Chapter 1
Introduction

AN EVALUATION OF THE POSSIBLE RISKS FROM ELECTRIC AND MAGNETIC FIELDS (EMFS) FROM POWER LINES, INTERNAL WIRING, ELECTRICAL OCCUPATIONS, AND APPLIANCES

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FINAL REPORT JUNE 2002

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EXECUTIVE SUMMARY OF THE CALIFORNIA EMF RISK EVALUATION FOR POLICYMAKERS AND THE PUBLIC

WHY AND HOW THE EVALUATION WAS DONE:

On behalf of the California Public Utilities Commission (CPUC), three scientists who work for the California Department of Health Services (DHS) were asked to review the studies about possible health problems from electric and magnetic fields (EMFs) from power lines, wiring in buildings, some jobs, and appliances. The CPUC request for review did not include radio frequency EMFs from cell phones and radio towers. Reviewer 1, Vincent Delpizzo, Ph.D., is a physicist and epidemiologist; Reviewer 2, Raymond Richard Neutra, M.D., Dr.P.H., is a physician epidemiologist; and Reviewer 3, Geraldine Lee, Ph.D., is an epidemiologist with training in genetics. All three have published original research in the EMF area and have followed the field for many years. They were assisted in their reviews by DHS toxicologists, physicians, and epidemiologists.

THE CONCLUSIONS AFTER REVIEWING ALL THE EVIDENCE:

- *To one degree or another, all three of the DHS scientists are inclined to believe that EMFs can cause some degree of increased risk of childhood leukemia, adult brain cancer, Lou Gehrig's Disease, and miscarriage.*
- *They strongly believe that EMFs do <u>not</u> increase the risk of birth defects, or low birth weight.*
- *They strongly believe that EMFs are not universal carcinogens, since there are a number of cancer types that are not associated with EMF exposure.*
- *To one degree or another they are inclined to believe that EMFs do <u>not</u> cause an increased risk of breast cancer, heart disease, Alzheimer's Disease, depression, or symptoms attributed by some to a sensitivity to EMFs. However,*
- *All three scientists had judgments that were "close to the dividing line between believing and not believing" that EMFs cause some degree of increased risk of suicide, or*
- *For adult leukemia, two of the scientists are "close to the dividing line between believing or not believing" and one was "prone to believe" that EMFs cause some degree of increased risk.*

HOW AND WHY THE CONCLUSIONS DIFFER FROM THOSE OF OTHER RECENT REVIEWS:

While there are important differences between the three DHS reviewers' conclusions, the DHS scientists are more inclined to believe that EMF exposure increased the risk of the above health problems than the majority of the members of scientific committees convened to evaluate the scientific literature by the National Institutes of Environmental Health Sciences Working Group (NIEHS) in 1998, the International Agency for Research on Cancer (IARC) in 2001, and the British National Radiological Protection Board (NRPB) in 2001. These other committees all assessed EMFs as a "possible" carcinogen for childhood leukemia. Thus, like the DHS panel, these other three panels were not much swayed by theoretical arguments of physicists that residential EMFs were so weak as to make any biological effect impossible. NIEHS additionally assessed EMFs as a possible carcinogen for adult lymphoid leukemia and NRPB assessed a possible link with Lou Gehrig's Disease. The three DHS scientists differed in that they had a somewhat higher degree of belief that EMF is linked with these three diseases and gave credence to evidence of a link to adult brain cancer and miscarriage that the other panels either didn't consider or characterized as "Inadequate." There are several reasons for these differences. The three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much

support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them.

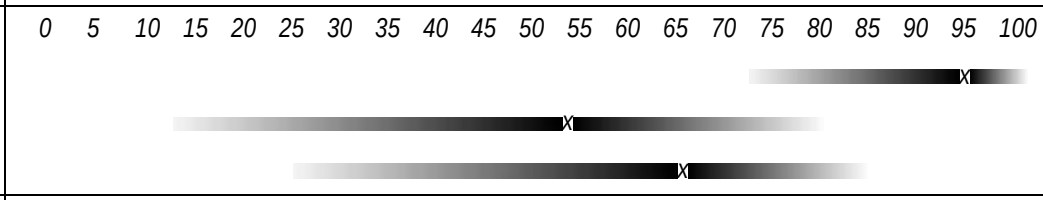
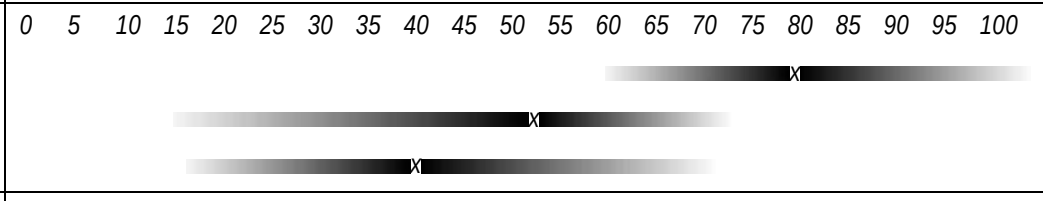
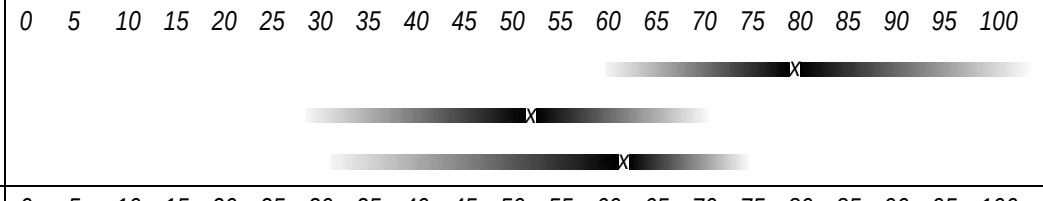
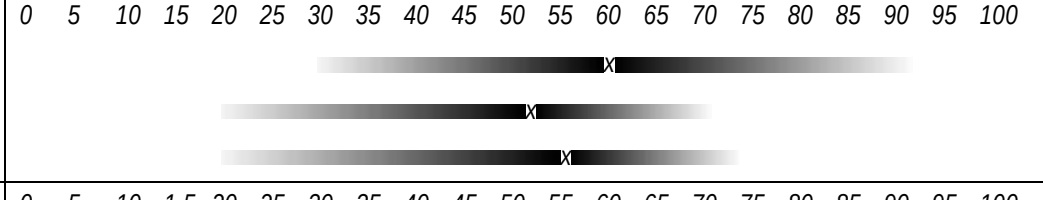
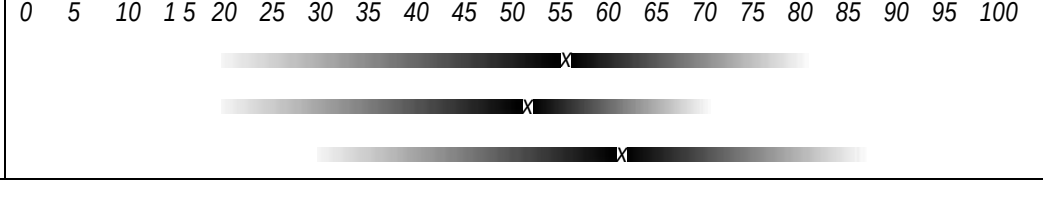
With the exception of miscarriage, which is common, the other diseases for which EMFs may be a contributing cause (childhood leukemia, adult brain cancer, Lou Gehrig's Disease) have low incidence, with rates between 1/100,000 and 1/10,000 a year. Even doubling such rates and accumulating them over a childhood or a lifetime leaves accumulated lifetime risks between 1/1,000 and 1%. Thus the vast majority (99%–99.9%) of highly exposed people would still not contract these diseases. Furthermore, calculations suggest that the fraction of all cases of the above-mentioned conditions that one could attribute to EMFs would be no more than a few percent of the total cases (if any). However, if EMFs do contribute to the cause of these conditions, even the low fractions of attributable cases and the size of accumulated lifetime risk of highly-exposed individuals could be of concern to regulators. Indeed, when deemed a real cause, estimated lifetime risks smaller than these (1/100,000) have triggered regulatory evaluation and, sometimes, actual regulation of chemical agents such as airborne benzene. The uncommon, accumulated high EMF exposures implicated by the evidence about these conditions come from unusual configurations of wiring in walls, grounded plumbing, nearby power lines, and exposure from some jobs in electrical occupations. There are ways to avoid these uncommon accumulated exposures by maintaining a distance from some appliances, changes in home wiring and plumbing, and power lines. However, to put things in perspective, individual decisions about things like buying a house or choosing a jogging route should involve the consideration of certain risks, such as those from traffic, fire, flood, and crime, as well as the uncertain comparable risks from EMFs.

While rodent and chicken egg studies provide little or no support for EMF effects, some studies on early-model higher emitting video display terminals (VDTs) and two new epidemiology studies in humans suggest that EMFs might cause a substantial proportion of miscarriages. Miscarriages are common in any case (about 10 per 100 clinically diagnosed pregnancies) and the theoretical added risk for an EMF-exposed pregnant woman might be an additional 10 per 100 pregnancies according to these two studies. If truly causal this could clearly be of concern to individuals and regulators. However, the type of EMF exposures implicated by these two new epidemiological studies (short, very high exposures) probably come from being within a few inches of appliances and unusual configurations of wiring in walls and grounded plumbing, and only rarely from power lines. Since the majority of people come into contact with non-obvious sources of these fields on a daily basis, it may not be possible to avoid the majority of such exposures in modern life, even if we avoided the obvious sources like some appliances.

Seventy-five percent of the women in the studies had at least one of these brief high exposures during a given day. Even one exposure a day, if experienced regularly during pregnancy, seemed to increase the risk of miscarriage. Nonetheless, the majority of pregnant women with such exposures did NOT miscarry.

FOR PURPOSES OF POLICY ANALYSIS, HOW DID THE THREE SCIENTISTS EXPRESS THEIR JUDGMENT THAT THE ABOVE DEGREES OF RISK MIGHT BE REAL?

