minutes, However, the cAMP accumulation in the field-exposed bones decreased within 5 minutes and remained lower than the control levels throughout the 11-minute observation period.

For the bone resorption experiments, the neonates were injected subcutaneously with $^{45}Ca^{++}$ 72 hours before the cranial bones were removed. Following incubations of 6 to 24 hours, to equilibrate exchangeable Ca^{++} , the bones were irradiated for 1 to 5 hours. Within 30 minutes after removal from the field, treatment with various concentrations of PTH was begun. After preincubation and field exposure, some bones were “killed” by alternate freezing and thawing. Those not frozen were called “live” bones. The bones were then cultured in medium (37° C, 5% carbon dioxide) and were decalcified. The percentage of bone calcium released during 72 hours of culture was determined by comparing ^{45}Ca radioactivity in the medium versus that remaining in the bones. The percent release for “dead” bones was subtracted from the percent release of live bones. The results of the experiments were based on pooled samples.

The main result of the bone resorption experiment was that a field exposure for 1 to 5 hours altered $^{45}Ca^{++}$ release measured 72 hours after hormone treatment and field exposure. At submaximal PTH doses [2.3 nanomolar (nM) and 6.9 nM], 1- to 5-hour field exposures inhibited bone resorption (35% and 44%, respectively), but at the maximal dose of PTH, 23 nM, field exposures did not inhibit resorption. In the absence of PTH, basal bone resorption of 6.17% was increased to 8.66% (a 40% increase) after a 1 -hour field exposure (a 5-hour field exposure was not tested in this part of the study), but basal cAMP levels were not affected. The investigators noted that the data from this study showing that PEMF inhibited the hormonal action of PTH, cAMP accumulation, and bone resorption are consistent with the hypothesis that field perturbation occurs at the membrane level.

5.6.2. Modulated Radiofrequency Fields

No data were found.

5.6.3. Unmodulated Radiofrequency Fields

No data were found.

5.6.4. Summary

The preceding studies show that pulsed magnetic fields inhibit the hormonal action of parathyroid hormone, which is to increase the concentration of cAMP, decrease the rate of collagen synthesis in bone cell cultures, and increase the rate of bone resorption. This action occurs at plasma membrane PTH receptors. These experiments indicate that pulsed magnetic fields interfere with the signal transduction system which is mediated by the binding of PTH to its plasma membrane receptor. Inasmuch as cell proliferation is also thought to be mediated through the activation of multiple signal transduction systems, it is possible that ELF also has the potential for causing changes in some of these systems and thus could have an effect on cell growth including the growth of preneoplastic lesions and tumors.

5.7. MELATONIN AND OTHER HORMONES

In the previous section, the effects of ELF fields on parathyroid hormone-dependent aspects of collagen synthesis were examined. Another endocrine gland, the pineal, and its hormones have been associated with certain forms of breast and prostate cancer in humans and with cancer induction in animals.

5.7.1. Background: Melatonin and Cancer

Various investigators have reported an association of melatonin secretion with cancer in humans, particularly certain forms of prostate and breast cancer. Fraschini et al. (1988) examined 254 cancer patients and found increased serum melatonin levels in 99 cases (38.9%), decreased levels in 15 cases (5.9%) and no change in 140 cases (55.2%). Mean serum melatonin levels were significantly higher in cancer patients compared with 98 healthy controls ($p<0.0001$). Regardless of cancer type, serum melatonin levels were higher in cancer patients compared with controls: breast and lung cancer, $p<0.001$; colorectal and gastric cancer, $p<0.005$; soft tissue sarcoma, $p<0.01$; and lymphoma, $p<0.025$. Fraschini et al. (1988) also observed that 66.7% of the patients whose tumors responded to chemotherapy also exhibited increased serum melatonin levels following chemotherapy.

Cohen et al. (1978) proposed that reduced pineal melatonin secretion may be a factor in breast cancer risk. Bartsch et al. (1981, cited in Wilson et al., 1988) reported that women with breast cancer had reduced urinary melatonin levels. Danforth et al. (1982) noted altered melatonin secretion in patients with estrogen-positive breast cancer. Bartsch et al. (1985) reported that men with cancer of the prostate had lower nocturnal melatonin levels than men without the disease. Stevens (1987) suggested that ELF field-induced exposure in rats may result in loss of gonadal downregulation, resulting in increased circulating estrogen levels which may in turn stimulate mammary tissue proliferation and hence increase breast cancer risk.

Tamarkin et al. (1981) reported that melatonin alters dimethylbenz[a]anthracene (DMBA) mammary carcinogenicity. Fifty-day-old rats were given 15 mg of DMBA and were divided into four groups: (1) DMBA + vehicle; (2) DMBA + daily melatonin injections (beginning at day 50); (3) DMBA + pinealectomy (at day 20); and (4) DMBA + pinealectomy + melatonin. Group 2 had significantly fewer mammary tumors than group 1 (controls), indicating that melatonin inhibited carcinogenesis by DMBA; group 3 had more tumors than group 1, indicating that removal of the pineal enhanced carcinogenesis; and group 4 had fewer tumors than groups 1 or 3, indicating that melatonin ameliorated the adverse effects of pinealectomy.

From their studies, which demonstrated that rats constantly exposed to light had increased DMBA-induced mammary tumors, Shah et al. (1984) and Mhatre et al. (1984) concluded that constant light from birth effectively deprives female rats of melatonin and leads to a constant availability of estrogen and elevated circulating prolactin, which increases the turnover of the breast epithelial cells, thereby rendering the breast tissue more vulnerable to the carcinogenicity of DMBA. Some experiments in rodents have shown an increase in mammary cancer on administration of estrogen and of prolactin (Henderson and Pike, 1981).

Immune and neuroendocrine functions cooperate closely to protect the organism from external attacks (Maestroni et al., 1988). Maestroni et al. (1988) demonstrated in experimental studies with mice that melatonin has a general “up-regulatory” effect on the immune system. Exogenous melatonin can counteract the effect of acute stress and/or of pharmacologic corticosterone on antibody production, thymus weight and antiviral resistance. Maestroni et al. (1988) suggest that activation of T lymphocytes is necessary for the immuno-enhancing and anti-stress action of melatonin.

Melatonin can either stimulate or inhibit cell proliferation, apparently depending on dosage. Blask and Hill (1986) have shown that physiologic levels of melatonin inhibit cancer cell growth, while sub- and super-physiologic levels of melatonin do not. A melatonin-induced proliferation of the erythroid- and myeloid-bone-marrow cell compartments has been observed which apparently extends to all body cells (Di Bella et al., 1979). The growth of lung, stomach, and breast cancers; lymphoma; and bone sarcoma were depressed with melatonin treatment; the survival time of patients was increased and symptoms alleviated (Di Bella et al., 1979). This treatment is potentiated by simultaneously lowering the levels of circulating growth hormone. In vitro, melatonin exhibits oncostatic properties against certain cancer cell lines including carcinomas and breast cancer (Blask and Hill, 1986; Rodin, 1963). Melatonin has also been used in the treatment of leukopenia, in both chronic and acute lymphoblastic leukemia and during antiblastic chemotherapy (DiBella et al., 1979). In contrast, there have been other reports indicating that the pineal gland either has no effect on or stimulates the growth of some tumors (Kachi et al., 1988).

The inconsistent results of animal studies on the pineal gland and its hormones could be due to the dependence of pineal response on the photoperiodic environment (Reiter, 1988). Of particular importance is the timing of the administration of melatonin, which is most effective in pineal-intact animals when given late in the light period (Reiter, 1988).

5.7.2. Extremely Low Frequency Fields

Based on experimental evidence that shows an effect of light and ELF electric and/or magnetic fields on pineal melatonin production, and on the relationship of melatonin to mammary carcinogenesis, Stevens (1987) has proposed a hypothesis that the use of electric power may increase the risk of breast cancer.

Pineal production of the hormone melatonin, which shows a distinct circadian rhythm, is suppressed by light. The circadian rhythm is evident in blood and pineal gland levels of melatonin: low levels in daylight and high levels at night (Tamarkin et al., 1985). Melatonin, in turn, suppresses prolactin production by the pituitary and estrogen production by the ovary (Mhatre et al., 1984).

If circulating levels of melatonin are reduced (by pinealectomy or constant-light exposure), the growth of DMBA-induced mammary tumors in the rat is accelerated (see Section 5.7.1). Stevens (1987) proposes a scheme through which long-term exposure to ELF fields may act

as a “functional pinealectomy” and enhance mammary DMBA-induced carcinogenesis in rats (Figure 5-1). The hypothesis is based on the idea that melatonin level affects production of prolactin and estrogen, and that it is the action of these hormones that increases breast cancer risk by increasing stem cell turnover. In addition, Wilson et al. (1988) propose that ELF may also have an effect on steroid hormone-promoted prostate cancers.

Wilson et al. (1981, 1986) demonstrated that melatonin production can be suppressed by a 60-Hz field. Male Sprague-Dawley rats were acclimated to a daily 14-hour light: 10-hour dark photoperiod at 21° C and 20% to 40% relative humidity (Wilson et al., 1981). At 56 days of age, 20 animals in electrical contact with the reference ground electrode were exposed to a uniform, vertical 60-Hz field (field strength, 1.7 to 1.9 kV/m) in a parallel-plate exposure system. The animals were exposed 20 hours per day for 30 days. At the end of exposure, animals were killed in groups of 10 (5 exposed, 5 sham-exposed) at four different times during the light/dark cycle (1400 [light], 2200 [dark], 0200 [dark], and 0800 [light] hours). All conditions were the same for the exposed and sham-exposed animals except for the presence or absence of the electric field. Pineal glands were removed and quick-frozen usually within 2

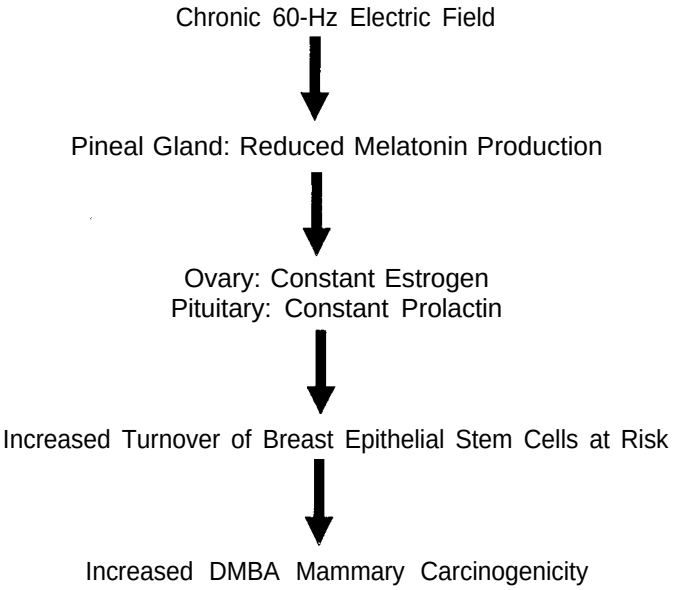

Figure 5-1. Proposed mechanism by which chronic exposure to a 60-Hz electric field may increase dimethylbenz[a]anthracene (DMBA) -induced mammary carcinogenesis in rats.

SOURCE: Adapted from Stevens, 1987.

minutes of death. Pineal melatonin was assayed by gas chromatography/mass spectrometry using an internal standard and the data were analyzed by analysis of variance.

Exposed rats, killed at 0200 hours, showed a significant ($p<0.05$) reduction in melatonin levels compared with control rats. During the dark phase, there was a significant increase ($p<0.01$) in pineal melatonin of the sham-exposed animals, but no increase in the field-exposed animals ($p<0.20$), based on the internal standard. In a duplicate experiment, the melatonin data followed the same pattern; however, there were large variances in the data, so the two sampling times in the dark period (2200 and 0200 hours) were combined and the light-period sampling times (1400 and 0800 hours) were combined. Melatonin levels for sham-exposed rats differed significantly ($p<0.002$) between light and dark periods; in contrast, no significant differences were seen in melatonin levels of exposed animals between dark and light periods ($p>0.05$).

In a similar study Wilson et al. (1983) reported that exposure to 60 kV/m also suppressed the nocturnal increases in melatonin. The suppression of the normal nocturnal increase for melatonin was consistent with a reduction in serotonin N-acetyl transferase (SNAT) activity (the rate-limiting enzyme in the synthesis of melatonin from serotonin). Further studies, in which rats were exposed for 3 weeks to 60-Hz, 39 kV/m electric fields, demonstrated that the time required for recovery of the melatonin rhythm after cessation of field exposure was less than 3 days, indicating the overall metabolic competence of the pineal is not permanently compromised by electric-field exposure (Wilson et al., 1986).

5.7.3. Modulated Radiofrequency Fields

No data were found.

5.7.4. Unmodulated Radiofrequency Fields

Elder et al. (1984) reviewed the effects of RF fields on endocrine gland function and concluded that changes reported in hormonal activities and blood chemistry are similar to those observed during increased thermoregulatory activity and heat stress and are generally associated with SARs > 1 W/kg. This conclusion is supported by Elder et al. (1987a, b) in an update of the previous report (Elder et al., 1984). The endocrine effects reported by Elder **et** al. (1984) appeared to have occurred in the presence of colonic temperature elevations of 0.3° C or more.

5.7.5. Summary

In the preceding sections, studies have been presented that demonstrate that exposure for 3 to 4 weeks to a 60-Hz ELF field suppresses the nocturnal production of melatonin in rats, but that the overall metabolic competence of the pineal is not permanently compromised.

Studies in humans have shown increased serum melatonin levels following chemotherapy and decreased urinary levels in some cases of breast and prostate cancer. In addition, animal and in vitro studies have demonstrated that metalonin can inhibit tumor induction with chemical carcinogens, can inhibit the growth of established tumors, and can enhance the cellular immune response. The results of these studies suggest that there is a relationship between cancer and pineal gland function. In other studies, however, melatonin has had either no or stimulatory effects on tumor growth. Some of the inconsistencies in these studies could probably be resolved with improved techniques for dealing with the circadian aspects of pineal gland function.