The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the range of added personal risks suggested by the epidemiological studies were "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. For the conditions with the most suggestive evidence of EMF risk, the three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIEWER	DEGREE OF CERTAINTY IN SOME AMOUNT OF ADDED PERSONAL RISK
CHILDHOOD LEUKEMIA (REVIEWED THE 19 EPIDEMIOLOGY STUDIES)	1 2 3	
ADULT LEUKEMIA (REVIEWED THE 43 EPIDEMIOLOGY STUDIES)	1 2 3	
ADULT BRAIN CANCER (REVIEWED THE 29 EPIDEMIOLOGY STUDIES)	1 2 3	
LOU GEHRIG'S DISEASE (ALS) (REVIEWED THE 7 EPIDEMIOLOGY STUDIES)	1 2 3	
MISCARRIAGE (REVIEWED THE 10 VDT, 3 ELECTRIC BLANKET, 2 PERSONAL EXPOSURE STUDIES)	1 2 3	

WHAT ASPECT OF THE "EMF MIXTURE" WOULD NEED TO BE MITIGATED (IF ANY)?

A variety of electrical phenomena are present in the vicinity of power lines, in-home wiring, plumbing, and appliances. These include EMFs with a variety of frequencies and orientations, stray currents from contact with grounded plumbing, and air pollution particles charged by electric fields. The epidemiological studies primarily implicate the magnetic fields or something closely correlated with them. Some researchers think that associated high- or low- frequency stray contact currents or charged air pollution particles are the true explanation rather than magnetic fields. The actions one would take to eliminate the fields are not always the same as one would take to eliminate the currents or the charged particles. There are some situations where different costly measures would be required to address the above-mentioned three possible explanations. There are other situations where one or more inexpensive avoidance actions will address all three. This additional uncertainty about what aspect of the mixture might need to be mitigated will thus provide a challenge for policymakers. The California EMF program funded policy projects to explore options that could be pursued in the face of these uncertainties (see www.dhs.ca.gov/ehib/emf). These are available to guide CPUC and other state agencies in policy formation. DHS is making no recommendations at this time.

WHAT RESEARCH GAPS EXIST?

Determining whether stray contact currents or charged air pollution particles are really common enough to explain the epidemiology would be highly policy relevant. Certain suggestive test tube and animal studies await replication. Epidemiology of common conditions which could be studied prospectively, like miscarriage and sudden cardiac death, would be policy relevant and could give a better understanding of what aspect of the EMF mixture might be biologically active.

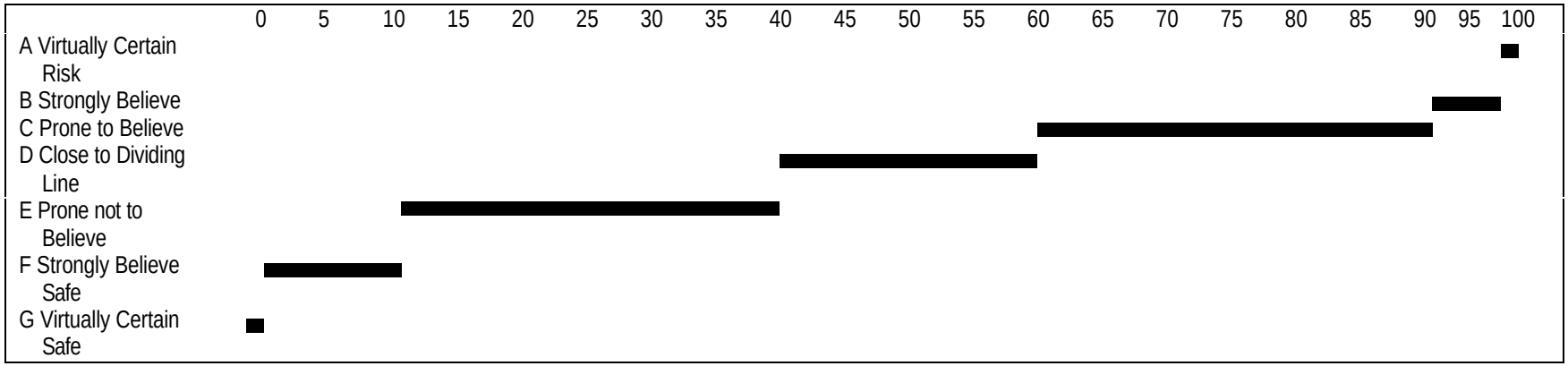
1 WHO DID THE EVALUATION AND WHAT FORM DID THE CONCLUSIONS TAKE?

On behalf of the California Public Utilities Commission (CPUC), three scientists who work for the California Department of Health Services (DHS) were asked to review the studies about possible health problems from electric and magnetic fields (EMFs) from power lines, wiring in buildings, some jobs, and appliances. The CPUC request for review did not include radio frequency EMFs from cell phones and radio towers. Reviewer 1, Vincent Delpizzo, Ph.D., is a physicist and epidemiologist; Reviewer 2, Raymond Richard Neutra, M.D., Dr.P.H., is a physician epidemiologist; and Reviewer 3, Geraldine Lee, Ph.D., is an epidemiologist with training in genetics. All three have published original research in the EMF area and have followed the field for many years. To integrate and extend their body of knowledge, the EMF Program contracted with specialists in biophysics, statistics, and animal experimentation to prepare a background in critical literature review in their respective fields and to make sure that the literature review was up to date through June 2000 (P. Gailey, Ph.D., G. Sherman, Ph.D., W. Rogers, Ph.D., and A. Martin, Ph.D.). The first three were involved with the writing of the 1998 National Institutes of Environmental Health Sciences (NIEHS) report. Furthermore, for each chapter of the review, another DHS epidemiologist or toxicologist was asked to read the original literature and consulted extensively with whichever of the three core reviewers was writing that chapter. This ensured that the writer based his/her evaluation on an understanding of the evidence that was as objective and consistent as possible. All three reviewers worked for the EMF program for at least five years and to some extent they influenced each other's thinking through their constant interaction and the review of each other's chapters. All three did their reviews according to the Risk Evaluation Guidelines (REG) that had been developed earlier and approved by the program's Science Advisory Panel (SAP). The Guidelines specified that the conclusions about any hazard should be done using two systems. The first was developed by the International Agency for Research on Cancer (IARC) and has been used by the NIEHS. It rates an agent as a Definite, Probable, Possible carcinogen or Not a carcinogen, or specifies that the evidence is "Inadequate" to rate the agent. In addition, the California Guidelines specified that in order to accommodate the probability-based computer models of the program's policy projects each of the DHS reviewers would individually assign a number between 0 and 100 to denote their degree of certainty that epidemiological associations between EMFs and certain diseases indicated that EMFs increased the risk of those diseases to some degree. They indicated their best judgement graphically with a little "x" and placed a shaded bar on either side of that "x" to indicate how uncertain they were. The best judgement and the uncertainty ranges could be used in quantitative policy analysis. The Guidelines, which were modified with advice from public comment and the SAP and the DHS reviewers, attached pre-agreed-upon English language phrases to various ranges of this degree of certainty. These are presented below in Table I.

If all three judges had best judgments above 50 out of 100, but that fell in different categories in Table I, judges were said to be "inclined to believe" that EMFs increased the risk of that disease to some degree.

TABLE I. EVERYDAY ENGLISH PHRASES TO DESCRIBE DEGREES OF CERTAINTY OF CAUSALITY (GRAPH ILLUSTRATES THE RANGE OF CERTAINTY NUMBERS TO WHICH THE PHRASES PERTAIN)

ARE THE HIGHEST EMFS AT HOME OR AT WORK SAFE, OR DO HIGH EMFS INCREASE THE RISK OF ..... TO A DEGREE DETECTABLE BY EPIDEMIOLOGY?	DEGREE OF CERTAINTY ON A SCALE OF 1 TO 100
Virtually certain that they increase the risk to some degree	>99.5
Strongly believe that they increase the risk to some degree	90 to 99.5
Prone to believe that they increase the risk to some degree	60 to 90
Close to the dividing line between believing or not believing that EMFs increase the risk to some degree	40 to 60
Prone to believe that they do not increase the risk to any degree	10 to 40
Strongly believe that they do not increase the risk to any degree	0.5 to 10
Virtually certain that they do not increase the risk to any degree	< 0.5



2 A SUMMARY OF WHAT HAS CHANGED SINCE THE CALIFORNIA EMF PROGRAM WAS FIRST PROPOSED IN THE EARLY 1990S

Between the time CPUC mandated a targeted California research program in 1993 to the time of this writing, considerable information has accumulated. In addition, three expert panels, the NIEHS Working Group (Portier & Wolfe, 1998), the IARC (IARC, 2001), and the British National Radiological Protection Board (NRPB, 2001b) have indicated that EMFs are a possible cause of childhood leukemia.

Biophysics: Biophysical arguments based on physical principles and simplified biological models have produced lower and lower predictions as to what magnetic field intensities theoretically would be capable of producing biological effects. Nevertheless, theoretical modeling still would claim that most residential and occupational epidemiological results are "impossible" (Weaver et al., 1998). It would also claim that bioeffects from magnetic field experiments using intensities less than 100 mG* are "impossible" (Adair, 1999). A milliGauss (mG) is a commonly used measure of magnetic field strength. An average living room would have a 0.7 mG field. The standard international unit is a microTesla (μT). One μT equals 10 mG. Both units appear in this document. Those who adhere to these biophysical theories still discount the relevance of experimental results at higher intensities because of this "impossibility" threshold and would require robust bioeffect laboratory results from ambient levels of exposure. This is an unusual burden of proof since ambient levels of other pollutants often do not produce effects large enough to see in the laboratory. It should be noted that the majority of panelists at IARC, NIEHS, and NRPB who declared EMFs as "possible" carcinogens obviously did not accept some physicists arguments that bioeffects from high-end residential exposures were "impossible."