The suppressive effects of ELF on pineal melatonin production and the general oncostatic properties of melatonin in several endocrine-stimulated tumors provide indirect evidence for the hypothesis that ELF exposure may be a risk factor in the growth of these tumors. Studies that incorporate all three parameters, ELF exposure, melatonin production, and breast cancer induction, are needed for further evaluation of this hypothesis.

In other studies, pineal neurological activity and melatonin synthetic activity were inhibited by static magnetic fields when the orientation of the field was changed by as little as 5 degrees, a change which is only a factor of 10 higher than ambient magnetic residential fields (Welker et al., 1983; Semm et al., 1980). These studies and the role of the retina as the magnetoreceptor (Olcese et al., 1985; Reuss and Olcese, 1986) are discussed in greater detail in Section 5.10.1.

5.8. GROWTH AND DIFFERENTIATION

5.8.1. Extremely Low Frequency Fields

Several studies have demonstrated a growth-enhancing effect of ELF exposures on both normal and neoplastic cells in vitro. The stimulation of the growth of neoplastic cells is of particular concern in the therapeutic treatment of bone fractures with ELF fields in cases where a neoplastic lesion may be present. Because osteogenesis is thought to occur as a result of

differentiation of osteoblasts (Akamine et al., 1985), information on the effect of ELF on cellular differentiation is of interest.

McLeod et al. (1987) demonstrated that protein biosynthesis in neonatal bovine fibroblasts (measured by [^{3}H]proline incorporation into extracellular and intracellular protein) was reduced by low frequency sine wave electrical fields. Stable low-frequency current with DC flow limited to less than 0.1% of the AC amplitude was provided by a programmable current source. Current was passed through the exposure samples for 12 hours via platinum electrodes that were separated from the bath by media bridges and convection barriers. Experiments were performed over a range of current densities (0.1 μA/cm^2 to 1 mA/cm^2, root mean square) and frequencies (0.1 to 1000 Hz). A frequency- and amplitude-dependent reduction in the rate of incorporation was observed. The data indicated an optimal frequency range for the alteration of extracellular matrix protein synthesis. Peak sensitivity was at 10 Hz, with a current density of only 0.5 μA/cm^2, at which a notable reduction in protein incorporation in the matrix component was produced. Furthermore, the response was dependent also on the orientation of the cells relative to the direction of the applied electric field. The incorporation of radiolabel into intracellular protein reflected the pattern seen in the extracellular matrix (no other details were given). The investigators concluded that currents of physiological strength can stimulate a reduction in biosynthesis and thereby may influence tissue growth, remodeling, and repair.

Whitson et al. (1986), on the other hand, applied 60-Hz, 1000 V/cm (100 kV/m) electric fields (the authors acknowledge that a magnetic field may also be produced) to human fibroblasts in vitro for up to 48 hours, and evaluated DNA repair and cell growth or survival. No effects were observed on any of the parameters examined.

Akamine et al. (1985) examined the effects of a pulsed EM field (PEMF) on the growth and differentiation of F9 cells, a clonal line of embryonal carcinoma (EC) cells. EC cells are described as stem cells of teratocarcinoma that resemble undifferentiated cells of early embryos. These cells can be induced to differentiate to endodermal cells in vitro by treatment with retinoic acid.

The current was produced by a generator outside a carbon dioxide incubator connected to two coils located inside the incubator. The coils were positioned so that the generated magnetic component was normal to the culture surface and so that the induced electric field becomes stronger as one moves out along a radius on the culture surface. PEMF was begun 12 hours after plating the cells, and the stimulation was continued for 84 hours. The pulse

width was rectangular, the pulse width was 130 seconds, and the frequency was 100 Hz. The magnetic field at the center of the field was either 1.0 G (0.1 mT) or 10.0 G (1 mT). Immediately after exposure the cells were counted and examined for morphological changes and biochemical assays were conducted for cellular differentiation, based on the production of plasminogen activator and the synthesis of glycopeptides.

As evidenced by increased cell numbers, PEMF stimulated the growth of F9 cells with retinoic acid (294% of control at 10 G, 176% of control at 1 G) and without (137% of control at 10 G, 150% of control at 1 G). Based on morphological observations, retinoic acid stimulated cellular differentiation in 90% of the cells not exposed to the field, in 58% of the cells exposed to 1 G, and in 46% of the cells exposed to 10 G. Retinoic acid-stimulated cellular differentiation was also inhibited when based on production of plasminogen activator, but not when based on glycopeptide profiles. Thus, the PEMF promoted the growth of the embryonal carcinoma cells in the presence and absence of retinoic acid and inhibited retinoic acid-induced differentiation based on morphological observations and on the production of plasminogen activator. Because field-stimulated growth of carcinoma cells was observed in these studies, the investigators advised caution in the treatment of malignant tumors with PEMF.

The clonogenic capacity and surface properties of two human cancer cell lines (Colo 205 and Colo 320, derived from adenocarcinomas of the colon) have been studied by Phillips et al. (1986a, b) and Phillips and Winters (1987) using a standardized 60-Hz EM-field exposure system. Changes in colony-formation (a measurement of proliferative capacity) of the cells were assessed using a soft agar culture technique, and changes in surface properties were evaluated using a monoclonal antibody binding assay, a transferrin binding assay, and cell lysis by human NK (natural killer) cells.

Exposures to four different fields were performed concurrently in four exposure chambers. Exposures consisted of only an electric field [E+; current density = 300 microamperes per square meter $\mu A/m^2$) = 30 $\mu A/cm^2$)] a magnetic field [M = 1.0 G, 0.1 millitesla root-mean-square (mTrms)], combined electric and magnetic fields (E+M+; at intensities indicated), and unexposed control (E-M-). Electric fields were produced by transfer of a uniform current density through closed system cylindrical cell-exposure chambers that had been filled completely with the cell suspension. A rotating magnetic field was produced using two sets of Helmholtz coils, and the insulated glass incubator with plastic cell chamber holders

was installed within the area of uniformity for the field. The temperature of the chambers never varied more than 0.15° C and the temperatures of the exposure groups showed no consistent variation.

Cells were exposed continuously for 24 hours. The cells were then removed from the chambers and prepared for the assays. Viability was greater than 90% following field exposure. In five out of five experiments with Colo 320 DM and in four out of five experiments with Colo 205, cells exposed to M+ and E+M+ produced more colonies than the sham-exposed control cells, statistically significant at the $p<0.01$ or $p<0.05$ levels (Kruskal-Wallis nonparametric analysis of variance). The cells exposed to E+ only demonstrated a mixed response (i.e., in some experiments, the numbers of colonies formed by E+ cells was significantly decreased, while in others the numbers of colonies formed by E+ cells was either significantly increased or remained the same).

The changes in cell-surface properties were assessed by quantifying the binding to the cells of monoclonal antibodies produced against Colo 205 and Colo 320 DM tumor-associated antigens. These properties were also altered by field exposure, as evidenced by a general increase in the expression of tumor-associated antigen in E+M+ and M+ cells. The alterations were not as dramatic as those observed in the cloning assay, but in several cases the increases in antibody binding were statistically significant ($p<0.01$ or $p<0.05$). The effects on surface properties of the target cells were consistent with changes in plasma membrane structure and function following EM-field exposures described by other investigators (Luben et al., 1982).

Transferrin is the major iron-transport protein in the body and is an obligatory growth factor for many cells when cultured in serum-free medium (reviewed by Phillips et al., 1986b). Transferrin receptors are located on the cell surface, more so on the surfaces of malignant or proliferating normal cells, than on normal nondividing cells, and the number of receptors on a cell is inversely related to cell density. These may be the receptors for NK cells, In three separate experiments, the number of transferrin receptors quantitated on Colo 205 cells exposed to M+ and E+M+ fields were close to or exceeded the maximum theoretical number of receptors determined for the cell line and were independent of cell density. Thus, the cells were no longer subject to the regulatory influence of cell density. E+ cells expressed fewer transferrin receptors than were predicted on the basis of cell culture density.

After the initial cloning assays were completed, the cells from the four groups were transferred for maintenance in long-term culture. After 4 months, increased numbers (approximately twofold more than E-M- controls) of transferrin receptors were still present on E+M+ and on M+ cells, while decreased numbers (approximately one-fourth of E-M- controls) were present on E+ cells; lysis, measured by a standard ^{51}Cr-release assay, was decreased approximately 70% in both E+M+ and M+ cells but was increased about 53% for E+ cells. After 8 months in culture, the cells still exhibited an increased reproductive capacity and increased numbers of transferrin receptors.

In summary, this study has shown that exposure of Colo 205 cells to EM fields resulted in effects on cellular function, as evidenced by increased reproductive capacity of the cells, particularly for cells exposed to combined electric and magnetic fields or to the magnetic field alone. The increased proliferative response was correlated with increased numbers of transferrin receptors (also indicative of growth potential) in ColoLT cells exposed to electromagnetic and magnetic fields combined and to magnetic fields alone. The EM-induced increases in transferrin receptors were also consistent with changes in cell surface properties, as were increases in the numbers of tumor-associated antigens, and changes in susceptibility of the cells to lysis by NK cells, especially in cells exposed to E+M+ and M+ fields. The persistence of these effects suggest that under the conditions of these experiments, EM exposures are capable of producing significant permanent changes in cellular structure and function.

It has been suggested that the mechanism for the healing of nonunion bone fractures with PEMF is related to revascularization of injured osseous structures. To test this hypothesis, Yen-Patton et al. (1988) examined the effects of PEMF on the rate of repopulation of denuded areas of endothelial cell monolayers and the rate of endothelial cell neovascularization in culture. Human umbilical vein endothelial cells and bovine aortic endothelial cell cultures were subjected to injury-simulating denuding of a vessel wall and were then exposed, along with uninjured controls, to the ELF. The field was generated by 22.5-cm x 22.5-cm Helmholtz coils (waveform 200 seconds wide, shaped as a burst of 20 to 21 closely spaced events); the burst, 5 milliseconds wide, was repeated at 15 Hz, resulting in a calculated induced voltage of 1.3 mV/cm (0.13 V/m) in the tissue culture dish. The magnetic field intensity at the center of the Helmholtz coils was approximately 1 G, and the rate of change of the magnetic field was 8.5 x 10^4 G/sec during field expansion and 4.3 x 10^5 G/sec during field collapse. Under these

conditions, temperature changes in tissue culture media are <0.001 (C (Bassett 1987, as cited in Yen-Patton et al., 1988).

Reendothelialization was assessed by scintillation counting of live cultures that had been incubated with tritiated thymidine for up to 96 hours, and injury response (wound healing) was defined as the difference between thymidine incorporation of injured and uninjured cultures" Cultures were disrupted by passaging with EDTA-trypsin and monitored for tube formation (indicative of vascularization) at various intervals for up to 23 days.

In the presence of EM fields, there was a small but statistically significant enhancement in growth rate of partially denuded endothelial cell monolayers as evidenced by increased tritiated thymidine incorporation (40% response in the human cells, and 20% response in the bovine cells). The cells exposed to the fields and entering the denuded regions were elongated and formed a sprouting pattern, while those outside the field had a more cuboidal morphology.

Cells that were disrupted and passaged with ethylenediamine tetraacetate-trypsin reorganized into three-dimensional vessel-like structures after 5 to 8 hours of exposure to the EM fields and in the presence of endothelial cell growth factor, heparin, and a component fibronectin (protein) matrix. In the absence of EM fields, vascularization of confluent layers of cells was observed only after long-term incubation (2-3 months). The investigators concluded that the discrete stages of neovascularization that were observed with field exposure were qualitatively comparable to stages of in vivo angiogenesis. With regard to carcinogenicity, angiogenesis (possibly promoted by EM fields) is essential to neoplastic growth, as well as to the progression of benign to malignant tumors (Folkman, 1975).

5.8.2. Modulated Radiofrequency Fields

No data were found.

5.8.3. Radiofrequency Fields

No data were found for nonthermal effects of RF fields on growth or cellular differentiation that could be related to cancer promotion.

5.8.4. Static Electric Fields

Becker and Esper (1981) examined the effects of electrostimulation, at levels used to stimulate osteogenesis, on the growth of human fibrosarcoma cells (HT 1080) in culture. Stainless steel electrodes were inserted through the side walls of two chambers of a plastic triwell culture dish. The two wells were connected by a conducting agar bridge. The chambers, containing coverslips, were seeded with the cells and incubated for 48 hours. A current of 360 nanoamperes (nA) was transmitted between the two electrodes at an average voltage of 1.1 V for 24 hours. The third chamber, the control, received no current. The cells on the coverslips were fixed for counting immediately after exposure.

Cell counts revealed an approximately threefold increase in the cell population in both experimental chambers relative to the control chambers. Unlike the McLeod et al. (1987) study in which an AC field reduced protein synthesis, Becker and Esper (1981) used a DC field with no AC component. These preliminary results suggest that, because the growth of human fibrosarcoma was stimulated in this study with currents and voltages used to stimulate osteogenesis, it would be prudent not to administer electrostimulation to patients with suspected premalignant or malignant lesions located within the current pathway (Becker and Esper, 1981).

5.8.5. Summary

The preceding studies show that currents of the strength used to stimulate bone repair can stimulate alterations in biosynthesis and thereby may influence the growth, remodeling, and repair of normal tissue. These fields also stimulated the growth of human fibrosarcoma cells and embryonal carcinoma cells, and inhibited differentiation of embryonal carcinoma cells, suggesting a tumor-promoting potential for ELF. The investigators in these studies advise that caution should be exercised in the treatment of tumors with PEMF or the treatment of broken bones with the fields in patients who also have tumors.

5.9. IMMUNOLOGIC/HEMATOLOGIC EFFECTS

The immune system is the physiological defense against a large spectrum of agents including bacteria, viruses, fungi, parasites, toxins from organisms, miscellaneous chemical substances, and neoplasms. Two types of effects are possible: immunosuppression and immunopotentiation. lmmunosuppression may result in an increased susceptibility to infection

by microorganisms or to the development of tumors while immunopotentiation involves a generalized increase in immune responsiveness such as hypersensitivity (allergy) or autoimmunity. Impairment of the immune system could result in adverse health effects. The immune system consists of cells that are specialized for defense, broadly classified into lymphoid cells and phagocytic cells that produce humoral substances such as antibodies and complement.

Assays of lymphocyte function, an important factor in cellular immunity, are used frequently to assess immune competence. Another, less specific, indicator of immune status is the peripheral blood cell count, particularly the lymphocyte fraction. Therefore, studies that assess hematological effects, as well as those that assess immune status, have been included in this section.

5.9.1. Extremely Low Frequency Fields

Fotopoulos et al. (1987), conducting an investigation of the effects on humans of exposure to 60-Hz electric and magnetic fields, reported preliminary results of blood chemistry, hematologic, and immunologic assays. Twelve subjects participated in four experimental sessions, spaced 1 week apart: two sessions involved 6 hours of exposure to a 60-Hz, 9-kV/m, 16-A/m (2×10^{-2} mT) field, and two identical sessions involved exposure of humans to a sham field. The subjects served as their own controls. The order of field presentation was counterbalanced under double-blind conditions. Blood samples were collected in two sessions before the exposuresto establish baseline conditions and then on the days of the experiments immediately before and after exposure to the real or sham field. Details of exposure conditions were published elsewhere and are not available.

Expected circadian variations were observed before and after the 6-hour exposure sessions among the hematologic, chemical, and immunologic variables studied, and many of the variables did not exhibit significant changes under field exposure conditions compared with sham controls. There were no significant differences in levels of calcium, glucose, uric acid, albumin, potassium, or sodium between field-exposed and sham-exposed subjects. However, lactic acid dehydrogenase (LDH) levels were significantly higher in the pre-exposure compared with postexposure periods ($p=0.004$) on the first day but not the second day of field exposure.

No differences were observed in white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), or platelets. The differential cell count revealed a significant increase ($p=0.043$) in percent lymphocytes only on the second day of field exposure.

There were no field effects on total T-cells, B-cells, natural killer, and suppressor cells, based on monoclonal antibody assays, and there was no effect on cell-mediated immunity, based on a lymphocyte blastogenesis assay using T- and B-cell-specific mitogens. However, pre-exposure levels were significantly higher than postexposure levels on the first day of field exposures and not on the second day. This pattern was similar to the pattern with LDH. The increases in lymphocyte counts on the second day of exposure and decreases in T-helper cell counts on the first day of exposure suggest that the low frequency electric and magnetic fields used in this study could enhance certain elements of the cell-mediated immune response in humans. The investigators consider the findings in this study to be preliminary and defer interpretation of the results until additional work is done.

Seto et al. (1986) examined the hematologic effects of ELF fields on three generations of Sprague-Dawley rats that were conceived, born, and raised in an electric field. The animals (42 to 44 from each generation) were exposed to a 60-Hz, 80-kV/m, unperturbed vertical field 21 hours/day until they were approximately 120 days of age. Sham-exposed controls (42 to 44 from each generation) were conceived, born, and raised under identical conditions, but were not exposed to the field. The cell counts for the 135 field-exposed and 135 sham-exposed rats were analyzed statistically by multivariate analysis of variance, univariate analysis of variance, and tests of simple effects.

Red cell parameters, which included RBC, Hgb, Hct, MCV, MCH and MCHC, were not affected by field exposure. “Subtle” but statistically significant decreases in total white cell counts ($p=0.006$), lymphocyte counts ($p=0.027$), and eosinophil counts ($p=0.035$) were observed. The investigators commented that the observed hematologic variations related to field exposure were similar to those observed in animals experiencing mild stress, implying that the field (80-kV/m) could have induced the effects through stress. They further stated that such effects are not likely to be reliably replicated by an experiment in which sample sizes smaller than the ones in this study are used.

Ragan et al. (1983) examined numerous hematologic and serum chemistry variables in female Sprague-Dawley rats (10-20/group) exposed to unperturbed 60-Hz electric fields at 100 kV/m for 15, 30, 60, or 120 days. The field strength delivered by the apparatus with no animals or cages installed was 100 kV/m. Each study was replicated once. The data underwent rigorous statistical evaluation, and although no consistent effect of the field was detected, statistically significant effects (using Student's t test) were observed in certain variables at certain time points. For example, at 15 and 120 days of exposure duration the white count was lower ($p<0.02$) and at 60 days it was higher ($p<0.01$) in the exposed as compared with the sham-exposed groups. Lymphocyte values correlated with the total leukocyte counts. There were no significant differences between exposed and sham-exposed rats in numbers of neutrophils, monocytes, eosinophils, and basophils. Platelet numbers were significantly increased ($p<0.02$) after 60 days of exposure, but not at other time points. Bone marrow cellularity was increased ($p<0.05$) in replicate 2 at 30 days of exposure. Similar occasional changes were seen in RBC parameters (RBC counts, Hgb concentration, RBC volume, MCV, MCH, and MCHC) and in serum chemistry values (iron, triglycerides, alkaline phosphatase, alpha and beta globulins), The investigators drew no definite conclusions but inferred that the 60-Hz field is of potentially low toxicity and emphasized the need for appropriate experimental design and statistical analysis in studies of this type.

A study was conducted in which ECR-SW strain mice were exposed to a 240-kV/m, 60-Hz field 18 to 22 hours/day, 7 days/week for a total of 4500 hours of exposure (about 32 weeks) before they were killed for tests (Fam 1980). Ten males and 10 females were used for complete blood counts. Statistical analysis (analysis of variance and t statistics) indicated no differences in the blood count values of the males at the $\alpha = 0.05$ level, but there was a significant difference between the exposed females and their controls in several parameters. For example, exposed animals had a lower white blood cell count ($\alpha = 0.0021$), a lower hemoglobin ($\alpha = 0.0104$), a lower mean corpuscular hemoglobin ($\alpha = 0.024$), and a higher percentage of bands ($\alpha = 0.0143$). The investigators were not certain if the effects on the females were due to field exposure or if they were the result of lower food and water consumption. There were no statistically significant effects on lymphocyte counts in males or females. At the end of the study, heart, lungs, liver, spleen, kidney, and ovary or testes were

examined microscopically. There were no histological findings that could be attributed to exposure.

Lyle et al. (1988) tested the effects of 60-Hz sinusoidal electric fields with intensities of 0.1, 1.0, or 10 mV/cm (0.01, 0.1, or 1.0 V/m) on T-lymphocyte cytotoxicity. The field exposure apparatus consisted of six polystyrene culture flasks positioned vertically and joined in series by short agar bridges, with carbon electrodes in the medium of the end flasks and cell-bearing medium in the middle four flasks. Experimental conditions included field, sham, and plastic control (no agar bridges). Cytotoxicity was measured using the 4-hour chromium release assay. The effector (cytotoxic) cells used in the cytotoxicity assays were of the murine T-lymphocyte line, CTLL-1. These are normal T-lymphocytes that are cultured in interleukin-2, the T-cell growth factor, to stimulate growth. The target cells were an allogeneic H-2^d B-lymphoma cell line, MPC-11. The assays were performed with electric fields present only during the 4-hour assay, and using CTLL-1 cells pre-exposed for 48 hours to the electric field. In addition, the effects of a 48-hour field exposure on growth of the CTLL-1 cells cultured in the presence of “optimal” growth factor concentrations (1:2 dilution) or in the presence of suboptimal concentrations (1:32) were determined.

When the cells were exposed to the field only during the 4-hour assay, a nonsignificant 5% decrease in cytotoxicity reaction of the CTLL-1 effecters against the target MCP cells was observed in the field-exposed versus sham-exposed flasks. Forty-eight hours of exposure of the effector cells to the 60-Hz, 10-mV/cm (1.0 V/m) field before the assay resulted in a 25% inhibition of cytotoxicity ($p<0.005$, Student’s T test), in comparison to the sham controls for that experiment; the 1.0-mV/cm (0.1 V/m) field produced a 19% inhibition in comparison with the sham controls for that experiment ($p<0.0005$); and the 0.1 -mV/cm (0.01 V/m) field produced a 7% (nonsignificant) inhibition. The field had no effect on the proliferation of the CTLL-1 effector cells in the presence of interleukin-2, an indication that the inhibition seen in the 48-hour cytotoxicity study was not due to the inhibition of cell proliferation but rather to an alteration of the mechanism for cytotoxicity itself. The investigators concluded that, under the conditions of the study, cytotoxicity shows a dose response to a 60-Hz sinusoidal electric field between 0.1 and 10 mV/cm, with a detection threshold that lies between 0.1 and 1.0 mV/cm.

Morris and Phillips (1982) observed no effect on the primary antibody response to keyhole limpet hemocyanin in mice following their exposure to 60-Hz, 0.15 to 0.25 kV/m fields for 30 or 60 days, or on the mitogen stimulation response of spleen cells to B- and T-cell mitogens in

mice exposed to the same fields for 90 or 150 days. The reason for the difference in the results of this study and the study of Lyle et al. (1988) is not clear. The main difference in the two studies was field strength which ranged from 0.01 to 1.0 V/m in the Lyle study and from 0.15 to 0.25 kV/m in the Morris and Phillips study. In addition, in the Lyle study, cells were exposed in vitro, while in the Morris and Phillips study the whole animal was exposed.

5.9.2. Modulated Radiofrequency Fields

To test the effects of RF radiation on cells already challenged by a commonly encountered viral agent, Roberts et al. (1987) assayed mitogen responsiveness after exposure of influenza virus-infected human mononuclear leukocytes to continuous or pulse-modulated 2450-MHz RF radiation, specific absorption rate of 4 mW/mL (4 W/kg). Mononuclear leukocytes (MNL) were exposed or sham-exposed to influenza virus then exposed or sham-exposed to the RF radiation as continuous waves or pulse modulated at 60 or 16 Hz. The four groups of cells were then stimulated with the mitogen phytohemagglutinin (PHA). RF radiation exposure caused no changes in leukocyte viability or in mitogen-stimulated DNA synthesis by human mononuclear leukocytes infected in vitro with influenza virus when compared with sham-RF radiation-exposed cells.

Lyle et al. (1983) tested the effects of a 450-MHz microwave field, 1.5 mW/cm^2, sinusoidally amplitude-modulated at 60 Hz on the same allogeneic cytotoxicity system as that described previously for the study of Lyle et al. (1988). An anechoic exposure system was used. The chamber temperature was kept to within 0.1 degrees of 35° C throughout the 4-hour exposure period, and the temperature within the sample well measured before and after the exposure did not differ significantly from the air temperature. The investigators characterized the cytotoxic response to the field with various manipulations of the procedure. The calculated field strength in the culture fluid was in the range of 10 to 30 mV/cm (1 to 3 V/m), somewhat higher than with the 60-Hz field tested by Lyle et al. (1988).

Cytotoxicity to the target cell (MPC-11) by the CTLL-1 line was significantly inhibited (20%, $p<0.05$ to $p<0.0005$ for five different experiments) when the 4-hour cytotoxicity assay was conducted in the presence of the field; similar suppression was observed when the effector cells (CTLL-1) were exposed to the field for 4 hours before the target cells were added for the cytotoxicity assay. The investigators attributed the suppression to an effect on the effector cells, not the target cells. The results were similar when the cells were exposed to the field

during only the first 2 hours of the assay (exposure during the last 2 hours produced only partial inhibition). This suggests a preferential effect on the recognition phase of cytotoxicity. Cytotoxicity was also assessed in two experiments 1, 4, 9, and 12.5 hours after field exposure of the effector cells. In both experiments inhibition decreased as the time interval increased (for experiment #1: 24% inhibition, $p<0.05$, during assay; 17%, $p<0.025$, 1 hour; 14%, $p<0.025$, 4 hours; 14%, $p<0.05$, 9 hours) and after 12.5 hours the cytotoxic inhibition was no longer observed. The assay was then conducted after T-cells were exposed during the 4-hour assay to various amplitude modulation frequencies (16, 40, 80, and 100 Hz). All modulation frequencies produced suppression, but it was maximal at 60 Hz (20%).

Lyle et al. (1988) suggested that the differences in their experiments of 1988 and 1983 (the 60-Hz modulated 450-MHz microwave field of the 1983 study produced a rapid inhibition when the 4-hour cytotoxicity assay was conducted in the presence of the field, whereas the 60-Hz field in the 1988 study produced inhibition only after 48-hours of field exposure) could have been due to either different characteristics of the two fields or different culture conditions between the two sets of experiments (Lyle et al., 1988).

5.9.3. Unmodulated Radiofrequency Fields

A study of the long-term effects (including immunologic and hematologic parameters) of RF radiation was conducted, using 14-week-old male Wistar-Furth rats (Smialowicz et al., 1981). Sixteen animals were exposed to 970-MHz EM radiation [SAR = 2.5 mW/g (2.5 W/kg), 22 hours daily for 70 consecutive days]. The exposure system consisted of 16 individual circularly polarized waveguides and similar nonenergized chambers served as sham-irradiated controls. No differences were observed in the body weights, hematologic profile, or in vitro lymphocyte responses to mitogens between the two groups. The only effects observed were increased levels of triglycerides, albumin, and total protein which were thought by the investigators to be related to thermal stress.

Chou et al. (1983) examined the effects of long-term exposure to continuous wave (CW) microwave radiation on New Zealand rabbits. Two groups of 16 animals each were exposed to 2450-MHz fields in two experiments of 90 days each. The incident power densities of the first and second studies were 0.5 and 5 mW/cm^2, respectively. After adapting to the anechoic chamber exposure system, eight rabbits were exposed for 7 hours daily, 5 days a week for 13 weeks, and eight were sham exposed. SARs were 5.5 W/kg in the head and 7 W/kg in the

back at 5 mW/cm^2. There were no changes in body weights, blood cell counts and morphology, clinical chemistry parameters, protein electrophoresis, lymphocyte blast transformation, and histology of the exposed animals in comparison with controls; and there were no changes in the eyes of the exposed animals. The only effect, decreased food consumption, was observed during exposure to the 5-mW/cm^2 exposure.