Mechanistic Research: EMFs, particularly those above 1000 mG, have been shown to have a number of physiological effects on cells (Portier & Wolfe, 1998), but the physical induction mechanisms of these effects are not clearly understood. No consensus has arisen on a mechanistic explanation of how the various epidemiological associations might have occurred. Repeated studies of the effects of pulsed and non-pulsed EMFs below 100 mG on chick embryos, in several laboratories, have continued to show "non-robust" effects (Martin, 1988), (Berman et al., 1990), (Martin, 1992), (Moses & Martin, 1992), (Moses & Martin, 1993), (Martin & Moses, 1995), (Litovitz et al., 1994), (Farrell et al., 1997a), (Farrell et al., 1997b), (Leal et al., 1989), (Chacon et al., 1990), (Ubeda et al., 1994), (Koch & Koch, 1991), (Singh & et al., 1991), (Espinar et al., 1997), (Blackman et al., 1988), (Yip et al., 1994a), (Yip et al., 1994b), (Coulton & Barker, 1991), (Youbicier-Simo et al., 1997), (Piera et al., 1992), (Pafkova & Jerabek, 1994), (Pafkova, Tejnorova & Jerabek, 1994), (Pafkova et al., 1996), (Veicsteinas et al., 1996). A statistically significant effect is said to be "non-robust" when its size is not greater than the differences between control groups in various experiments. Several independent researchers (Liburdy et al., 1993), (Blackman, Benane & House, 2001), and (Ishido, Nitta & Kabuto, 2001) have published studies on the effect of low intensity (12 mG, 60 Hertz) magnetic fields on the ability of melatonin to inhibit cancer cell proliferation in vitro. Thus, there are some studies that, while not universally accepted, purport to show biological effects at EMF intensities declared by biophysicists to be incapable of producing such effects.

Animal Pathology: A large number of animal pathology studies have been carried out that tested a few aspects of the EMF mixture and, with some exceptions, did not show a carcinogenic, reproductive, or immunological effect (Portier & Wolfe, 1998). This has led some scientists to conclude that EMFs are probably safe.

Two laboratories in the former Soviet Union (Beniashvili, Bilanishvili & Menabde, 1991), (Anisimov et al., 1996) and one in Germany (Loscher et al., 1993), (Mevissen, Lerchl & Loscher, 1996a) reported co-promotional effects of magnetic fields on the occurrence of breast tumors in rats, though this result did not recur in two experiments in the United States (Anderson et al., 1999), (Boorman et al., 1999a) that partially replicated the conditions in the German experiments.

Epidemiology: Epidemiological studies on workers and children have tentatively implicated a wider range of diseases than the leukemia and brain cancer that dominated discussion in the early 1980s and 1990s (Portier & Wolfe, 1998). Published statistical summaries of the body of epidemiological evidence have suggested that chance is an unlikely explanation for the associations seen for childhood leukemia (Greenland et al., 2000), (Ahlbom et al., 2000), adult leukemia (Kheifets et al., 1997a), adult brain cancer (Kheifets, 2001), male breast cancer (Erren, 2001), and Amyotrophic Lateral Sclerosis (Ahlbom, 2001). This leaves bias, confounding, or EMF causality as alternative explanations. (See pp 21-22 below for definitions.) Parts of this evidence have convinced the NIEHS, the IARC, and the NRPB that EMFs are a **possible** carcinogen.

For childhood leukemia, the association now seems more consistent with measured 30-300 Hz magnetic fields than with proximity to power lines (Greenland et al.,

* A milligauss (mG) is a measure of magnetic field intensity. A typical living room measures about 0.7 mG. The average exposure during the day of a typical white-collar worker would be around 1 mG, a utility worker exposed to high fields during the day might average around 7 mG, while an electric train operator's exposure might average around 100 mG.

2000). Furthermore, alternative explanations of the associations, such as traffic and social class, seem much less likely (Reynolds et al., 2001), (Langholz, 2001). The study of Linet et al. on childhood leukemia (Linet et al., 1997) was originally and prominently interpreted as showing no effect. It has now been shown to contribute important support in pooled analyses that indicate that the association between the highest exposures to EMF and childhood leukemia are unlikely to be due to chance (Greenland et al., 2000).

An epidemiological literature is developing that associates magnetic fields with diseases and conditions that are more common than cancer, such as sudden cardiac death, dementia, suicide (NIEHS, Portier & Wolf, 1998), and spontaneous abortion (Li et al., 2002), (Lee et al., 2002). From a cost/benefit perspective, the confirmation of the associations with these more common diseases would have greater utilitarian policy implications (Florig, 2001) than the confirmation of EMF associations with rare diseases, such as childhood cancer or Lou Gehrig's Disease (amyotrophic lateral sclerosis).

Exposure: A number of epidemiological studies and exposure surveys have given a significantly better description of the range of exposures to some aspects of the EMF mixture, both in the occupational and in the general environment (Portier & Wolfe, 1998), (Li et al., 2002), (Lee et al., 2002), (Zaffanella & Kalton, 1998), (Zaffanella & Hooper, 2000). It has become clear that the 24-hour average of the minute-by-minute 50-60 Hz magnetic field exposures is primarily influenced by stray ground currents, internal wiring, and the power grid rather than by appliances. Maximum fields (the highest exposure during the day) are probably contributed by use of appliances, electrical transportation, or passing briefly by internal wires, current-bearing plumbing, or very close to above or below ground power lines.

Which Aspects of the "EMF Mixture" Might Be Bioactive?: As the decade of the 1990s began, a few childhood leukemia studies suggested that associations were stronger between leukemia and proximity to power lines than between the disease and measured fields (NAS et al., 1997). With more studies, this pattern has disappeared (Greenland et al., 2000). The earlier impression led to investigations of correlates with power lines and measured magnetic fields. Resonance between the static magnetic field of the earth and alternating 60 Hz fields was evaluated, as were transient changes in magnetic field, as potential explanations for the epidemiology. As indicated on page 32, the results do not strongly implicate these aspects of the EMF mixture (Kaune et al., 2002).

A new hypothesis has arisen (Kavet et al., 2000), (Dawson et al., 2001). It proposes that contact currents from low frequency voltages, and not exposure to magnetic fields, might explain some of the epidemiological associations. Others (Graham and Ludquist personal communication, 2001) suggest that the high frequency components of these currents are bioactive. In occupational settings, micro-shocks have been invoked to explain the persistent association between magnetic field exposure and ALS (NRPB, 2001b), (Ahlbom, 2001). These hypotheses have not yet been tested.

Scattered associations with electric fields have been reported (Coghill, Steward & Phillips, 1996), (Miller et al., 1996), but this association has not been consistent. A hypothesis and some evidence have developed with regard to electric fields near transmission lines and their effects on the charge and concentration of particulate air pollutants (Henshaw et al., 1996). If true, this would suggest that one should bury lines to block their electric fields and that rephasing would not be effective. However, this hypothesis has not been sufficiently supported by evidence.

Two recent studies of miscarriage and personal EMF exposure suggest that maximum fields or average change between consecutive exposures may convey risk (Li et al., 2002), (Lee et al., 2002). Studies of the effect of personal exposure on urinary melatonin metabolites in utility workers have suggested the possibility that the rate of change of the magnetic field may be bioactive (Burch et al., 1998). This, too, would have implications for any mitigation. One laboratory has reported that the super-imposition of random EMF noise in the laboratory can block the effects of orderly low-frequency magnetic fields (Litovitz et al., 1994). No replication of this study has been attempted yet.

Radio Frequency Research: Public concern and research on the question of radio frequency and low-frequency-modulated radio frequency have increased in the last decade. Although this area may turn out to be relevant to the low frequency literature reviewed here, exploration of it was beyond the resources, mandate, and expertise of the review team.

Funding: Funding for EMF research in the United States has dropped from the levels in the late 1980s. The Department of Energy research program of $10 million per year has been eliminated and the amount of resources devoted to EMF research by the utility industry and the Electric Power Research Institute has decreased from $10 million per year at its peak to $3.5 million in 2000. The National Institutes of Health have no special study section with EMF experts to review research proposals in this area, so proposals are judged by experts in other areas and compete for scarce research dollars.

3 How to Read This Document

This document is not just a summary of the facts from the vast literature on the possible health effects of extremely low frequency (ELF) electric and magnetic fields. Instead the bulk of the main document presents a much more detailed rationale for the conclusions drawn, and the evidence is summarized in graphical and tabular form.

In preparation for this evaluation, the California EMF Program held a two-day epidemiology workshop to discuss some of the most relevant epidemiological findings and methodological issues. The proceedings of that workshop, which were pivotal to some of the conclusions reported here, were published in a peer-reviewed Supplement (5) of the journal *Bioelectromagnetics* on January 22, 2001.

4 What is New in this Evaluation

New Evidence

There have been many adequate reviews, including some very recent ones (NAS et al., 1997), (Portier & Wolfe, 1998), (IARC, 2001). The NIEHS review, in particular, was regarded as the starting point for this evaluation. The NIEHS Working Group carried out their evaluation in June 1998. Several important studies have been published between the conclusion of the NIEHS Working Group review and this evaluation, including three major studies on childhood leukemia (Green, Miller & Agnew, 1999b), (Green et al., 1999a), (McBride et al., 1999), (UKCSS, 1999). The deadline for including studies in our evaluation was June 24, 2000. This is later than the deadline originally mentioned in the Risk Evaluation Guidelines (REGs). Since the DHS evaluation began later than initially envisaged, the reviewers felt that it was unwise to disregard recently published, and possibly important, studies simply to observe a previously set but otherwise arbitrary date. Only one large study (van Wijngaarden et al., 2000) that dealt with suicide emerged during this extended deadline period.

In addition, the reviewers considered studies sponsored by the California EMF Program (Li et al., 2002), (Lee et al., 2002) and in the Epidemiology Workshop satisfying the criteria for inclusion in this evaluation, as specified in the Guidelines. In this final draft, the DHS scientists also discuss articles that were brought to their attention during the public comment period.