Wright et al. (1984) studied the effects of high frequency radiation in Wistar rats and Cynomologus and Rhesus monkeys, exposed for 28 and 24 days, respectively, 23 hours/day. The rats were exposed to 28 MHz (125 mW/cm^2) fields for 28 days and examined for histopathologic effects or were exposed to 220 mW/cm^2 for 13 days and thyroid function was assessed. The Cynomologus monkeys were exposed to 28 MHz (25 mW/cm^2) for 24 days and examined for hematologic changes. The Rhesus monkeys were exposed to 125 mW/cm^2 (28 MHz) radiation for 11 days and electrolytes were measured. There were no histopathologic changes in the rat or hematologic changes in the monkey that could be attributed to exposure. The rats did exhibit reduced uptake of iodine by the thyroid, reduced levels of plasma thyroid-stimulating hormone, and reduced ratio of protein bound to nonprotein bound iodine. However, these animals were exposed to a 220-mW/cm^2 field (likely to induce thermal changes in man), and the thyroid effects were thought to be compensatory responses to an induced heat load.

Ottenbreit et al. (1981) examined the effects of microwaves on the colony-forming capacity of human neutrophil precursor cells (CFU-C) in a methylcellulose culture system. Bone marrow specimens were aspirated from children with acute leukemia in remission, or from children with other disorders who had marrow aspirations performed for evaluation of clinical status, or for diagnostic determinations. The cells collected from the top layer of a Ficoli-Hypaque gradient were used for the assay. The cells were allowed to stand overnight, were suspended in microcapillary tubes, and were exposed to 2450-MHz CW microwaves for 15 minutes in a fluid-filled waveguide irradiation system. Irradiation of the cells for 15 minutes at 31, 62, 125, 250, 500, and 1000 mW/cm^2 was conducted with bath temperatures set at 37° C for the two lowest power levels and at 7, 22, 37, and 41° C for the last four power ranges, respectively. Sham-exposed controls were treated in the same way, but the microwave power was not turned on. The cells were then cultured with 20% fibroblast conditioned medium at 37° C, 7.5% humidity. Colonies were counted on days 6 or 7, and days 12-14.

When colonies were scored on days 6 or 7, there was no reduction in the number of colonies formed by field-exposed cells at power levels of 31 and 62 mW/cm^2. As the power level was increased to 1000 mW/cm^2, there was a corresponding reduction in the number of colonies formed by the microwave-exposed cells ($p<0.05$, Student's t test, at the four highest levels). The maximum reduction occurred at 500 and 1000 mW/cm^2. At days 12-14, there was a similar dose-dependent reduction in colony numbers. Additional experiments showed that the effects observed were not related to temperature rise, or to the state of cell cycle, and were irreversible. The investigators hypothesized that, because CFU-C require the addition of exogenous stimulators for cell growth (fibroblast conditioned medium in this case), it is possible that microwave irradiation alters the membrane receptors of CFU-C making some of them unresponsive to the stimulation factors. In addition, the investigators suggested that the cells from patients with leukemia or other disorders might react differently to EM radiation than CFU-C from normal individuals. Ottenbreit et al. are currently investigating this possibility.

In a series of in vitro studies designed to characterize direct RF radiation effects on immune function, specifically the effects of RF radiation on the immunoglobulins in solution when bound to the lymphocyte cell surface, Liburdy and Wyant (1984) observed that RF radiation (10 MHz; 8500 V/m, applied electric field; $\leq$ 0.134 W/kg, internal absorbed power; 20 V/m, internal electric field) altered the physical separation of immunoglobulin (Ig) and of Ig-bearing T- and B-lymphocytes during liquid gel chromatography and immunoaffinity cell chromatography, respectively. Human serum was exposed to the 10-MHz electric field during chromatography. The gel column was placed perpendicular to the electric field surrounded by a jacket of circulating water for conductive cooling. The temperature of the gel, maintained at 25° C, increased approximately 0.05° C during the first 15 minutes and then stabilized at 25 ± 0.01° C during the 18-hour exposure period. To further ensure that changes in the elution profile were not from temperature increases, two chromatography separations were performed at 24 and 26° C in the absence of RF radiation field. No alterations in the elution pattern were detected.

The elution profiles for the three immunogolbulins examined (IgM, IgA, and IgG), were altered by field exposure during elution, as evidenced by accelerated elution of all three peaks. This is thought to reflect an increase in the steric resistance of Ig molecules to the gel pores. The investigators were able to almost completely rule out the possibility that RF radiation-induced alterations in the gel matrix could have influenced the results.

Effects on lymphocyte separation were investigated by performing immunoaffinity cell chromatography during exposure to 2500-MHz RF radiation (194 V/m, $\leq$ 0.117 W/kg, 10 mW/cm^2). This chromatography procedure separates lymphocytes based on antigen-antibody interactions at the cell surface. Spleen cells from female Balb/c(H-2d) were fractionated at 4.0° C over Ig-derivatized agarose beads (derived with polyclonal antibody directed against all mouse Ig$^+$ classes) into Ig$^-$ and Ig$^+$ lymphocyte subpopulations. Because they were derived with polyclonal antibodies directed against all mouse Ig classes, all Ig$^+$ lymphocytes were expected to interact with the beads when no field is present. RF radiation exposures, on the other hand, resulted in premature elution of 19% of the Ig$^+$ (B-cell) population. This premature elution resulted in a difference in distribution among cell fractions collected and indicates an RF radiation-induced alteration of specific Ig binding between B-lymphocyte cell surfaces and the column. Temperature fluctuations did not exceed ± 0.03° C. Although these effects occurred at SARs well below the recommended safety limit for humans in the United States of 0.4 W/kg, averaged over any 6-minute period, the investigators advise caution in extrapolating from in vitro to in vivo conditions. The results do suggest alterations in the structure of membrane-bound proteins that apparently affect receptor binding on the cell surface (Elder, 1987b).

There were two other in vitro studies in which thermal effects were carefully excluded. Szmigielski (1975) reported that radiation at 3 GHz with a power level of 5 mW/cm^2 decreased the viability of rabbit granulocytes. Lin et al. (1979) reported that radiation of 2.45 GHz with a power level of 60 to 1000 mW/cm^2 reduced the numbers of granulocyte and macrophage colony-forming units from preparations of mouse bone marrow.

5.9.4. Summary

5.9.4.1. Extremely Low Frequency Fields

Preliminary data from the analysis of pre- and postexposure blood samples from humans exposed to ELF fields of 60 Hz, 16-A/m (2 x 10^{-2} mT) and 9-kV/m for two sessions of 6 hours each resulted in the following observations (Fotopoulos et al., 1987): (1) no statistically significant differences in concentrations of calcium, glucose, uric acid, albumin, potassium, or sodium; (2) a significant decrease in lactic acid dehydrogenase after one of the two exposure sessions; (3) no significant differences in red and white cell blood counts, hemoglobin,

hematocrit, mean corpuscular volume, or platelets; (4) a significant increase in the peripheral lymphocyte count after one of the exposure sessions; (5) no significant difference in total T-cells, B-cells, natural killer cells, helper cells, or suppressor cells, based on monoclonal antibody assays; (6) no significant effect on cell-mediated immunity; (7) although the level of T-helper cells is typically higher in the morning than the afternoon, the difference was significantly larger in exposure days than days of sham exposure. Although the authors consider the data preliminary until more work is done, they point out that these field exposures might be enhancing the cell-mediated immune response in humans.

Seto et al. (1986) examined the hematologic effects of ELF on Sprague-Dawley rats that were exposed to a 60-Hz, 80-kV/m, unperturbed vertical field 21 hours/day through three generations. ‘Subtle” but statistically significant decreases in total white cell counts, lymphocyte counts, and eosinophil counts were observed. Red cell parameters were not affected by field exposure. The investigators implied that the field could have induced the effects through stress.

In another study, no consistent effects were observed in rats exposed to unperturbed 60-Hz fields at 100 kV/m for 15, 30, 60, or 120 days (Ragan et al., 1983). In two of eight experiments, the white count was lower and in one it was higher in the exposed compared with the sham-exposed groups, Platelets were significantly increased after 60 days of exposure, but not at other time points. Bone marrow cellularity was increased only in replicate 2 at 30 days of exposure. Occasional changes were also seen in red blood cell parameters and in serum chemistry values. The authors drew no definite conclusions, but inferred that the field had potentially a low level of toxicity.

A study was conducted in which small numbers of ECR-SW strain mice were exposed to a 240-kV/m, 60-Hz field 18 to 22 hours/day, 7 days/week for a total of 4500 hours of exposure (about 32 weeks) before they were killed for tests (Fam, 1980). No statistical differences were observed in the blood count values of the males at the $\alpha = 0.05$ level. However, exposed females had lower white blood cell counts, lower hemoglobin values, lower mean corpuscular hemoglobin values, and a higher percentages of bands, all of which were statistically significant. The investigators indicated that the effects on the females could have been due to either field exposure or decreased food and water consumption.

Morris and Phillips (1982) observed no effect on the primary antibody response to keyhole limpet hemocyanin in mice following their exposure to 60-Hz, 0.15- to 0.25-kV/m fields, for 30

or 60 days, or on the mitogen stimulation response of spleen cells to B- and T-cell mitogens in mice exposed to the same fields for 90 or 150 days.

An in vitro, field strength-related suppression of murine T-lymphocyte-mediated cytotoxicity was observed following a 48-hour exposure to 60-Hz sinusoidal electric fields at field strengths between 0.01 and 0.1 V/m, with a threshold for significance that lay between 0.01 and 0.1 V/m (Lyle et al., 1988). The inhibition was preferentially expressed during the early recognition phase of the immune response. The field had no effect on the proliferation of the CTLL-1 effector cells in the presence of interleukin-2, an indication that the inhibition of cytotoxicity was not due to the inhibition of cell proliferation but rather to an alteration of the mechanism for cytotoxicity itself.

In conclusion, the effects of 60 Hz electric fields on immune function in vivo are small and inconsistent when present at all. This is the overall conclusion from one human study and two studies each in rats and mice at field strengths ranging from 0.15 to 240 kV/m. However, in one in vitro study of a murine cytotoxic T-cell line, a 48-hour exposure to 60-Hz electric fields of only 0.1 and 1.0 V/m suppressed the cytotoxicity of these T-cells; no effect was seen at 0.01 V/m.

T-cell cytotoxicity, important in the elimination of certain infectious agents, allograft rejection, and tumor immunity (reviewed in Lyle et al., 1988), can be quantified in vitro with the 4-hour chromium release assay. The results of these assays have been shown to correlate directly with in vivo anti-tumor activity. Immunotherapy trials have shown that when the T-lymphocyte growth factor, interleukin-1, is administered with cultured cytotoxic T-lymphocytes, cures of cancer in animals and remissions in selected patients can occur (reviewed in Lyle et al., 1988). The suppression of T-lymphocyte-mediated cytotoxicity by ELF has been observed in vitro only, using only one clone of cytotoxic murine rather than human lymphocytes. These results, though limited, suggest the possibility that weak EM fields, in suppressing the effectiveness of cytotoxic lymphocytes, could provide a growing clone of antigenic tumor cells to develop the mass needed to overcome a continuing immune attack.

5.9.4.2. Modulated and Unmodulated Radiofrequency Fields

Studies of the effects of modulated and unmodulated RF fields on immune function have shown responses only at intensities large enough to cause appreciable heating, with the five exceptions noted below. This conclusion is based on studies in virus-infected human

mononuclear leukocytes, Wistar-Furth rats, New Zealand rabbits, rats of an unknown strain, and monkeys of an unknown strain. The exceptions are:

- Lyle et al. (1988) showed that exposure to 60-Hz modulated 450-MHz RF fields inhibits the cytotoxicity of the same mouse T-cell line in which they found to be susceptible to 60-Hz electric fields.

- Ottenbreit et al. (1981) found that the colony-forming properties of neutrophil precursor cells from childhood leukemia patients in remission are inhibited by a 15-minute exposure to 2450-MHz unmodulated radiation at the higher power levels of 500 and 1000 mW/cm^2.

- Liburdy and Wyant (1984) observed a change in the liquid gel elution patterns of human immunoglobins IgM, IgA, and IgG in solution after exposure to 10-MHz RF radiation (SAR = 0.13 W/kg). These investigators also measured changes in the separation patterns of lymphocyte-immunoglobin complexes in an immunoaffinity cell chromatography assay; these changes were induced by RF radiation of 2500 Hz and a SAR of 0.12 W/kg. This study shows that the RF radiation alters the structure of membrane-bound proteins on the lymphocyte surface.

- Szmigielski (1975) showed that RF radiation decreased the viability of rabbit granulocytes.

- Lin et al. (1979) showed that RF radiation reduced the numbers of granulocyte and macrophage colony-forming units from preparations of mouse bone marrow.

5.10. CENTRAL NERVOUS SYSTEM EFFECTS

This section examines some of the evidence that the central nervous system (CNS) is a target for ELF and RF interactions. Reports have been published showing that alterations in cellular morphology of brain tissue, changes in the electroencephalogram, and changes in pineal gland melatonin and electrical activity occur in response to magnetic and electric fields. No attempt is made here to review the literature on circadian rhythms in behavioral activity, although the CNS is clearly involved in coordinating circadian variations in hormone levels.

5.10.1. Extremely Low Frequency Fields

Welker et al. (1983) measured the melatonin and N-acetyltransferase content of the pineal gland in Sprague-Dawley rats before and after changes in the orientation of static magnetic fields. The strength of the earth's magnetic field was 0.62 Oe (0.062 mT) at a 63° inclination with respect to the horizontal plane. The animals were placed into cages with Helmholtz coils oriented so the static field experienced by the animals could be changed to various strengths.

The investigators found that when the field was either inverted (-63°) or changed by small amounts (-5°, +5°, +15°), the pineal content of both substances decreased significantly. This occurred when the field was perturbed at night (when the pineal gland is active), but not during the day. The same group of investigators had shown earlier (Semm et al., 1980) that the firing rate of single pineal cells decreases gradually over periods of about 72 minutes when the vertical component of the field is increased by 0.5 Oe (0.05 mT).

In a later paper from the same laboratory, Olcese et al. (1985) showed that this response disappeared when the optic nerve was cut, indicating that the retina of the eye is the magnetoreceptor. Later, they showed (Reuss and Olcese, 1986) that the response does not occur when the optic nerve is intact in total darkness and that dim red light must be present for the magnetic field stimulus to be effective.

The inhibition of melatonin synthesis by a change of only 5(in the orientation of a static magnetic field of 0.062 mT = 62 μT is an interesting finding. It is equivalent to the finding that the introduction of a small component either perpendicular to the field of 62 sin (5) = 4.5 μT, or a change in the parallel component of 62 [1 -cos (5)] = 0.24 μT is sufficient to inhibit melatonin synthesis. Ambient residential 60-Hz fields are within this order of magnitude.

The effects of long-term exposure to ELF fields on histology of nerve tissues of rabbits, pigs, rats, and mice were examined by light and electron microscopy. (Hansson 1981a, b; Hansson et al.,1987).

Rabbits were exposed under two different conditions: (1) from conception to 6 months of age, outdoors, in a 400-kV substation; they were exposed continuously to a 50-Hz electric field, at approximately 14 kV/m; and (2) from conception to 8 months of age, in a laboratory with a controlled environment; 14 kV/m at 50 Hz, 23 hours/day, 7 days/week (Hansson, 1981 a, b). In both situations, controls were shielded from the field (sham-exposed) in Faraday cages or were unexposed.

The most severe effects were observed in the rabbits that were exposed outdoors in a substation. Cerebellar tissues from exposed rabbits exhibited changes in almost all Purkinje nerve cells examined. Nissl granules formed by clusters of granular endoplasmic reticulum arranged in parallel that were seen in control animals had almost disappeared from tissues or exposed animals and were replaced by lamellar bodies. These structures were in continuity with the endoplasmic reticulum, thus reducing the surface area of endoplasmic reticulum

exposed to the cytoplasmic matrix; the changes extended to the dendrites. The hypolemmal cisterns normally studded along with the Purkinje cell dendrites, had vanished. In addition, microtubules showed altered distribution and reduction in number. Filaments and membranous structures were observed in increased frequency.

In rabbits that received 4 or more weeks of exposure postnatally, there were changes in the glial cells of the cerebellum (and similar, but less definite ones, in the hippocampus) that included replacement of normally slender processes with shorter, thicker more irregular ones; the nuclei of the glial cells could be stained with S-100 antibodies, which was not observed in the controls. (S-100 is a ligal cell marker protein that can be demonstrated ultrastructurally with antibodies against S-100 using quantitative immunohistochemical methods.) The number of large astrocytes in the granular layer was increased. Concentrations of S-100 in the cerebellum and hippocampus were increased. Changes somewhat similar to these, but less severe, were observed in the rabbits exposed under laboratory conditions, rats exposed to fields of 50 or 60 Hz, 14 kV/m for 22-23 hours/day, in mice exposed to fields (60 Hz, 10 kV/m) during the first 4 weeks of age, and in minipigs exposed for almost a year and a half to electric fields (60 Hz, 30 kV/m, 20 hours/day) (Hansson et al., 1987). The investigators concluded that long-term exposure to power-frequency electric fields induces effects on the nervous system of exposed animals, but they did not discuss the physiological significance of the changes.

The work of Hansson (1981 a, b) has been criticized on the basis that the animals were maintained out-of-doors under ill-controlled conditions and environmental factors other than the field [such as noise, ozone production, and vibrations that were related to high voltage installations (Kornberg, 1976; Michaelson, 1979, both cited in Portet and Cabanes, 1988) could have influenced the results (Portet and Cabenes, 1988). In addition, a reduction of growth observed in the rabbits exposed outdoors was not reported for animals exposed in the laboratory. In similar studies, Portet et al. (1984, cited in Portet and Cabanes, 1988) did not observe lesions in the cerebella of neonate rabbits exposed to electric fields, Experimental details were not available.

5.10.2. Modulated Radiofrequency Fields

Electroencephalogram (EEG) changes (which consisted of enhanced low frequency components and decreased high frequency activities) were observed in rabbits exposed to a RF field 2 hours/day for 6 weeks at 1.2 MHz (15-Hz modulation) at levels of 0.5 to 1 kV/m

(~1.3-2.6 W/cm^2) (Takashima et al., 1979). The effects were described as nonthermal. because the estimated current density of 0.082 mA/cm^2 was below that needed to cause noticeable thermal effects. The EEG signals were computer processed to obtain power spectra.

5.10.3. Unmodulated Radiofrequency Fields

Webber et al. (1980) observed ultrastructural damage, apparently of a nonthermal nature (SAR not known), in mouse neuroblastoma cells grown in culture and exposed to microwave pulses. The cells were exposed to short pulses at high fields [1.7 to 3.9 kV/cm (170 to 390 kV/m)] from a magnetron radar transmitter with a radar modulator. The voltage pulses from the power supply and modulating system were converted to 1-second RF pulses in a 2.7-Hz band (330 pulses/second, 0.0335 duty cycle). The waveguide apparatus termination was constructed for insertion of a glass slide horizontally between two section of S-band waveguide. The coverslip carrying the cells was placed on the glass slide, with cells facing upward. A section of waveguide that terminated in a short circuit was mounted 4.16 cm above the slide.

The cells were (1) exposed to 1.7 kV/cm (170 kV/m) for 30 seconds, (2) exposed to 3.0 kV/cm (300 kV/m) for 60 seconds, (3) exposed to 3.9 kV/cm (390 kV/m) for 60 seconds, or (4) not exposed to the field. To test the effects of heat on the cells, coverslips carrying the cells were dipped into saline at the following temperatures for 30 seconds: 37, 41, 45, 50, 62, 70, and 80° C. The cells were examined by electron microscopy after field or heat exposure.

The most striking damage observed in cells exposed to 1.7 kV/cm (170 kV/m) was in the form of breaks in the cell and mitochondrial membranes. The cristae lost their normal pattern and formed myelinated figures inside the mitochondria. Parts of the cell membrane were expelled and appeared as membrane-bound sacs outside the cell surface. Exposure of the cells to this field for 30 seconds is expected to result in a temperature rise from 37° to 41° C. To determine if the effect was heat-related, cells were exposed to temperatures corresponding to temperature increases induced by microwave exposure. Cells exposed to heat alone (41° C as well as 45° C) remained viable and maintained a normal structure without any cell damage. Cells exposed to 50° C showed considerable damage; however, the cell membranes remained intact. Cells exposed to 3.9 kV/cm (390 kV/m) for 60 seconds were damaged severely. The cell content was totally disorganized and the membranes-had completely broken down

appearing denatured. However, cells heated to 62° C, the corresponding temperature for this exposure, exhibited greater integrity of the cell membranes (including the mitochondrial and nuclear membranes). Because of the different nature of the damage to field-exposed compared with temperature-exposed cells, the investigators suggested that the damage could have been due to nonthermal effects.

5.10.4. Summary

Long-term exposure of animals to moderate or high-intensity EM fields at 50 or 60 Hz resulted in changes in the cerebellar Purkinje nerve cells that included rearrangement of the endoplasmic reticulum and disappearance of the hypolemmal cisterns of the dendrites (Hansson et al., 1987). Glial reactions that showed an increased concentration of S-100 in the cerebellar hemispheres were the most consistent findings. These changes indicated that disturbances had taken place in the interaction between plasma membrane structures and the cytoskeletons of cells of the nervous system.

Neuroblastoma cells exposed to microwave pulses in culture exhibited ultrastructural damage as evidenced by breaks in the cell and mitochondrial membranes (Webber et al., 1980). The effects were apparently nonthermal.

The studies of Semm et al. (1980), Olcese et al. (1985), and their colleagues show that changes in magnetic fields are perceived by the retina. This stimulus decreases the firing rate of neurons in the pineal gland and inhibits its melatonin content if applied at night when the pineal is actively secreting melatonin. The finding that the retina is able to detect changes in magnetic fields provides a mechanism whereby the CNS function is affected by these fields.

Alterations in Ca^{++} efflux from nervous tissue have been described (see Section 5.3.2.1). Blackwell and Saunders (1986) reviewed the literature on CNS effects of RF and microwave exposure and concluded that although calcium ions play a critical role in many metabolic and physiological processes, the significance of changes in calcium ion exchange in brain tissue for the health and safety of people exposed to microwave and RF radiation is difficult to determine, and that furthermore, the evidence that calcium ion exchange in living nervous tissues is altered by amplitude-modulated RF and microwave and radiation is inconclusive (Blackwell and Saunders, 1986).

Michaelson and Lin (1987) also reviewed the effects of low-intensity microwaves on the CNS and concluded that to date there is no convincing evidence of the existence of

low-intensity microwave effects on the human CNS. The animal studies that are the basis for reported effects suggest that the mechanisms for these effects involve microwave-induced nonuniform temperature distributions and/or thermal gradients (Michaelson and Lin, 1987).

5.11. SUMMARY AND CONCLUSIONS FOR SUPPORTING EVIDENCE OF CARCINOGENICITY

The literature on effects of EM fields on biological processes relevant to carcinogenesis has been reviewed in this chapter. In this section, the summaries of other sections of Chapter 5 are reviewed and overall conclusions are derived to the extent possible.

5.11.1. Summary

Table 5-7 summarizes in brief phrases the effects that have been observed for each biological process and each of the major categories of EM fields. These summary phrases have been derived from the section summaries and text. The first observation apparent from Table 5-7 is that the evidence for any one process is widely scattered among different types of exposure. The scattering is even more widespread than the table suggests, since it obviously cannot show the large variety of frequencies, intensities, and durations of exposure that have been used within each broad class of exposure. The table demonstrates the gaps in the current information; for example, transcription of genetic information into messenger RNA, translation into proteins, and parathyroid hormone effects on bone cells have been studied only with low-frequency pulsed magnetic fields. This is understandable, since this work has its origins in the successful use of pulsed magnetic fields for clinical healing of recalcitrant bone fractures.

The following conclusions can be made:

- None of the types of time-varying fields considered in this document cause DNA breaks, gene mutations, or sister chromatid exchanges, (Static magnetic fields with high field strength have affected DNA in solution and have caused sex-linked recessive lethal mutations in Drosophila, but the significance of this effect is not known). This lack of a DNA and gene mutation effect is expected, since these fields do not have enough energy to break chemical bonds.

- Effects on DNA synthesis have not been studied extensively enough to draw definite conclusions. Apparently RF fields cause inhibition and ELF magnetic fields cause an enhancement of DNA synthesis only within a limited range of frequency and intensity “windows.”

TABLE 5-7. SUMMARY OF SUPPORTING EVIDENCE FOR CARCINOGENICITY

Subject	ELF Fields				RF Fields
	E-Fields	B-Fields	Combined E and B	Modulated RF Fields	
DNA Damage: Breaks Repair	No breaks No DNA repair	No breaks –	No breaks –	– –	No damage
DNA Synthesis	Delayed S phase	Enhancement (frequency and intensity windows)	–	Inhibition	Inhibition
Gene Mutations	No effect (1 study)	No effect (2 studies)	–	No effect (1 study)	No effect (10 studies)
Chromosome Aberrations	Breaks, aneuploidy (inconsistent)	Breaks, aneuploidy, decondensation (inconsistent)	Breaks –	Spark discharges caused breaks	Breaks, uncoiling, numerical aberrations, dicentrics condensation (inconsistent)
Sister Chromatid Exchange	No effect (4 studies)	No effect (3 studies)	No effect (2 studies)	No effect (2 studies)	No effect (1 study)
Mitosis	Mitotic index reduced early, but recovers. Cell cycle delayed	–	Cell cycle delayed	Inconsistent (2 studies)	No effect (1 study)
Transcription of Genes	–	Enhanced, both normal and newly-induced sites (all waveforms)	–	–	–
Translation	–	Altered pattern of protein synthesis	–	–	–
Cell Transformation	–	–	–	Initiation of C3H/10T1/2 cells	
Calcium Efflux, Brain Tissue	Inhibition Frequency and Amplitude "Windows"	–	Enhancement Amplitude and frequency "windows"	Frequency and intensity "windows"	No effect (3 studies)
Parathyroid Hormone	–	Blocks action of PTH at the cell membrane	–	–	–
Intracellular Enzymes	ODC is induced. Same effect as TPA.	–	–	Protein kinase C inhibited. Frequency Windows." ODC is induced	–
Hormones	Inhibits nighttime melatonin output of pineal gland	–	–	–	–

TABLE 5-7. SUMMARY OF SUPPORTING EVIDENCE FOR CARCINOGENICITY (continued)

Subject	ELF Fields				
	E-Fields	B-Fields	Combined E and B	Modulated RF Fields	RF Fields
Growth and Differentiation	Inhibits protein synthesis in fibroblasts	Inhibits differentiation and stimulates growth of embryonal carcinoma cells	Increases reproductive capacity of carcinoma cells	–	–
Immunological Systems	No effect in vivo (3 studies) Inhibits cytotoxicity of T lymphocytes in culture.	–	No effect in humans (1 study)	Cytotoxicity same as ELF. No effect on leukocytes.	No effect in rats, rabbits, monkeys. Cell-immunoglobulin binding is altered.
Central Nervous System	–	Inhibition of pineal activity via retinal magnetoreceptors	Morphological changes in glial and Purkinge cells of cerebellum	EEG shifts to lower frequencies (ELF modulation). Disruption of mitochondria and cell membranes, different than heat damage (radar modulation).	–

- Chromosomal aberrations is a frequent finding for both RF and ELF fields, but it often does not occur. In one measurement of aberrations in peripheral lymphocytes in electrical switchyard workers, chromosome breaks occurred immediately after they were exposed to spark discharges, but in similar populations, with no spark discharge exposure, no aberrations occurred. This indicates that high frequencies may be more effective than low frequencies in causing aberrations, but these conclusions are only tentative, and specific studies are needed to address this important issue.

- ELF electric and combined electric and magnetic fields have delayed the cell cycle and caused transient reductions in the rate of cell division, but RF fields have caused no consistent effect. ELF magnetic fields have not been tested for their effect on the mitotic cycle, and little testing of RF has been done.