The document has features that were not present in the NIEHS document. One of these—presenting a graded degree of certainty of causality—was described above. Also discussed are the aspects that make up the EMF mixture that characterizes the exposure of persons who come near the power grid, the internal wiring of houses, and common household appliances. These are described in Chapter 3. The reviewers stress the notion of "mixture" because different aspects of EMF exposure (e.g., 60-cycle magnetic fields and high-frequency transients) would require different actions for abatement. For each of the diseases considered, there are explicit discussions about whether the epidemiological associations observed, if real, would convey a risk from lifetime exposure that would be of regulatory interest. This is a parameter of interest to the social justice policy framework, which focuses on the individual risks of the most highly exposed. In Table IX, the baseline mortality for conditions considered possibly associated with EMFs are discussed. The reviewers ask if the attributable burden of mortality from even a very small fraction of that baseline would be of regulatory interest when compared to the mortality burden thought to be avoided by regulation of other agents. The attributable burdens of mortality or morbidity are parameters of interest to the utilitarian policy framework, which aims at the most good for the most people at the least cost. The document also attends to any evidence suggesting inequitable exposure or vulnerability to EMFs. This is relevant to the environmental justice policy framework, which is concerned with unfair distributions of risk.

Each health condition considered had at least two epidemiological studies in which there was a statistical association with some surrogate for EMF exposure. The list of conditions is similar to that discussed in the NIEHS document and includes

- Adult and childhood leukemia
- Adult and childhood brain cancer
- Male and female breast cancer
- EMF as a "broad spectrum" carcinogen for all cancers
- Miscarriage
- Other reproductive and developmental conditions
- Amyotrophic lateral sclerosis (Lou Gehrig's Disease)
- Alzheimer's disease
- Acute myocardial infarction

- Suicide
- Other adverse non-cancer health outcomes (depression, electrical sensitivity)

5 QUALITATIVE BAYES OR DEGREE OF CERTAINTY APPROACH TO EVALUATION

The DHS scientists found the usual process of describing the pattern of evidence in some detail and then expressing an opinion (without explaining the rationale for that opinion) to be insufficiently transparent. Accordingly, they supplement the usual IARC procedure with an additional form of presentation and an additional form of judging whether EMFs are a cause of disease. The following table shows the questions that were systematically addressed. For definitions of epidemiological terms in the table see pages 20-22 (Sections 12.1.1-12.1.3).

TABLE II. QUESTIONS RELEVANT TO DEVELOPING A DEGREE OF CERTAINTY ABOUT CAUSALITY

EXPLANATIONS OF A STATISTICAL ASSOCIATION OTHER THAN A CAUSAL ONE
Chance: How likely is it that the combined association from all the studies of EMF and disease is due to chance alone?
*Bias: How convinced are the reviewers that EMFs rather than a study flaw that can be **specified and demonstrated** caused this evidentiary pattern? If no specified and demonstrated bias explains it, how convinced are they that EMFs caused these associations rather than **unspecified** flaws?*
*Confounding: How convinced are the reviewers that these disease associations are due to EMFs rather than to another **specified and demonstrated** risk factor associated with EMF exposure? If not due to a specified risk factor, how convinced are they that they are due to EMFs rather than to **unspecified** risk factors?*
*Combined effect: How convinced are the reviewers that these disease associations are due to EMFs rather than to a combined effect of chance and specified or **unspecified** sources of bias and confounders?*
ATTRIBUTES SIMILAR TO HILL'S (HILL, 1965) THAT ARE SOMETIMES USED BY EPIDEMIOLOGISTS TO EVALUATE THE CREDIBILITY OF A HYPOTHESIS WHEN NO DIRECT EVIDENCE OF CONFOUNDING OR BIAS EXISTS
Strength of association: How likely is it that the meta-analytic association is strong enough to be causal rather than due to unspecified minor study flaws or confounders?
Consistency: Do most of the studies suggest some added risk from EMFs? How likely is it that the proportion of studies with risk ratios above or below 1.0 arose from chance alone?
Homogeneity: If a large proportion of the studies have risk ratios that are either above or below 1.0, is their magnitude similar (homogeneous) or is the size of the observed effect quite variable (heterogeneous)?
Dose response: How clear is it that disease risk increases steadily with dose? What would be expected under causality? Under chance, bias, or confounding?
Coherence/Visibility: How coherent is the story told by the pattern of associations within studies? If a surrogate measure shows an association, does a better measurement strengthen that association? Is the association stronger in groups where it is predicted? What would be expected under causality? Under chance, bias, or confounding? How convinced are the reviewers that the magnitude of epidemiological results is consistent with temporal or geographic trends?
Experimental evidence: How convincing are the experimental pathology studies supporting the epidemiological evidence? What would be expected under causality, bias, chance, or confounding?
Plausibility: How convincing is the mechanistic research on plausible biological mechanisms leading from exposure to this disease? What would be expected under causality, chance, bias, or confounding? How influential are other experimental studies (both in vivo and in vitro) that speak to the ability of EMFs to produce effects at low dose?
Analogy: How good an analogy can the reviewers find with similar agents that have been shown to lead to similar diseases? What would be expected under causality, chance, bias, or confounding?
Temporality: How convinced are the reviewers that EMF exposure precedes onset of disease and that disease status did not lead to a change in exposure?
Specificity and other disease associations: How predominantly are EMFs associated with one disease or subtypes of several diseases? What would the reviewers expect under causality, chance, bias, or confounding? How much is their confidence in EMF causality for disease X influenced by their confidence that EMFs cause disease Y?

As a heuristic device, and following Huticinson and Lane (Hutchinson & Lane, 1980), the REGs suggested that these questions about the pattern of evidence be posed so that one could say the pattern is more likely under the hypothesis that EMFs contributed to the cause of that health condition or more likely under the hypothesis that chance, bias, or confounding produced the pattern. This allows the reviewers to provide the reader a rationale for the relative weight given mechanistic, animal pathology, and epidemiological evidence and to understand which parts of the evidence suggest causality and which speak against causality.

The DHS reviewers coined the term "Qualitative Bayes Approach" to characterize a form of verbally justifying judgments about hazard that paid attention to the insights of Thomas Bayes, an 18th-century mathematician. His insights would suggest starting with some initial degree of certainty that any given agent is capable of being harmful based on knowledge about agents in general. Evidence is then accumulated on this specific agent and this changes the degree of suspicion or certainty. Imagine a prehistoric hunter deciding whether to try out some jungle fruit he has never seen before. He has an initial degree of suspicion high enough that he does not partake right away. He takes some fruit home and feeds it successively to several types of captured birds. As each species seems to survive, it seems less and less likely that the fruit would be harmful to humans. But since the leaves of the tree bearing that fruit resemble those from a tree that bears a poisonous fruit (causing the initial suspicion to be very high) the hunter's specific experiments might still leave him fairly suspicious and lead him to cruelly feed the fruit to a captive from another tribe. Only if the captive survived would his initial suspicions be allayed. This example illustrates Thomas Bayes's two key insights. As evidence builds we update our degree of certainty of harm, but, at any point in time, that updated degree of certainty also depends on how suspicious we were initially. This idea is expressed mathematically by a simple formula. The first term of the Bayes formula is the "prior odds," that is, the odds that a given hypothesis is thought to merit *a priori*, before examining the evidence. In this document it is called the prior because it is not based on subsequent research.

The second term, the "likelihood ratio," is a multiplier, calculated (or, in this case, qualitatively discussed) after scientific evidence has been collected and evaluated. The term "likelihood ratio" is most properly restricted to the case where one compares the statistical likelihood of a result under one specific hypothesis relative to that under another hypothesis, usually the null. It expresses the likelihood of the observed pattern of evidence if EMFs do indeed cause disease, divided by the likelihood of that pattern if EMFs do not cause disease. The third term, the "posterior," is the product of the first two and represents the odds of the risk being true after the prior has been modified by our evaluation of the evidence.

Because of the difficulty of translating complex evidence into numbers, we only use the ideas behind the formula as a way of explaining how certain or uncertain we were to begin with and to explain the basis for the weights we gave a particular stream of evidence in order to update our degree of certainty. The Bayesian perspective used by the California reviewers recognizes that a reassuring pattern of evidence from a stream of evidence that often misses a harmful effect does not allay one's suspicion much, even though an alarming pattern of evidence from that same stream of evidence might increase suspicion a lot. Going back to the hunter-gatherer example: if birds sometimes survive eating fruits that are lethal to humans, then reassuring evidence from bird experiments would not allay suspicion as much as the death of the birds after eating the fruit would increase our suspicion. In the terminology of probability, the relative likelihood conveyed by a positive or negative result depends on the false-positive rate and false-negative rate characteristic of that stream of evidence. The mathematical basis for this insight is discussed in the REGs (www.dhs.ca.gov/ehib/emf). It resulted in realizing that any stream of evidence, judged by the extent to which it usually produced false-positive and/or false-negative results, could be classified into four possible types: 1) capable of strengthening OR weakening one's certainty, 2) predominantly capable of strengthening certainty (like the bird feeding example given above), 3) predominantly capable of weakening certainty and, 4) uninformative, neither capable of strengthening nor weakening one's confidence. While this structured discussion helped organize the reviewers' judgments, it did not involve a mathematical combination of weights as would be the case in a quantitative Bayes evaluation. It should be noted that the Hill's attributes are like the bird-feeding example. If they are present they strengthen confidence, but if they are absent, confidence falls only a little.

The DHS reviewers considered the following streams of evidence: biophysical evidence about the physical induction mechanism, research into physiological and pathophysiological mechanisms, research into animal pathology and epidemiological evidence. Clearly if all these streams of evidence were non-supportive, one's degree of certainty would fall, and if they were all supportive it would rise. If some streams of evidence are unsupportive and some are supportive, the DHS reviewers considered the inherent proclivity of each stream of evidence to give false positive or false negative results as a guide to what weight its results should be accorded. If apparently supportive evidence is shown clearly to be due to artifacts, this would lower the degree of certainty.