- Pulsed magnetic fields of the type used for clinical bone healing have enhanced the transcription synthesis of mRNA at genetic sites that are normally active and have altered the molecular weight distribution of proteins synthesized with the fields present. The protein molecular weight distribution is different with different waveforms (pulsed versus sinusoidal) and frequencies (60 Hz vs. 72 Hz). No other type of field has been investigated for this effect.

- Cultures of the NIH C3H/10T1/2 cells, which are widely studied systems for investigating cell transformation from normal to malignant patterns of growth, have been shown to undergo transformation under special conditions. Microwave 2450-MHz power, modulated with pulses at a rate of 120 pulses per second, were administered to the culture at intensities low enough to cause no effect. Subsequently the cells were

treated with TPA, the phorbol ester which is known to cause promotion of chemically-initiated cells. The cells undergo transformation under these conditions, indicating that this pulsed microwave power has the properties of a chemical initiator of malignant transformation. Only one experiment has shown this phenomenon, so no conclusions can be made about whether ELF or RF fields could produce the same effects.

- The release of calcium ions from chick brain tissue into the medium surrounding the tissue has been affected by ELF electric fields, crossed ELF electric and magnetic fields and RF radiation modulated at the same frequencies which cause the ELF effects. The original investigations with ELF electric fields showed an inhibition of calcium release, whereas an enhancement of release occurred in the other experiments. This phenomenon has not occurred in three RF studies, but magnetic ELF fields have not been examined for this effect. The conditions under which this occurs are very precise and not understood. It occurs only at certain frequencies (e.g., odd multiples of 15 Hz with some frequencies missing) with no response at frequencies between. At some fixed frequencies, it occurs only at certain field strengths with no response below and above this intensity “window.” In at least at one of the “windows” the orientation of the alternating magnetic field must have a component perpendicular to the static earth’s magnetic field. The crossed electric and magnetic alternating fields producing this effect are extremely small (16 V/m electric and 73 nT magnetic field), and in the range of ambient magnetic ELF fields in residences. With the two exceptions discussed below all of the other effects reviewed in this document are induced by fields at least hundreds of times higher than this. The biological significance of this phenomenon is not clear beyond the fact that brain tissue is somehow affected by these unique field conditions.

- The effects of pulsed ELF magnetic fields on the interaction between parathyroid hormone (PTH) and bone cells have been studied to elucidate the mechanisms of the clinically successful bone healing ability of these fields. These fields block the inhibitory effect of PTH on collagen synthesis by the cells, and the action of the field occurs at the plasma membrane where the hormone binds with its membrane receptor. The significance of this is that pulsed magnetic ELF fields can alter the chemical signalling process between an exogenous hormone and the cellular activity induced by the hormone. No other type of field has been tested for this effect.

- The intracellular enzyme ornithine decarboxylase, which is active during cell proliferation and DNA synthesis of most cells, is induced by ELF electric fields and by ELF modulated RF fields in three different cell lines. Information on the effect of other fields has not been found. The same enzyme is induced by the phorbol ester TPA, the most actively studied chemical promoting agent. cAMP-independent protein kinase, one of the chemical intermediates involved in this cell proliferation response, is inhibited in human lymphocytes by modulated RF fields, with an apparent frequency “window.”

- Electric ELF field exposure to rats for 20 hours per day for 30 days causes an inhibition of the nocturnal synthesis of melatonin by the pineal gland. Information on the effect of other fields has not been found. This finding could have great significance in explaining the potential carcinogenicity of ELF fields, since there is a wealth of literature describing the oncostatic properties of melatonin, not only for chemically-induced

mammary tumors in rats, but also (according to one report) in the treatment of human leukemia. Other experiments in rats have shown that pineal neurological activity and melatonin synthetic activity have been inhibited by changing the orientation of the static magnetic field through an angle of as small as 5(, a change which is only a factor of 10 higher than ambient magnetic residential fields. This implies that exposure of humans to weak time-varying magnetic fields at night could have an inhibitory effect on pineal melatonin synthesis. Experimental evidence to support this hypothesis is not available. Information on the effect of ELF magnetic fields and RF fields on melatonin synthesis has not been found. ELF electric, magnetic, and combined fields of the strength used to stimulate bone repair can also cause alterations in biosynthesis. Inhibition of protein biosynthesis in fibroblasts, inhibition of differentiation and stimulation of growth of embryonal carcinoma cells, and increase in the reproductive capacity of colon carcinoma cells are all phenomenon that are induced by ELF fields and are characteristics of malignant growth. The extent to which they occur in the whole organism under realistic exposure conditions is not known, but these phenomena are consistent with the suggestion of carcinogenic effects in humans and animals.

- In one human study and three animal studies, exposure to ELF fields caused small but inconsistent changes in white blood cells. Exposure of rats, rabbits, and monkeys to unmodulated RF fields also caused small inconsistent changes. However, one investigator working with T-lymphocytes in culture found that both ELF electric fields and modulated RF radiation inhibit their ability to kill their normal target cells. The reasons for this difference between the in vivo and in vitro response is not known, but it does call into question how directly one can infer that whole animal responses can be predicted from cell culture experiments for these effects. Information on the effect of magnetic fields on lymphocyte function or dynamics has not been found.

- Exposure to combined ELF electric and magnetic fields 23 hours/day for the first 6 to 8 months of life caused a disappearance of Nissel granules and disruption of the endoplasmic reticulum in Purkinje cells and a disruption of the morphology of glial cells in the cerebellum. This occurred most severely in rabbits but also occurs to a lesser extent in rats, mice, and mini pigs exposed for various durations. Six-week exposures of rabbits to ELF modulated RF fields caused a downward shift in the frequency of the electroencephalogram (EEG). The ELF modulation frequency of 15 Hz was in the same range as the EEG frequencies that were enhanced. The finding that the intact retina is needed for a functioning pineal gland response to magnetic fields implies that the CNS can be a sensor for ELF fields and raises the possibility that other neuroendocrine functions of the CNS could be affected.

5.11.2. Conclusions

The finding that several biological phenomena, which are in some way related to postulated mechanisms of carcinogenesis, are induced by time-varying electric and magnetic fields is far from proof that these fields are carcinogenic by themselves or that exposure to them are risk factors for humans. There are reasons for both questioning and affirming the relevance of each finding. One of the primary difficulties in accepting the relevance of most of

these findings is the fact that they are induced by field strengths many times higher than the ambient residential exposures which are hypothetically causing human cancer. Of the effects summarized in this chapter, only three phenomena occurred under conditions similar to the low ELF electric and magnetic fields characteristic of ambient exposure [10 V/m and 2 milligauss (mG) = 0.2 μT]: (1) calcium efflux from chick brain tissue induced by crossed electric and magnetic fields; (2) calcium efflux from chick brain tissue after exposure of the developing embryo to electric fields; and (3) inhibition of nocturnal melatonin synthesis by small changes in the orientation of static magnetic fields.

The above statements are made under the assumption that human carcinogenicity is indeed caused by 60-Hz fields with a field strength on the order of 2 mG. If the causative agent really is the internal currents induced by these ambient fields, then it is conceivable that the higher frequency components always accompanying ambient 60-Hz fields are the relevant aspects of exposure. If the effects are really caused by high peak fields with high frequency components, then the phenomena observed at higher field strengths would be relevant. In this case more of these phenomena would be relevant, but precise quantitative evaluation is difficult to carry out, given the current degree of knowledge.

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6. RESEARCH NEEDS

6.1. INTRODUCTION

In order for the Agency to evaluate the public health hazard of electromagnetic (EM) fields and to be in a position to recommend preventive measures, more information is needed in several areas. The research topics that need to be investigated to supply this information are summarized as follows:

- Health Hazards Evaluation
  - Cancer
  - Reproductive effects
  - Central nervous system neuroendocrine, immunological effects
- Exposure Evaluation
  - Characterization of high frequency transients and harmonics of fields from electrical power sources
  - Relative contribution of sources to total exposure
    - High-voltage transmission lines
    - Distribution lines to homes and industries
    - Power distribution transformers
    - Appliances
    - Ground currents in households, industrial buildings, office buildings, and schools
    - Transportation systems (e.g., electric trains)
- Mitigation (exposure reduction)
  - Reduction of ground currents
  - Redesign of appliances
  - Redesign of wiring and routing of distribution lines
  - Supression of transients and high frequencies
  - Avoidance of hazardous sources

This section deals only with research needed for evaluation of the cancer hazard, although we recognize that other areas also need further research,

6.2. INFORMATION NEEDS ARISING FROM THE EVALUATION IN THIS DOCUMENT

The evaluation carried out in this document has raised several unanswered questions about the carcinogenic potential of EM fields. The major information needs that have been identified are outlined in this section. Before these needs can be translated into a research

program, the ongoing research that is now being carried out must be taken into account. This is not being attempted in this section; rather, the emphasis here is on the issues about population hazards that need to be dealt with before an evaluation of the public health hazards and the determination of meaningful preventive measures can be made.

6.2.1. Epidemiology Research Needs

The association between cancer occurrence and exposure to either extremely low frequency (ELF) or radiofrequency (RF) fields is not strong enough to constitute a proven causal relationship, largely because the relative risks in the published reports have seldom exceeded 3.0 in both childhood residential exposures and in occupational situations. Two possible explanations for this are: (1) our imprecise knowledge of the causal aspects of exposure (field strength, frequency, time patterns of exposure, and synergistic factors) prevents us from identifying exposure indices that distinguish exposed from unexposed populations, or (2) the observed effects are actually caused by some other factor not related to the EM-fields but which co-varies with EM-field strength. A third possible explanation is that exposures have been too weak to produce an observable effect, This cannot be evaluated because there is currently no reasonable basis for making predictions of the expected human response.

To evaluate the first two possibilities, two things need to be done: (1) define job categories in electrically-related occupations to reflect actual exposure to EM fields. These definitions would be used as the basis for selecting cohorts for study. These studies should be designed to investigate a variety of exposure parameters, which need to be judiciously selected using the most recent concepts of likely mechanisms of carcinogenesis; and (2) investigate, with improved study designs and exposure measurements, those populations that have already showed some excess risk from EM fields or have potentially high exposures, such as military communications and radar workers; amateur radio operators; telephone and electrical utility workers; electric-arc welders; aluminum smelter workers; engineers, scientists, and computer operators working with electrical equipment; people living near radio and TV broadcast towers; users of electric blankets; and Hodgkin’s lymphoma patients. In designing these studies, special attention needs to be given to confounding variables in order to avoid an incorrect attribution of the effects to EM fields simply as a consequence of the intense scrutiny

given to them. More information about the risks of RF and modulated RF exposure is needed before any conclusions can be made about either their safety or hazard.

6.2.2. Laboratory Research Needs

Both animal and in vitro studies are needed to discover the relevant exposure factors and their interaction, to gain some understanding of the mechanisms of action, and to extrapolate "effective doses" to the human exposure situation.

For long-term animal studies, the most obvious need is to conduct a carcinogen bioassay with magnetic field ELF exposures. The experiment planned by the Ontario Hydroelectric Power Company (described in Section 4.6) will be the first animal carcinogen bioassay to be done with 60-Hz magnetic fields. It may or may not confirm the human findings and will generate additional research topics regardless of the outcome. Since the University of Rochester study is already examining the effect of ELF electric fields on the growth rate of mammary carcinomas in rats, there is not a high priority need at this time to initiate another chronic experiment with electric fields, However, this same type of study is needed for ELF magnetic fields. If these studies show that a carcinogenic response is induced in animals by these ELF exposures, then whether RF fields modulated at the same ELF frequencies will produce comparable effects is the next logical question, since modulated RF exposures are common and some laboratory phenomena (Table 5-7) have the same effect with or without the RF component.

For in vitro studies, several biological phenomena, having some relationship to possible mechanisms of carcinogenesis, have been Induced by EM fields. The discussion in Section 5.11 summarizes the large amount of missing information relative to the biological effects of EM fields and forms the basis for this discussion. The overall goal of the research program would be to select the most promising candidate mechanisms of cancer induction at ambient electric and magnetic field strengths and frequencies and to experimentally investigate, in laboratory in vitro tests and in whole animals, the way in which each process depends upon several field exposure parameters, such as type of field (alternating electric and magnetic fields, geomagnetic fields), field strength, and frequency and time patterns of exposure (steady, intermittent, time of day). The leading research areas identified in this review are:

- Biological response to weak fields

  If ambient 60-Hz magnetic fields [which have strengths on the order of 5 miiligauss (mG) or less] are really causing a cancer response, then tissue currents on the order of 10^{-4} microamperes per square centimeter ($\mu A/cm^2$) must be able to induce some kind of change in cellular metabolism. Of the processes reviewed in this document, there are only three that occur at field strengths comparable to this: (1) calcium release from chick brain tissue in response to crossed electric and magnetic fields; (2) the change in melatonin secretion in rats induced by a small change in the orientation of the static magnetic field; and (3) calcium release from chick brain tissue induced by electric fields. Since the first phenomenon empirically exhibits frequency selectivity, there is at least a theoretical possibility that weak currents of the correct frequency could induce an effect even though they are within the range of thermal noise. There is a need to establish a mechanism that would explain how magnetic fields could induce such a calcium release from brain tissue. ion cyclotron resonance and the quantum beat models are two possibilities, and experiments are needed to test those hypotheses However, nuclear magnetic resonance has been suggested as another possibility, and that has not been examined.

  The effect of low-strength alternating magnetic fields on melatonin secretion has not been measured, and the single observation that a very small change in magnetic field orientation has induced an inhibition of synthetic activity needs to be verified. Of particular interest is the ELF frequency and intensity dependence of this inhibition, In addition, it would be of interest to ascertain whether modulated RF fields affect pineal melatonin synthesis.

- Chemical signalling pathways for controlling cell proliferation

  Since the transduction of hormone and other chemical signals into the cell is a necessary step in the hormonal control of cell proliferation, and since this transduction process is defective in transformed cells, the influence of EM fields on signal transduction has a potentially important role in the development of cancer. The experiments on ornithine decarboxylase (ODC) (Section 5.6), gene transcription (Section 5.3), and parathyroid hormone (Section 5.5) raise the possibility that electric and magnetic fields interfere with the normal functioning of signal transduction pathways. The effects of EM fields on one of the major pathways, the receptor-mediated activation of phos-

phoinositide turnover, has not been explored but should be because this pathway is involved in several phenomena related to ceil proliferation. This pathway involves diacylglycerol (DAG), which is a structural analogue of the tumor promoter TPA, both of which activate protein kinase C (PKC), and, ultimately, ODC. It also involves inositol trisphosphate (IP3), which is known to release calcium from intracellular stores and the plasma membrane. Both DAG and IP3, through calcium release, activate PKC which phosphorylates growth factor receptors and proto-oncogenes and is believed to play a role in the control of cell proliferation. As our understanding of these pathways becomes more detailed, we will be able to postulate chemical synergisms and antagonisms with EM fields. Further study of parathyroid hormone as a mediator of bone healing response to magnetic fields will lead to a better appreciation of the interaction between hormones and EM fields in the control cellular proliferation.

In addition to the chemical events associated with the cell membrane, the influence of EM fields on the dynamics of charged membrane-bound proteins needs to be studied. There is a possibility that the alternating electric field at the membrane or currents induced by these fields directly affect enzymatic reactions, such as ion transport reactions, carried out by these proteins. There is also the possibility that the fields modify the opening and closing of ion-conducting channels in the membrane, and they could affect the stability of membrane receptors.

- Gene expression

  The influence of EM fields on the expression of genetic activity, both with respect to transcription to mRNA's and in translation of genetic information into protein synthesis, is needed. It is important to study how this process is connected to chemical signalling pathways.

- Cell transformation

  The single experiment showing that modulated microwave radiation acts as an initiator of the transformation of C3H10T1/2 cells to malignancy needs to be verified and repeated with ELF magnetic and electric fields. The interaction of EM-field exposure with other factors known to influence transformation in this well-studied system may lead to clues as to the mechanism of this transformation.

- Melatonin Activity

  Although it is well known that melatonin inhibits the growth of hormonally dependent tumors and that electric field exposure inhibits the synthesis of melatonin by the pineal gland, the effect of ELF fields on these end points has not been directly studied. In addition, the question of whether ELF magnetic fields inhibit melatonin secretion is especially important in view of the postulated human response to magnetic fields. This mechanism becomes especially important to the induction of leukemias and lymphomas by EM fields in view of the successful treatment of clinical leukemia with melatonin (Section 5.7.1).

- Ion cyclotron resonance interaction

  Several questions need to be answered about the ion cyclotron resonance phenomenon:

  - In artificial membranes impregnated with channel proteins of various ion specificities, does the ion cyclotron resonance field open an ionic conduction channel, as one experiment with cell suspensions suggests?
  - Does the calcium release from brain tissue depend on an ion cyclotron resonance process?
  - Are other intracellular processes dependent on specific ions triggered by plasma membrane ion gating induced by ion cyclotron field conditions? This process has been implicated as a mechanism of diatom locomotion mediated by intracellular calcium ions and hypothetically for rat behavioral patterns mediated by lithium, but more examples are needed, perhaps with sensory cells and with cells in which field-sensitive biochemical reactions are taking place.

In planning and executing this research, it is important to recognize that effects of fields on the whole animal are likely to be unpredictable based on the results of laboratory in vitro systems, so that there is a constant need to verify these effects in the whole animal before being able to make valid inferences about effects in humans.

7. SUMMARY AND CONCLUSIONS

7.1. INTRODUCTION

In this chapter each of the major chapters in the document are summarized; a final section presents a discussion of the relationships among the individual chapters and the overall conclusions.

7.2. MECHANISMS OF INTERACTION BETWEEN TISSUE AND ELECTROMAGNETIC FIELDS

The basic processes by which energy from electromagnetic (EM) fields of radiofrequency (RF) and extremely low frequency (ELF) frequencies is coupled to the body are described in this section. The frequency dependence of the RF power absorbed by an organism is dominated by the body size, so that mice, rats, and humans have different RF absorption characteristics. For ELF fields and the lower RF frequencies near the source, the relationship between the electric and magnetic fields is not fixed, as it is for RF fields, and they are evaluated separately in this document. From the point of view of EM fields, the body is composed of a solution of ions; it is an electrical conductor and the penetration of electric fields into the body is very poor at ELF frequencies. Since the body is composed of nonmagnetic materials, an external time-varying magnetic field permeates the body, inducing ionic currents.

The human evidence, as described in the next section, suggests that magnetic fields, rather than electric fields, are associated with cancer incidence, and mechanisms have been sought to explain how weak currents induced by ELF magnetic fields could interact with cells and body tissue in such a way as to induce a carcinogenic response. Three classes of models for this interaction are reviewed. (1) The surface compartment model deals with the movement of ions towards and away from the inner and outer surfaces of the plasma membrane of the cell, and deals with ion-selective membrane channels, ionic pumps, and membrane ion fluxes. The model describes the movement of ions in response to perturbations of electric fields and magnetically induced currents around the cell. (2) The ion cyclotron resonance hypothesis was developed in part to explain the frequency sensitivity of calcium ion efflux studies of brain tissues. If the relationship among the frequency of time-varying magnetic field, the strength of a parallel static magnetic field, and the ionic charge to mass ratio of an ionic species is correct, then the ion will resonate, or synchronously follow circular paths in a plane perpendicular to the field. In one experiment demonstrating this

effect, conditions were set up for calcium cyclotron resonance, and the movement of benthic diatoms was measured. The authors interpreted the experiment as showing that calcium ions entered into the cell under these specific conditions and stimulated the motion of the cells, whereas the cell is normally impermeable to calcium. This type of mechanism could be the basis of an induced selective ion permeability of the plasma membrane and might ultimately be capable of explaining both frequency selectivity of these effects and the sensitivity to small induced currents. (3) Another class of models deals with cooperative motions of an ordered array of lipid bilayer molecules and describes how a weak field affecting the motion of the whole array could be transferred to just one site in the array. These theories have not yet been tested in the context of ELF biological processes. At the present time, these basic models of tissue interaction with EM fields cannot be linked to the biochemical or cellular processes involved in the development of malignant growth.

7.3. HUMAN EVIDENCE

The effects of human exposure to EM fields from several sources have been reported. This document discusses ELF fields separately from higher frequency exposure where possible. Children with residential exposure are more appropriate subjects than adults for evaluating the effects of ELF fields, since children have relatively little exposure to higher frequency fields and occupational chemicals as a consequence of their normal activity patterns. Consequently, studies of childhood cancer associated with residential exposure to 60-Hz power frequency fields are discussed separately from occupational exposure to adults, which involves a mixture of both ELF and RF fields,

7.3.1. Studies of Children

There have been seven case-control studies of cancer in children examining residential exposure from power transmission and distribution systems. Two additional studies have examined childhood cancer in relationship to father's occupation. Six of the seven residential exposure studies showed positive associations with ELF field exposure; three were statistically significant and the other three had odds ratios greater than one but not statistically significant. Where different cancer sites were evaluated, leukemia, nervous system cancer, and, to a lesser extent, lymphomas were found to be in excess in the five residential studies showing positive associations. Electric fields were not found to be a critical factor thus far. Surrogates of magnetic field exposure differed among the seven studies. Wire code configurations and proximity to distribution lines were used in six of the seven studies, and measurements were

taken in two of the seven studies, There is a reasonably good, but not perfect, correlation between measured magnetic fields and wire code configurations. In two of the studies in which magnetic field measurements were made, cases were observed in those exposed at or above 2 to 3 milligauss (mG) [0.2 to 0.3 microtesla (μT)]. Although one study found a suggested dose-response relationship with respect to surrogate measures of exposure, reliable dose-response information is not available due to the use of dichotomized exposure categories and due to small numbers of cases within the exposure groupings. Issues pertaining to personal exposures and latency have not been addressed. The two paternal occupational studies found statistically significant associations between neuroblastoma and brain cancer, respectively, in children and their fathers' exposure to electric and magnetic fields. There was also one report of a cluster of a rare tumor type (endodermal sinus tumors) in adolescent girls exposed to EM fields from power distribution lines. A summary description of the studies can be found in Section 3.2.3.

The consistently repeated pattern of leukemia, nervous system cancer, and lymphoma in the childhood studies and the dismissal of several confounding exposure factors in the Savitz et al. (1988) study argue in favor of a causal link between these tumor types in children and exposure to ELF magnetic or electric fields, However, the fact that the odds ratios are small and in many cases not statistically significant indicates that the association may not be strong and therefore argues against a causal relationship.

7.3.2. Studies of Adults

7.3.2.1. Residential Exposure to Power Frequency Fields

In a total of five studies, four case control and one cohort, of cancer mortality or incidence in adults exposed to EM fields of 50 to 60 Hz, three of the case-control studies of leukemia were nonpositive and the fourth case-control study of adult cancers was clearly positive. The cohort study produced a positive excess risk of lung cancer. In contrast to the childhood cancer studies, the adult studies were more difficult to interpret because they lacked the statistical power to detect a relative risk of the magnitude typically observed in the childhood studies and because there was little evidence that the cases were exposed to levels of EM fields higher than fields to which the controls were exposed. Therefore, no conclusions can be made about a cancer response and adult exposure to residential fields.

7.3.2.2. Occupational Exposure to Extremely Low Frequency and Mixed Frequency Fields

Twenty-eight reports dealing with cancer incidence or mortality in workers in electrical and electronic occupations have been reviewed. These exposures have involved 50 or 60 Hz power frequency fields as well as mixtures of higher frequency fields which are typically poorly defined. The studies have been carried out in Europe, New Zealand, and the United States. Many of them were re-examinations of previous studies or evaluations of vital records, cancer registry, or occupational data bases, and thus the populations were not formed to test the specific hypothesis of whether EM-field exposure is associated with increased cancer risk. Most of them used death certificates as a source of occupational information; this information furnishes only a very crude indicator of actual exposure to EM fields. Many of these are proportional mortality studies, which are less informative than studies of cohort and case-control designs because their results are affected by extraneous causes of death.

In these studies three types of cancer predominate: (1) hematopoietic system, especially leukemia and specifically acute myeloid leukemia; (2) nervous system cancer, including brain tumors; and (3) malignant melanoma of the skin. These cancer sites are found consistently across different geographic regions, age groups, industries, occupational classifications, and study designs, Given this diversity of studies, in addition to the likelihood that across broad job categories the exposures to various chemicals is not uniform, it is difficult to identify any single agent or group of confounding exposures that could explain the consistent finding of these same cancer sites.

7.3.2.3. Radiofrequency Exposure

Reports that focused primarily on exposures to RF radiation have shown mixed results, but most of the studies were difficult to interpret. Two early reports concerning microwave exposure of US. embassy personnel in Moscow and radar exposure of U.S. Navy personnel showed only a slight tendency for increased cancer risk at all sites, and somewhat higher odds ratios for hematopoietic system cancers. A study of personnel in a World War II radar research and development laboratory found no convincing evidence of increased cancer incidence, but errors of exposure misclassification are likely. A series of reports of ham radio operators found a statistically elevated incidence of acute myeloid leukemia and other neoplasms of the lymphoid system, but no clear dose-response trend was seen with longer exposure, where the degree of exposure was inferred by FCC operator license class. One

report of military exposure to radar found increasing rates of hematopoietic cancer of specific sites, but a lack of detail limits the ability to interpret the results.

7.3.3. Summary of Human Evidence

The strongest evidence that there is a causal relationship between certain forms of cancer, namely leukemia, cancer of the nervous system, and, to a lesser extent, lymphoma and exposure to magnetic fields comes from the childhood cancer studies. Several studies have consistently found modestly elevated risks (some statistically significant) of these three site-specific cancers in children. In two of the studies in which magnetic field measurements were made, cases were observed in those exposed above 2 to 3 mG (0.2 to 0.3 μT) but not in children exposed below that level. This is supported by the fact that children have relatively few confounding influences that could explain the association. In fact, the few potential confounders and biases that might have had an effect on the results were examined by one of the authors in some detail and found not to be a serious problem. No other agents have been identified to explain this association. However, there are contradictory results within these same studies, and dose-response relationships could not be substantiated. Furthermore, there is little information on personal exposure and duration of residency in the EM fields.

Additional, but weaker evidence that there is an elevated risk of leukemia, cancer of the nervous system, and perhaps other sites comes from occupational studies of EM-field exposure. Although many of these studies have found an excess risk of these forms of cancer with employment in certain jobs that have a high potential for exposure to EM fields, few or no measurements have actually been taken in those occupations. Furthermore, information about occupation has come generally from sources that could be characterized as sketchy. The likelihood that misclassification or information bias is present in these studies is high. However, exposure misclassification, if random, tends to bias relative risks toward the null. Despite these weaknesses, the occupational studies tend to support the results of the childhood studies, since the excess relative risks occur at the same sites.

The studies of residential adult exposures to EM fields provide little evidence of a risk of leukemia, mainly due to a lack of statistical power and/or probably little exposure to levels of EM fields that have been found to be associated with cancer in children. These studies cannot be interpreted as evidence either for or against a causal association between cancer and EM-field exposures. On the other hand, the case-control study of cancer in Colorado residents does support an association of central nervous system cancer and lymphoma if

proximity to high-current electrical wiring configurations is assumed to be an adequate surrogate for exposure.

The studies of adults exposed to RF radiation produced mixed results, primarily because of limited sample size, inadequate length of follow-up, imprecise exposure data, and lack of information on potential confounders. These problems prevent conclusions to be made about causal relationships with RF exposure. However, the statistically significant excess risks of leukemia in amateur radio operators requires further examination.

7.4. ANIMAL EVIDENCE

7.4.1. Extremely Low Frequency Fields

No lifetime animal carcinogen bioassay studies of ELF fields have been reported in the literature. Several studies currently in progress are designed to observe the induction of a carcinogenic response to chronic magnetic field exposures.

7.4.2. Radiofrequency Radiation

Two chronic studies in mice have used unmodulated RF radiation at 800 megahertz (MHz) and 2450 MHz, respectively. Two studies in rats have used pulse modulated 2450 MHz of low power density and pulsed RF of all frequencies from 0 to about 20 MHz of high power density, respectively. One mouse study used pulsed RF radiation of 9270 MHz.