In the "Qualitative Bayes Approach" the DHS reviewers elicited their own expert judgment about the *a priori* (initial) probability of hazard after a special training session on how to avoid common errors of probabilistic estimation. It was important

to be explicit about the prior probability because some physicists were arguing on the basis of physical theory applied to simplified biological models of the cell, that any biological effect from residential EMFs was impossible and thus had a vanishingly small initial credibility. This meant that they would require extraordinarily strong specific evidence to change their initial impression. Previous risk assessments have not explicitly considered this issue.

The discussion then turns to the patterns of specific EMF evidence in biophysical, mechanistic, animal pathology, and epidemiological streams of evidence. Obviously, if all four streams of evidence pointed toward or away from an EMF effect, the reviewers' job would be easy. But what if some streams of evidence are supportive and some are not supportive? What weight should be given each stream of evidence? It was in the effort to address this problem that discussions of the inherent proclivity to give false positive and negative results came into play. This discussion was guided by a series of pre-agreed-upon questions described in the table above. The discussion included pro, con, and summary arguments. An example of such arguments are presented in the next table.

TABLE III. EXAMPLE OF PRO, CON, AND SUMMARY ARGUMENT

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all the associations (relative risks) are above 1.00 or statistically significant.	(F1) The narrow confidence limits in the meta-analytic summaries and the low likelihood of this pattern of evidence by chance leans away from chance as an explanation.	(C1) A non-chance explanation must be sought.

Considering this kind of structured discussion helped organize the reviewers' judgments, after he/she weighed all the information in the usual way, although it did not involve a mathematical combination of weights as would be the case in a quantitative Bayes evaluation. After consideration of this carefully structured discussion of the evidence (considering how much more—or less—likely the pattern of evidence would be if the risk hypothesis were true compared to the likelihood of that evidence if EMFs were safe), the reviewers expressed an expert judgment on the posterior probability of a causal relationship.

6 QUALITATIVE BAYES RISK EVALUATION COMPARED TO TRADITIONAL AND QUANTITATIVE BAYES RISK EVALUATIONS

The traditional risk assessment has a section in which a judgment is given as to whether the agent being evaluated is capable of causing cancer or some other adverse health effect. This is called the "hazard identification." The typical presentation is heavy in describing the relevant evidence and rather light in explaining the rationale for the conclusion. Often the weight, given mechanistic, animal pathology, and epidemiological streams of evidence, depends on a review panel's interpretation of adjectives which best describe the pattern of evidence. For example, is the pattern of evidence "sufficient" or should it be called "limited"? Can confounding and bias be "reasonably" discounted? Then there are pre-agreed-upon rules for combining the streams of evidence. Limited animal evidence plus limited epidemiological evidence results in one rank, sufficient animal evidence plus limited epidemiological evidence leads to another rank, and so forth. The combinatorial rules are straightforward, but the rationale for deciding that a stream of evidence is "limited" is not clearly defined and is subjective.

A completely quantitative Bayesian approach of the sort proposed by McColl et al. (McColl et al., 1996) or by Lindley (Lindley, 2000), would require assigning many quantitative parameters to a complex Bayesian Net model which would mathematically combine the subjectively assigned parameters to produce a posterior degree of certainty of causality. To the reviewers' knowledge, this kind of model has never been applied to any environmental agent. How experts such as physicians, combine streams of evidence to make judgements about causality has

been of great practical interest. As pointed out by Shortliffe (Shortliffe et al., 2001) there have been two general approaches. One is to infer statistically (Holman, Arnold-Reed & Klerk, 2001) or find by interview what rules experts usually employ. This assumes that the rules of thumb that experts use are optimal. As Holman (Holman et al., 2001) points out, however, this may not always be the case. The other approach is to use information to indicate what weights ought to be used. An example of this was de Dombal's (de Dombal et al., 1972) work using a Bayesian approach to diagnosing the acute abdomen on the basis of the prior probability of patients with certain diagnoses showing up in emergency rooms, and the relative likelihood of elements of medical history, physical signs, and laboratory test results in the several possible diagnoses. According to Shortliffe (Shortliffe et al., 2001), neither approach has so far been reduced to computer applications that render the combining of streams of evidence a cut and dried uncontroversial activity. It should be expected then, that the analogous task of risk evaluation will still rely on professional judgement and will not be free of controversy. For this reason, our stakeholders urged us to opt for transparency rather than computational elegance in our risk evaluation guidelines. In response to the third draft, the Electric Power Research Institute contracted with Professor Sander Greenland in late 2001 to prepare a quantitative Bayesian model based on the epidemiological evidence for childhood leukemia. Since his will be the only extant quantitative Bayesian epidemiological analysis, the reviewers contrast its proposed approach to their own. His model will provide a posterior dose-response curve based on a prior dose-response curve, the pooled epidemiological data, and prior estimates of selection bias and non-differential measurement bias. The all-important biophysical, mechanistic, and animal pathology streams of evidence will not be part of Greenland's model, although they could influence the prior dose-response curve in a subjective way. Calculations from Greenland's model would allow one to provide a probability that the posterior slope of the dose-response curve is not flat, that is, that there is some causal effect.

The following table compares the Qualitative Bayes evaluation to the traditional and to Greenland's Quantitative Bayes approach to risk evaluation as to a number of characteristics.

TABLE IV. COMPARISON OF USUAL RISK ASSESSMENT METHOD TO QUALITATIVE AND QUANTITATIVE BAYES METHODS

CHARACTERISTIC	USUAL METHOD	QUAL. BAYES	QUANT. BAYES
Evaluates all streams of evidence?	Sometimes	Yes	Focuses on epidemiology, other streams influence prior
Elicits prior probability?	No	Yes	Prior dose-response curve
Compares likelihood of each element of the evidence under the hazard and non-hazard hypotheses?	No	Qualitatively	Quantitatively with many of the parameters subjectively elicited
Pro, con, and summary arguments to make rationale transparent?	No, most risk assessments are skimpy in justifying hazard categories assigned	Yes	Not unless a supplementary document were to accompany the model
Combines relative likelihoods mathematically to derive posterior?	No	No	Yes, but in some versions non-epidemiol. evidence is folded into the prior subjectively
Elicits an expert posterior probability after considering all	No	Yes	No

CHARACTERISTIC	USUAL METHOD	QUAL. BAYES	QUANT. BAYES
elements of the evidence?			
Displays judgments of various judges separately?	Usually strives for semblance of consensus	Yes	Technically possible for different experts to elicit their own parameters
Frames intermediate degrees of certainty as "not a proven hazard?"	Often	No, reveals posterior probability	No, reveals posterior probability

Both the Qualitative Bayes and the Quantitative Bayes evaluations can provide a posterior degree of certainty that the epidemiological associations are causal, which, if in the range from 10 to 90 out of 100, will not seem trivial to the general public and will stimulate policy discussions. The statements, "possible," "there is no proven hazard," or "there is no consistent evidence," often used for this range of degrees of confidence, will not stimulate such discussions. Thus, both the Qualitative Bayes and Quantitative Bayes methods pose risk communication "problems" for those who believe that society should not begin policy discussions until most scientists are virtually certain that a hazard exists. The traditional hazard identifications would pose the same "problem" if they routinely used more nuanced categories of hazard assessment that distinguished between, say, a certainty level of 11/100 and one of 89/100. As now framed they pose a risk communication "problem" for those who believe that policy discussions should begin even before a hazard is firmly established.

Compared to traditional qualitative evaluations, the Qualitative Bayesian approach makes the evaluation more transparent, but it still accommodates different opinions. The DHS reviewers have no doubt that critics of their conclusions could use the Qualitative Bayes format to make their points. Some of the physicists who believe that they have a theory to prove that no residential EMF effect is possible would use priors so low that their posterior degrees of certainty would be low as well; the toxicologists who believe reassuring animal tests prove that EMFs are safe would make a case that the animal study results pull down their degree of certainty of a hazard to a level below their initial degree of certainty. In a contentious area such as EMFs, the reviewers doubt very much that any of the three styles of risk evaluation discussed in the table would force a consensus among subject matter experts who weigh and interpret the several streams of evidence differently. Even in the Quantitative Bayes model experts will use different priors and will elicit different subjective relative likelihood parameters for items like bias and confounding, for which there is no direct evidence. In the traditional method, experts will disagree on whether a stream of evidence warrants the adjective "limited" or "sufficient," and in the Qualitative Bayes approach experts will disagree on "how much more likely" the pattern of evidence is under the causal and non-causal hypotheses. But the reasons for these different judgments will be more transparent in the Qualitative Bayes style of risk evaluation and we believe that this is desirable in controversial areas.

7 How Credible Was the EMF Hypothesis to Begin With?

The three reviewers first considered the initial credibility of the hypothesis (before any targeted research had been done) that everyday residential and electrical occupational EMF exposures could influence the risk of disease. Like the majority of reviewers at IARC and NIEHS, the DHS reviewers were swayed only a little by theoretical biophysical arguments that such influences were impossible, since these arguments depend on assumptions about biological systems that may or may not be sophisticated enough to reflect reality and rule out an effect. The reviewers acknowledged, though, that this was probably the only agent they had encountered where these kinds of "impossibility" arguments had been made. However, a better understanding of biology (and not any change in physics theory) could conceivably explain how an organism could detect and be affected by the spatially and temporally coherent EMFs or other aspects of the EMF mixture emanating from power lines and appliances.

The reviewers considered the proportion of chemical agents that had tested positively for carcinogenicity at high doses (about 20%) as one benchmark (Fung et al., 1993). They also considered the fluctuation of disease rates starting in the late 19th century when electricity began to spread gradually from wealthy urban areas to other parts of the world. Any changes could put *a priori* bounds on the size and direction of any EMF effect. Milham (Milham & Ossiander, 2001) drew attention to

something that Court Brown and Doll (Brown & Doll, 1961) had pointed out more than 40 years ago, that an increased risk of leukemia mortality for 2- to 4-year-old children first appeared in the 1920s and increased in intensity in the 1940s. Thus some factor(s) (perhaps electricity, perhaps accuracy in diagnosis), in those modernized locations caused the registration of toddler leukemia deaths to increase threefold. The evidence from Court Brown, Doll, and others that childhood leukemia mortality registration had indeed increased during the early 20th century increased the prior probability of a moderately large EMF effect, at least for childhood leukemia. Since similar trends were not reported for other conditions, it was considered that modest protective or harmful effects from rare high exposures were compatible with the data.

The three DHS reviewers underwent special training in probability elicitation. They then judged that EMF effects were about as probable or a little less probable to influence the risk of disease as any man-made environmental pollutant taken at random. The three reviewers gave probabilities ranging from 5% to 12% *a priori*, that EMFs at or above the 95th percentile of typical residential US exposures would produce effects detectable by epidemiologists when compared to the 1st percentile of residential exposure or below.

8 The Weight Accorded Biophysical Arguments that Bioeffects from Residential and Most Occupational Fields were Impossible or that No Physical Induction Mechanism had Been Elucidated

While the reviewers do not doubt established physical theory, they believe that its application to simplified biological models is not sufficiently convincing to prove the impossibility of epidemiological or laboratory observations. However, the argument that environmental fields have very little energy lowered the prior probability that EMFs might have biological or pathological effects. The fact that there was no mechanistic explanation for how residential-level electric or magnetic fields might cause chemical or cellular changes, that there was no recognized molecule or organ capable of reacting or detecting residential magnetic fields, and the fact that recognized physiological effects of pulsed and very high magnetic fields did not have a well-understood physical induction mechanism did not decrease the updated degree of confidence much. This is because many known physiological and pathological effects go for a long time without a full mechanistic understanding.

9 The Weight Accorded Experimental Evidence On Any Pathophysiological Mechanisms by Which EMF Might Work

It has long been known that EMFs can affect biological processes, if their intensity is strong enough. In fact, safe exposure limits have been set to prevent these effects. A good review can be found in the book *Electromagnetic Fields (300 Hz to 300 GHz), Environmental Health Criteria 137*, published under the joint sponsorship of the United Nations Environment Program, the International Radiation Protection Association, and the World Health Organization (Geneva, 1993). In almost all cases, these levels are exceeded only in very rare occupational environments. Since they are almost never exceeded in the general environment, such levels are not a public health concern. A much more complex debate centers on whether these are the only possible effects or whether the temporal and spatial coherence of the man-made fields associated with electric power can be somehow discriminated from the incoherent endogenous currents and interact with biological processes at levels much lower than those for which exposure limits exist. The reviewers agreed that, as was also the case initially for many disease-causing agents, there is not a well-documented mechanism that explains how the EMF "mixture" at residential or occupational levels could initiate a biological response or, having initiated that response, how a chain of events could lead to damage or disease of various types. There are biological effects from aspects of the EMF mixture, particularly at exposure doses far above residential and occupational levels. At this time they do not provide a clear mechanistic understanding of how the EMF mixture could cause disease. The absence of a clear mechanistic chain of effects and the failure of many experiments with aspects of the EMF mixture to produce any mechanistic effects did not lower the reviewers certainty of causality much below what it was initially. The evidence that there are some mechanistic effects of some aspects of the EMF mixture at doses (thousands of mG) far higher than usually encountered in the environment did not boost the confidence of causality very much beyond the initial probability because the biophysical arguments suggest that they might not be relevant to effects at lower levels. The DHS reviewers accepted the unusually strict requirement that mechanistic results in the laboratory must be demonstrable at ambient levels of exposure.

It should be noted that the assumption of many of the mechanistic experiments is that the effects of magnetic or electric fields (like those of many chemicals and ionizing radiation) occur at a level of organization demonstrable in a chemical mixture, a mixture of cellular components, or a mixture of cells and does not depend on the presence of an intact multicellular organism. There are some well-recognized effects that violate these assumptions. For example, the intact shark, through a

special organ with an array of connected detectors, can detect tiny electrical fields emitted by distant prey. The exact biophysical mechanisms by which the individual detectors work cannot be documented using individual receptors at the ambient levels detected by the intact shark (Kalmijn, 1971), (Wissing, Braun & Schafer, 1988).

The lack of mechanistic understanding, which was initially the case for many harmful agents, is not as strong an argument against causality as the presence of such an understanding would be in favor of causality. Therefore the mechanistic line of evidence did not contribute much to the reviewers' judgments.

10 The Weight Accorded to Experimental Evidence not Clearly Connected With Particular Endpoints but Relevant to the Ability of Low-Level EMFs to Be Bioactive

A number of studies, both in vivo and in vitro, report bioeffects which, while they do not shed light on physical induction or pathophysiological mechanisms, do suggest that there are effects other than those mediated by well-understood mechanisms, such as induced currents. For example, the initial observations by Liburdy of inhibition of the melatonin antiproliferative action by 12 mG 60 Hz fields in 1993 (Liburdy et al., 1993) has been confirmed and extended by two other laboratories (Blackman et al., 2001), (Ishido et al., 2001). The series of studies using pulsed magnetic fields that showed non-robust effects on chicken embryos at intensities below 100 mG (Martin, 1988), (Berman et al., 1990), (Martin, 1992), (Moses & Martin, 1992), (Moses & Martin, 1993), (Martin & Moses, 1995), (Litovitz et al., 1994), (Farrell et al., 1997a), (Farrell et al., 1997b), (Leal et al., 1989), (Chacon et al., 1990), (Ubeda et al., 1994), (Koch & Koch, 1991), (Koch et al., 1993), (Singh & et al., 1991), (Espinar et al., 1997), (Blackman et al., 1988), (Yip et al., 1994a), (Yip et al., 1994b), (Coulton & Barker, 1991), (Youbicier-Simo et al., 1997), (Piera et al., 1992), (Pafkova & Jerabek, 1994), (Pafkova et al., 1996), (Pafkova et al., 1994), (Veicsteinas et al., 1996) also provide some evidence of bioeffects that would be considered “impossible” according to biophysical theory. These two areas of research have been greeted with suspicion. For example, Weaver (Weaver, Vaughan & Martin, 1999) dismisses in vitro effects as being artifactual, due to an insufficiently rigorous lack of temperature control, because biophysical theory suggests that tiny fluctuations in temperature would produce more effects than magnetic fields below 100 mG. The DHS reviewers were not convinced by this argument. These studies were no less rigorously conducted than most in vitro studies in other fields of research. There is no direct evidence that inducing magnetic fields also heats the tissues. If experimental controls beyond the current technological limits are required, then ALL in vitro and in vivo research should be called into question.

The reviewers had differing opinions on the extent to which this evidence should change the belief in the hypothesis from what it was when this issue was first raised. One could argue that any experiment that shows an effect where none is expected ought to increase the credibility that EMF can indeed interact with biological systems at energy levels that biophysical theory considers too low to be effective. These studies thus provide some grounds for mistrusting the prediction of simplified biophysical models that no effect is possible below 100 microTesla (μT). Reviewer 1 was compelled by the evidence as it stands, while the other two reviewers would require further experimentation to gain general acceptance of the results before putting a lot of weight on them. All three reviewers agreed that confirming or explaining away the results from these two groups of experiments would be important for those who put great weight on biophysical “impossibility” arguments.

11 The Weight Accorded to Animal Pathology Experiments

The reviewers agreed that, with few exceptions, animal pathology studies based on high exposures to certain aspects of the EMF mixture showed no effects. There were three reasons why the reviewers believed that animal bioassays of single ingredients of the EMF mixture might be prone to missing a true effect:

a) Finding the right animal species to test: While the reviewers recognized that most agents found to cause cancer in humans also cause cancer in some (but not all) animal species, they were also cognizant that there are known human carcinogens, such as cigarette smoke, alcoholic beverages, benzene, and arsenic, for which no animal model existed for many decades.

b) Testing one ingredient of a mixture: The reviewers all questioned whether the bioassay of one element of a mixture could be sensitive enough to detect problems in the entire mixture. For example, many reassuring assays on the carcinogenicity of caffeine would not reassure us about the carcinogenicity of coffee. The animal pathology studies to date have been on pure steady 60 Hz fields not on the mixture of ingredients found near power lines or appliances.

c) Assuming that high intensities of magnetic fields produce larger effects than moderate fields do: The reviewers also questioned the sensitivity of a bioassay involving a small number of animals and assuming a monotonically increasing risk from low to high-dose, when the epidemiological studies that prompted the bioassays did not suggest an ever-increasing response.

The epidemiology suggests that the effect, if any, at 100s of mG (Tynes, Reitan & Andersen, 1994b), (Floderus, Tornqvist & Stenlund, 1994), (Alfredsson, Hammar & Karlehagen, 1996), (Minder & Pfluger, 2001) is no greater than that of children at 3 mG (Greenland et al., 2000), or of highly exposed utility workers with 24 hr time weighted averages (TWAs) around 7 mG (Kheifets, London & Peters, 1997b), (Kheifets, 2001). One would not expect rodents at 1000 mG to demonstrate a large enough effect to be detected in a conventionally sized laboratory experiment with a few hundred animals.

Accordingly, the lack of response in most animal pathology studies did not lower the degree of certainty by much. Reviewer 1 and 3 had their degree of confidence increased somewhat by repeated, but unreplicated, results from one German laboratory (Mevissen et al., 1996b) and isolated results from two laboratories in the former Soviet Republics (Anisimov et al., 1996), (Beniashvili et al., 1991), which showed co-promotional effects on breast tumors. None of the reviewers were much influenced by the statistically significant increase in thyroid cancers in one of the bioassays (Boorman, McCormick & Findlay, 1999b), even though it had not appeared in control series of previous bioassays and was thus a very unlikely occurrence. This effect showed up in only one sex of rats and not in mice and thus did not pass conventional toxicological criteria for animal carcinogenicity.