7.4.2.1. Unmodulated Radiofrequency Radiation

For unmodulated RF radiation one of the mouse studies (Szmigeilski et al., 1982) shows that the radiation enhances the growth rate of spontaneous mammary tumors and in a separate experiment enhances the growth rate of skin tumors initiated by a chemical carcinogen, benzo[a]pyrene. In a shorter test (3 months), the same authors showed that the radiation also enhances the growth rate of transplanted lung carcinoma cells, an effect attributed to the lowering of cell-mediated immunity. Unfortunately, histopathology was not reported in the other mouse study (Spalding et al., 1971), so conclusions about carcinogenicity from that study are difficult to make.

The special nature of the response indicates that unmodulated RF radiation might be a promoter or cocarcinogen, since the growth rate of spontaneous breast tumors, BaP-induced skin tumors, and transplanted lung sarcoma cells is enhanced by the radiation. There is a remote possibility that body heating could have contributed to this response, since the

absorbed RF power is estimated to be at least one-half of the basal metabolic rate of the animals.

7.4.2.2. Modulated Radiofrequency Radiation

For modulated RF radiation of relatively low power density [i.e., excluding the high power electromagnetic pulse (EMP) experiment of Baum et al. (1976)], the mouse experiment (Prausnitz and Susskind, 1962) showed a reversible pattern of lymphoma and leukemia which, in serial sacrifices, occurred toward the end of the 14-month exposure period but was not present in animals after a 5-month recovery period. However, the short 4.5-minute daily exposure was intense enough to raise the body core temperature by 3° C, raising the possibility that thermal effects were a contributing factor in the response. The rat study (Guy et al., 1985) showed the induction of benign adrenal medulla pheochromocytomas and a statistically significant increase in carcinomas of all organ and tissue sites. There was also a statistically significant increase in glandular organ carcinomas which was unaccompanied by an increase in the incidence of benign tumors of these sites. Such an increase of tumors of all types in the aggregate without increase of tumors at any one of the sites is regarded as only minimal evidence of a carcinogenic response.

7.5. SUPPORTING EVIDENCE OF CARCINOGENICITY

Section 5.11. presents a summary of the effects of EM fields on a variety of basic biological phenomena relevant in some way to mechanisms of carcinogenesis; that information is not repeated here. ELF fields of relatively high intensity [producing induced body currents on the order of 10 microamperes per square centimeter ($\mu A/cm^2$)] have enhanced DNA synthesis, altered the transcription of DNA into mRNA, altered the molecular weight distribution during protein synthesis, delayed the mitotic cell cycle, induced chromosome aberrations, blocked the action of parathyroid hormone at the site of its plasma membrane receptor, induced enzymes normally active during cell proliferation, inhibited differentiation and stimulated the growth of carcinoma cell lines, inhibited the cytotoxicity of T-lymphocytes (which indicates an impairment of the immune system) in vitro but not in vivo, inhibited the synthesis of melatonin (a hormone that suppresses the growth of several types of tumors), and caused alterations in the binding of calcium to brain tissues. The large variety of exposure conditions and the lack of detail on the geometry of the biological samples in these studies precludes a systematic evaluation of the actual induced currents and field strengths at the tissue and cellular levels

that are causing these effects. In addition, the lack of reproducible results between laboratories limits the interpretation of much of this literature.

Radiofrequency fields modulated at the same ELF frequencies that cause some of the effects noted above also result in the same responses, indicating that the ELF component may be responsible for these effects. Unmodulated RF radiation has not caused any of the effects noted above except for chromosome aberrations. None of the EM fields havecaused gene mutations, sister chromatid exchanges, or DNA damage (as measured by DNA breaks, DNA repair, or differential killing of repair defective organisms) in a large number of studies.

Only three ELF effects have been induced at field strengths comparable to the low environmental exposures at which human cancer has putatively been caused: (1) the calcium efflux from brain tissue preparations using 16-Hz electric and magnetic fields that were perpendicular to each other, (2) calcium efflux from chick brain tissue after exposure of the developing embryo to electric fields, and (3) the inhibition of melatonin synthesis by the pineal gland when a static magnetic field of approximately the strength of the earth's magnetic field is changed through a small angle of rotation. The results of the first experiment are one of several phenomena that show a complex dependence on frequency, intensity, and orientation with respect to the earth's magnetic fields.

In view of all of the laboratory studies referred to in this section, there is reason to believe that the findings of carcinogenicity in humans are biologically plausible. However, the explanation of which of the biological processes is involved and the way in which these processes causally relate to each other and to the induction of malignant tumors is not understood. Most of the effects have been observed at field strengths that are many times higher than the ambient fields which are the putative cause of the childhood cancers in residential situations; as a consequence, many of the candidate mechanisms actually may not be involved in the response to low environmental fields. The same issue of low-dose extrapolation arises in the evaluation of chemical agents.

7.6. INTEGRATED DISCUSSION OF SEPARATE CHAPTERS

The occurrence of cancer in humans exposed to low frequency electric and magnetic fields has been observed under several different conditions in different populations. Residential exposure of children, but not adults, has been associated with leukemia, lymphoma, and brain cancer, and the same sites occur in multiple studies of children. The EM fields involved in these associations have been magnetic fields rather than electric fields, and

their frequency is made up of primarily 60-Hz components but with inevitable high-frequency components introduced by electric motors and the switching of currents on and off. These effects have been observed in children exposed to magnetic fields at or above 2 to 3 mG (0.2 to 0.3 μT). The types of EM-field exposures in the occupational studies are variable according to job category, with some jobs involving pulsed and modulated RF fields as well as 60-Hz power frequency components. It is not possible to rule out the involvement of electric fields in these studies. Exposure to electric fields is extremely variable under ambient conditions and is difficult to define.

There is some, but not well-established, evidence that higher frequency components have different effects than 60-Hz components. Electrical switchyard workers exposed to spark discharges just before blood samples are taken have chromosome aberrations, whereas similar workers with no such exposure do not. Chromosome aberrations have been induced by unmodulated RF fields as well as by ELF fields. A recent preliminary report of an epidemiologic study of telephone workers shows a different effect (rare breast tumors in males) in people working in the “central office,” where switching equipment is typically concentrated, than in cable splicers (leukemia) who presumably are exposed to predominantly 60-Hz power frequencies. Both electric and magnetic fields are more effective in inducing currents in the body if their frequency is higher, so that if induced currents are responsible for these effects, then the higher frequency components are expected to be more effective. If it is true that, as two studies indicate, the father’s occupation in electrical jobs is a factor in the development of leukemia in their children, then the question is raised whether the effect could be transmitted via heritable genetic damage in sperm. This speculative hypothesis needs to be investigated.

Although there are several candidate EM field-induced biological phenomena (discussed in Chapter 5) that could explain how a cancer response is caused in the whole organism by these fields, none of these or any combination of them has been verified experimentally, either in laboratory animals or in humans. Without understanding which combination of these is relevant to the carcinogenic process, it is not possible to hypothesize what aspect of EM-field exposure is responsible for biological effects; i.e., frequency, average peak field strength, duration, time of day, whole-body average versus local critical site, electric versus magnetic fields, orientation with respect to the earth’s static magnetic field. The choice of which aspect of the fields is the most relevant could be based on either knowledge of the correct mechanism of action or on empirical epidemiology correlations, but, given the current lack of information, neither method can serve as a basis for a dose-response analysis.

There are several indications that EM fields might contribute to the induction of cancer via indirect mechanisms, in contrast to a direct mutagenic action of DNA as is the case with nitrosamines, polycyclic aromatic hydrocarbons, or other DNA-alkylating agents.

First, EM fields have not caused gene mutations in any of the large number of experiments carried out with both ELF and RF fields (Section 5.1.3).

Second, there is no indication from the animal studies that RF fields cause a de novo induction of tumors (Section 4.1.2.7). On the contrary, the mouse experiments by Szmigielski et al. (1982) (see Section 4.4) indicate that unmodulated RF radiation acts as a growth stimulator for pre-existing tumors. The same growth-stimulating or promotion characteristics of RF fields could explain the induction of glandular tumors in the Guy et al. (1985) lifetime rat study of modulated RF radiation (Section 4.1.2.7), since many of the glandular tumors in that study had a naturally high spontaneous incidence.

A third factor indicating that there may be multiple causes of carcinogenic action is that 120-Hz pulse-modulated 2450 MHz radiation can act as an initiator of phorbol ester-promoted cell transformation in mouse embryo cell cultures (Section 5.3.3).

Finally, there are possible cancer induction mechanisms mediated by the central nervous system causing neuroendocrine influence on cellular proliferation (Section 5.7.5). These mechanisms involve possible extremely sensitive detection of magnetic fields by the retina (Section 5.10.4) with resulting neural control of pineal melatonin activity, which in turn modulates estrogen and prolactin levels in the blood supply to the breast, prostate, and other hormonally sensitive tissues (Section 5.7.1). Other speculative chains of events could be fabricated from the existing information in this document; this one is mentioned here only as an example that there are many possible explanations, but no verified ones.

In view of these indications, it is likely that if EM fields do contribute to the induction of cancer, the causal relationship will probably turn out to be dependent on many chemical factors and physiological conditions that are currently poorly understood.

There are two issues in the hazard evaluation of chemical carcinogens that are analogous to issues for EM fields. It may be helpful to explore whether the assumptions and conventions developed for chemicals are applicable to the EM fields problem.

One analogy is that EM fields are mixtures consisting of several frequencies, intensities, and combinations of electric and magnetic fields that (for ELF frequencies) occur in arbitrary proportions. One approach to the assessment of chemical mixtures is to identify hazardous components of the mixture and, assuming additivity of components, consider the risk of the mixture to be proportional to the risk of the hazardous components. If this concept were

applied to the EM fields problem, then magnetic fields from 60-Hz power usage in the home would be the only “hazardous component” identified, although there is some indication that occupational exposures of adults to mixed fields may cause the same effect. Laboratory studies under relatively controlled conditions of exposure have not been able to test the additivity assumption for EM-field components or for chemical components except for a few rare cases, but one feels more comfortable with the latter. With chemical agents, the basic phenomenon is ultimately some chemical reaction, which is expected to have additive properties at low enough concentrations, or at least to be monotonic in the sense that more chemical produces a greater effect. With EM fields, however, the ultimate causative interaction between fields and biological systems is unknown, and there is certainly no additivity with RF and ELF fields, or with ELF electric and ELF magnetic fields. The consequence of not being able to add the risks for different exposures is that the effects for each combination must be investigated and assessed separately.

Another analogy is the similarity between the “biologically effective dose” for chemical agents and the critical electrical measure of tissue “dose” which causes the effect for EM fields. For chemical agents the relationship between “administered dose” and “effective dose” has been studied occasionally, but only rarely. In the absence of this information, the default position for chemical agents has been to assume a linear relationship. Then there are several unresolved questions in determining whether the biological effect is proportional to the “effective dose.” These questions arise when, as is usually the case, the mechanism of action is not known. Here again the linearity assumption is made in the absence of knowledge, and the overall default position is that the adverse effect is proportional to the administered dose of the chemical agent. For EM fields, the “tissue doses” could be calculated, typically with great difficulty and uncertainty, but the same type of questions need to be answered about which of these dose metrics are relevant for EM-field exposure. As with chemical agents, the choice of a candidate mechanism of action dictates which tissue dose metric is appropriate, and there could be several mechanisms for each of the administered agents. For EM fields, the default linearity assumption may not be appropriate, basically because there are frequency and intensity “windows” of activity for more than one EM field-induced biological effect, and such “window” interactions cannot be ruled out as contributory to cancer causation. On the other hand, ambient human exposure involves a wide range of static magnetic fields, frequencies, intensities, and intermittent exposures, so that narrow windows of response may not be the dominant practical exposure consideration, and a higher average field may simply increase the probability that a “windowed” condition will occur.

In conclusion, several studies showing leukemia, lymphoma, and cancer of the nervous system in children exposed to magnetic fields from residential 60-Hz electrical power distribution systems, supported by similar findings in adults in several occupational studies also involving electrical power frequency exposures, show a consistent pattern of response that suggests a causal link. Frequency components higher than 60 Hz cannot be ruled out as contributing factors. Evidence from a large number of biological test systems shows that these fields induce biological effects that are consistent with several possible mechanisms of carcinogenesis. However, none of these processes has been experimentally linked to the induction of tumors, either in animals or humans, by EM fields. The particular aspects of exposure to the EM fields that cause these events are not known.

In evaluating the potential for carcinogenicity of chemical agents, the U.S. Environmental Protection Agency has developed an approach that attempts to integrate all of the available information into a summary classification of the overall weight of evidence that the agent is carcinogenic in humans. At this time such a characterization regarding the link between cancer and exposure to EM fields is not appropriate because the basic nature of the interaction between EM fields and biological processes leading to cancer is not understood. For example, if induced electrical currents were the causative factor, then exposure to electric as well as magnetic fields would be important and the effect would be more severe as the frequency increases. But if the direct magnetic field interaction were the critical factor, then the ambient static magnetic field as well as the alternating magnetic field would be critical and the effect may be confined to specific frequencies, resulting in an extremely complicated dose-response relationship. In addition, if they were shown to be causative agents, these fields probably exert their effects via other chemical and environmental factors rather than directly causing events known to be causally related to the carcinogenic process, having the direct property of causing cancer, as with genotoxic chemical agents.

Because of these uncertainties, it would be inappropriate to classify the carcinogenicity of EM fields in the same way as the agency does for chemical carcinogens. As additional studies with more definitive exposure assessment become completed, a better understanding of the nature of the hazard will be gained. With our current understanding we can identify 60 Hz magnetic fields from power lines and perhaps other sources in the home as a possible, but not proven, cause of cancer In people. The absence of key information summarized above makes it difficult to make quantitative estimates of risk. Such quantitative estimates are necessary before judgments about the degree of safety or hazard of a given exposure can be made. This situation indicates the need to continue to evaluate the information from ongoing studies

and to further evaluate the mechanisms of carcinogenic action and the characteristics of exposure that lead to these effects.

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