12 The Weight Accorded to Epidemiology Combined with Other Streams of Evidence

In the reviewers' judgement, it was epidemiological evidence that produced the most change in the degree of certainty from what it was *a priori*. Epidemiological studies are non-experimental statistical studies of human populations that compare rates of disease in groups with different levels of exposure or compare the proportion of exposed subjects in groups of healthy and diseased persons. The weakness of epidemiological evidence is that one cannot rule out the effect of factors associated with EMFs ("confounders") or completely avoid the limitations of collecting evidence in the real world instead of a controlled laboratory environment. These limitations may introduce errors ("bias") in the results. On the other hand, the strength of epidemiology is that it deals with the species of interest (humans) and the mixture and dose of interest (the EMF mixture as experienced by humans).

The individual studies, most of which were described in the NIEHS report, have been summarized in tables and graphs in this report. A structured evaluation of the epidemiological evidence was carried out for each of the 13 endpoints and summarized with the classification used by IARC and also by a statement of the degree of certainty that the observed epidemiological associations were causal in nature. In evaluating the credibility of epidemiological evidence, it is common to consider whether the risk being studied is "biologically plausible" and if "experimental evidence" exists to support the epidemiology. The three reviewers followed this practice considering the impact on the epidemiological findings of mechanistic evidence and evidence about bioactivity at near ambient levels under the heading of "plausibility" and of the animal pathology under the heading of "experimental evidence." However, these non-epidemiological studies were discussed in detail in separate chapters.

12.1 Issues Relevant to the Evaluation of the Epidemiological Evidence

Epidemiological results, because of the limitations of the data collected in a "real world" environment, need to be evaluated with particular care. The three major concerns are the effects of chance, bias, and confounding.

12.1.1 Chance

Epidemiological studies are expensive. Moreover, in the case of EMF and cancer, it may be virtually impossible to find sufficient subjects with both a rare disease and the rare high exposures. The very well-conducted studies carried out in some Scandinavian countries are based on so few subjects that a single additional case of cancer would change their findings. It is possible to reduce the effect of chance findings by combining results from a number of studies in a meta-analysis or even to merge the data collected for different studies in one large data set (pooled analysis). For health endpoints such as childhood leukemia (Greenland et al., 2000), adult leukemia (Kheifets et al., 1997a), adult brain cancer (Kheifets, 2001), amyotrophic lateral sclerosis (Ahlbom, 2001), male breast cancer (Erren, 2001), and miscarriage (Lee et al., 2002), (Li et al., 2002), pooled or meta-analytic analyses achieve conventional "statistical significance." This could be interpreted as follows: If these were randomized experiments without the possibility of bias or confounding, the statistical associations found would not be expected to occur by chance in 5 or fewer experiments out of 100 replications, if there really was no effect. Of course, epidemiological studies are not experiments, and it would be unethical and impractical to experimentally subject large numbers of humans to potentially harmful agents. This leads to the consideration of bias and confounding.

12.1.2 Bias

Any source of error in collecting the data may introduce a bias, which is a reason why the apparent result might not be the truth. A very common bias results from errors in assessing the true exposure of the subjects to the agent of interest, in this

case EMFs. Provided exposure of cancer cases and healthy controls is not assessed differently, this bias on average results in an underestimate of the risk, if one exists. When comparing the health risk of subjects exposed above one value to that of subjects below that value, non-differential misclassification of exposure* would not, on average, show an association if one does not truly exist. However, it may inflate the risk of intermediate exposure subjects and thus frustrate attempts to estimate a dose-response function. In most of the EMF studies, measurements were not taken for a long enough duration during the induction period of the disease to avoid this kind of misclassification. And there is even some argument about whether the right aspect of the EMF mixture has been measured. The three reviewers concluded that all of this may have led to an underestimate of any true effect of high versus low exposures and may have frustrated the ability to develop an appropriate dose-response curve.

Of the many errors that can creep into epidemiological studies, one in particular has been a source of argument with regard to a subset of the EMF epidemiological studies. We are referring to "selection bias" in some of the case control studies. A case control study is analyzed by comparing a series of cases with a disease to a series of healthy subjects as to their EMF exposure. If the cases display a higher proportion of high EMF exposure than the controls, this suggests a causal effect of EMFs. If, however, the probability of being selected for study is influenced both by whether one has the disease AND whether one had a high EMF exposure, then an apparent difference will appear between the cases and the healthy controls, which is the result of this biased selection and the result does not reflect any true effect of EMFs on the disease. One way to recruit healthy subjects is random telephone contact. This method excludes subjects of lower socio-economic status (SES), who may not have a telephone. Experience has shown that healthy controls of lower SES are sometimes less likely to participate in epidemiological studies than upper class subjects. In some studies, lower class subjects are more likely to live in neighborhoods with nearby power lines (Bracken et al., 1998). Since cancer patients of all social classes are easier to recruit (through a cancer registry) and more likely to be interested in participating, the effects of non-representative control selection may distort the comparisons between cases and controls and, therefore, the study results. In the case of EMF, it is claimed that the fact that there are more subjects living close to power lines among the cancer patients than among the healthy controls could be due to the fact that low SES subjects are more likely to live close to power lines and they are underrepresented in the control group. This issue of possible selection bias in case control studies is a particular issue for the North American case control studies on childhood leukemia. Hatch (Hatch et al., 2000) indicate that the association between childhood acute lymphoblastic leukemia (ALL) and front door magnetic fields greater than 3 mG was 1.9 (1.1-3.27) among full participants in their study but fell to 1.6 (0.98-2.61) when 147 partial participants were included. Although this difference was well within sampling variability, she suggested that it might be evidence of the presence of a selection bias which might be even more extreme if non-participants had their front doors measured and had been included in the analysis. Hatch (Hatch et al., 2000) concluded that "while confounding alone is unlikely to be an important source of bias....selection bias may be more of a concern...in case-control studies." The Scandinavian studies relied on cancer registries and lists of citizens and did not require permission of the subjects so that selection bias was not a problem. Ahlbom (2001) has shown that the results of the two groups of studies are not much different. The pooled analysis of all the studies he dealt with showed a relative risk for exposures above 4 mG as 2.0 (1.3-3.1), while the results after excluding the US studies was 1.7 (1.0-2.8). That is, the confidence interval of the two risk estimates overlap, indicating that there may or may not be some overestimate of the effect of living near power lines in the American studies, but that even if these are excluded, the association remains statistically significant. In the pooled analysis by Greenland et al. (2001), there was an effect of power line proximity ("wire code"), as well as an effect of measured magnetic fields. This might indicate some selection bias for power line proximity. Nonetheless, magnetic fields come only partially from power lines. Internal wiring and currents on plumbing form an important source (Zaffanella & Kalton, 1998). The only evidence we know of that examines personal EMF exposure from all sources and its relation to social class (Lee GM & Li D-K, personal communication) does not suggest differences in personal EMF exposure in different social classes. The evidence linking EMFs and adult leukemia, adult brain cancer, Lou Gehrig's disease, and Li's prospective miscarriage study come largely from study designs where selection bias is not possible (studies where rosters of healthy workers or subjects of high and low exposure are followed until death or health outcomes are determined from available records without requiring subject cooperation). Thus, although selection bias may have distorted the associations between EMF and childhood leukemia in some of the studies, the three reviewers did not believe that it totally explained the childhood leukemia findings and selection bias was not even an issue in the bulk of the studies related to adult leukemia, adult brain cancer, ALS, or in one of the two recent studies on EMF and miscarriage.

* "non-differential misclassification of exposure" is said to occur when errors of measurement occur equally in cases of disease and in healthy controls.

12.1.3 CONFOUNDING

The term "confounding" is derived from the Latin "confundere," to melt together. Epidemiologists use the term when the impact of two risk factors "melt together" and must be disentangled. If heavy alcohol consumption and smoking are both known to cause esophageal cancer, and people who drink also tend to smoke, then the effect of drinking will confound the effect of smoking and vice versa. Therefore one must correct for this confounding in the way the data are analyzed. Sometimes the non-effect of a factor which conveys no risk at all is confounded with the true effect of another factor. For example, it has been suggested that people who live near power lines also live on busy streets with lots of traffic and air pollution. This argument suggests that the effect of air pollution on childhood leukemia was confounded with the non-effect of the power lines, and the power lines were falsely implicated instead of the air pollution. Two conditions must pertain for an agent to be a strong confounder of the EMF effect on the various diseases discussed in this report. That agent must be strongly correlated with EMF exposure and it must have an effect on the studied disease that is even stronger than the apparent effect of EMF. If it is weakly correlated with EMF exposure it must have an effect on disease that is very strong indeed if it is to make EMF falsely appear to have an effect. Langholz (Langholz, 2001) has examined the candidate confounders for childhood leukemia and their association with power line proximity wire code. He concluded that while something connected with the age of home was a possibility, factors like traffic density, ethnicity, and smoking were not likely confounders. Indeed, not all studies of traffic and childhood leukemia suggest it as a risk factor (Reynolds et al., 2001), but a recent study of traffic and power line proximity and childhood leukemia (Pearson, Wachtel & Ebi, 2000) did suggest that there might be a joint effect. Hatch (Hatch et al., 2000) examined a variety of socioeconomic, and other confounders, and concluded that together, or alone, measured confounders would distort the association with ALL by less than 15%. Hatch also found no association between residential mobility, magnetic fields, or leukemia unlike Jones (Jones et al., 1993).

Electric shocks have been invoked to explain the relation between high-exposure jobs in the utility industry and ALS (Ahlbom, 2001), (NRPB, 2001a). If this were confirmed, they might also be invoked to explain the adult leukemia and brain cancer associations on the as yet unproven assumption that shocks could somehow cause cancer. However, the literature linking shock to ALS, unlike much of the literature linking high-EMF exposure jobs to ALS, depends on subjects remembering shocks. They are thus more vulnerable to recall bias than the EMF studies. Some of the studies suggest a protective, not a harmful, effect (Cruz et al., 1999); (Kondo & Tsubaki, 1981), (Gunnarson et al., 1992) and the size of the harmful effects of shock are less than the high EMF job effect (Deapen & Henderson, 1986), (Savettieri et al., 1991). No published study has demonstrated a correlation between shocks and high-EMF exposure jobs. Studies are underway to see if grounding currents are associated with measured magnetic fields and power line proximity. The three reviewers felt that the evidence for the confounders that had been proposed for EMF exposure did not have strong support and therefore their degree of confidence was not decreased by the pattern of evidence.

12.1.4 COMBINED EFFECT OF CHANCE, BIAS, AND CONFOUNDING

Although each of these possibilities by itself is unlikely to explain the association between EMF and cancer, is it possible that a combination of the three may be responsible for an artifactual finding? The DHS reviewers considered this possibility and concluded that this is not a credible explanation when many studies of different design have reported similar results. It is not impossible that individual studies may have their result completely explained by an extraordinary coincidence in which independent unlikely events occur simultaneously. However, for many diseases considered here the general pattern of results is not critically dependent on accepting each individual study as reliable. For example, in the case of childhood leukemia, it has been repeatedly shown that, even if a few studies are excluded, the results of meta-analyses, pooled analyses, or sign tests are not significantly altered.

In conclusion, the DHS reviewers, to different degrees, concluded that chance, bias, and confounding are not probable explanations for the reported associations when they have been reported repeatedly by independent investigators. In addition, the DHS reviewers considered other criteria, notably the Hill's criteria for causality, keeping in mind that these are not to be considered as strict rules to follow. Apart from consistency, which, as noted above made them doubt the non-causal explanation for a few endpoints, none of the Hill's attributes, when applied to the pattern of evidence, influenced their degree of certainty by much.

The DHS reviewers recognize the size of the associations between EMF exposure and the various diseases studied are not so far above the resolution power of the studies that confounding and bias could be definitively ruled out as explanations. They recognized that there was rarely an orderly progression of increased risk within studies and that the effects reported for groups with dramatically high exposures like electric train operators did not display dramatically high risks when compared to those with low or moderate exposures. There are also examples where the statistical results are not completely coherent. However, these evidentiary tests are prone to giving false negative results due to non-differential measurement error and sample size problems. Also, EMFs may have societally important effects that

are nonetheless truly close to the detection of epidemiology. Finally, an agent may act in an "on/off" fashion and would not produce a steadily increased effect. These patterns of evidence therefore lowered confidence some, but not a lot.

13 CONCLUSIONS

Having examined and discussed each of the health endpoints mentioned above in a separate chapter in the main document, the three DHS reviewers each assigned their best judgment IARC classification and degree of certainty (as a number between 0 and 100). These determinations are summarized in Table V. Column 1 displays the condition considered. Column 2 identifies the reviewer. Column 3 shows the IARC classification in which the number "1" denotes a definite hazard: "2A" a probable hazard, "2B" a possible hazard, and "3" evidence "inadequate" to make a classification. Column 4 displays the pre-agreed-upon phrases for describing zones of certainty. Column 5 shows the ratio of the reviewers imputed posterior odds to the reviewers imputed prior odds (more about this below). In column 6, the reviewers graphed their best-judgment degree of certainty as an "x" and indicated their uncertainty with a shaded bar on either side of that best judgment.

To provide an illustration, this method has been applied to two non-EMF examples in the first two rows. In row 1, Reviewer 2 has indicated that air pollution is a definite causal trigger of asthma attacks and that he is virtually certain of this. In row 2 he shows that he strongly believes that particulate air pollution causes excess deaths. There is relatively little uncertainty around either of these determinations.

Row 3 displays the prior degree of certainty that there would be epidemiologically detectable effects when comparing disease rates among persons exposed to EMFs at or above the 95th percentile of US residential levels to rates at or below the 1st percentile residential exposure. These prior degrees of certainty range from 5 to 12 on a scale from 0 to 100.

Column 5 is labeled "IRL" for "imputed relative likelihood." If the degree of certainty is converted to a probability scale (0–1.0) and, in turn, if one converted the probability to odds (probability/(1–probability)) the imputed prior odds can be compared to analogously calculated imputed posterior odds. One would base these on the "best judgment" posterior degrees of certainty graphed in Table V. The resulting "imputed relative likelihoods" provide some indication of how much the overall pattern of evidence in biophysics, mechanistic, animal pathology, and epidemiological streams of evidence have combined to move the reviewers from their respective starting degrees of certainty. For example, with regard to air pollution triggering asthma attacks, the existing evidence has caused Reviewer 2 to move 900-fold from his prior, while the childhood leukemia evidence has moved him 22-fold*. Royall (Royall, 1997) has suggested anchoring the interpretation of such relative likelihood numbers on the relative likelihoods derived by probability theory from the following hypothetical experiment: Suppose that a reviewer has two urns, one that contains only white balls, the other that contains half white balls and half black balls. He takes one of the two urns at random. To determine which urn he has ended up with, he begins repeatedly withdrawing a ball and then replacing it in the urn (after noting down its color) and mixing up the balls before pulling out yet another ball. If on only one draw he were to find a black ball, he would know that he was dealing with the urn containing 50% black balls. But what is the relative likelihood conveyed by drawing one or more consecutive white balls? Royall demonstrates that drawing 5 white balls in a row conveys a relative likelihood of 32, while drawing 10 consecutive balls conveys a relative likelihood of 1,024. Reviewer 2 views the asthma/air pollution data as being almost as strong as the evidence conveyed by drawing 10 consecutive white balls during the urn experiment, while the childhood leukemia evidence is equivalent to drawing just shy of 5 consecutive white balls.

* Reviewer 2 had a prior of 5 and a posterior for childhood leukemia of 54. The prior odds are 5/95 = 0.0526. The posterior odds are 54/46 = 1.174. The imputed relative likelihood is 1.174/0.0526 = 22.3.

TABLE V. PRIOR AND POSTERIOR DEGREES OF CERTAINTY AND DHS REVIEWERS' APPLICATION OF IARC CLASSIFICATION

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Air Pollution Triggered Asthma Attacks (Example: Not EMF-Related)	2	Human Risk	Virtually Certain	931	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
Particulate Air Pollution Triggered Deaths (Example: Not EMF-Related)	2	Prob. Risk	Strongly believe	171	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
Prior Confidence that EMFs Could Cause Epidemiologically Detectable Disease	1	N.A.	Prone not to believe	1	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	2		Strongly believe not	1	
	3		Strongly believe not	1	
Childhood Leukemia					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Strongly believe	140	
	2	2B	Close to dividing line	22	
	3	2A	Prone to believe	17	
Adult Leukemia					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Prone to believe	29	
	2	2B	Close to dividing line	21	
	3	2B	Close to dividing line	6	
Adult Brain Cancer					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Prone to believe	29	
	2	2B	Close to dividing line	20	
	3	2B	Close to dividing line	13	

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Childhood Brain Cancer					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	7	
	2	3	Prone not to believe	2	
	3	3	Prone not to believe	3	
Breast Cancer, Female					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	7	
	2	3	Prone not to believe	3	
	3	3	Prone not to believe	2	
Breast Cancer, Male					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	6	
	2	3	Prone not to believe	12	
	3	3	Prone not to believe	2	
EMF Universal Carcinogen?					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Strongly believe not	0.4	
	2	3	Strongly believe not	0.5	
	3	3	Strongly believe not	0.2	
Miscarriage					0 5 10 1 5 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	9	
	2	2B	Close to dividing line	20	
	3	2B	Close to dividing line	11	
Other Reproductive					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Strongly believe not	0.4	
	2	3	Strongly believe not	0.8	
	3	3	Strongly believe not	0.2	

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
ALS (Lou Gehrig's Disease)					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	9	
	2	2B	Close to dividing line	21	
	3	2B	Close to dividing line	11	
Alzheimer's					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	5	
	2	3	Prone not to believe	4	
	3	3	Prone not to believe	2	
Suicide					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	6	
	2	3	Close to dividing line	15	
	3	3	Close to dividing line	7	
Heart					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	6	
	2	3	Prone not to believe	8	
	3	3	Prone not to believe	3	

14 How different is this evaluation from the NIEHS, NRPB, and IARC findings?

As outlined in Table VI below, there are both common points and significant differences between the EMF Program's evaluation and those carried out at about the same time by the NIEHS (for the Federal EMF-RAPID Program), the NRPB (NRPB, 2001a), (NRPB, 2001b), and the IARC (Note: The NRPB did not use the IARC classification system but expressed their conclusion using common language expressions).

The following table compares these evaluations:

Table VI. A Comparison of DHS Reviewers' Degree of Certainty with That of Other Agencies

HEALTH OUTCOME	NIEHS WORKING GROUP	IARC	NRPB	DHS
Childhood Leukemia	2B*	2B	Possible	2B to 1
Adult Leukemia	2B* (lymphocytic)	Inadequate	Inadequate	2B to 1
Adult Brain Cancer	Inadequate	Inadequate	Inadequate	2B
Miscarriage	Inadequate	Not considered	Not considered	2B
ALS	Inadequate	Not considered	Possible but perhaps due to shocks	2B
Childhood Brain Cancer, Breast Cancers, Other Reproductive, Alzheimer's, Suicide, Sudden Cardiac Death, Sensitivity	Inadequate	Inadequate or not considered	No for Parkinson's Disease, Inadequate for Alzheimer's, Other endpoints not yet considered	Inadequate

It is clear from Table VI that, when applying the IARC guidelines, the DHS reviewers agreed with IARC and NIEHS reviewers that in many cases (e.g., childhood brain cancer and male and female breast cancer) the evidence would be classified by IARC as inadequate to reach a conclusion. One of the DHS reviewers agreed with the IARC and NIEHS on childhood leukemia. Two of the reviewers agree with NIEHS, but not with IARC, on adult leukemia. All three reviewers agreed with NRPB that EMF was a "possible" cause of ALS. Otherwise, the DHS reviewers regard the EMFs association more likely to be causal than NRPB, IARC, or NIEHS did.

It should be noted that all of the review panels thought that the childhood leukemia epidemiology warranted the classification of EMF as a "possible" carcinogen and thus did not agree with the biophysical arguments that EMF physiological effects (and therefore pathological effects) were "impossible."

There is a wide range of opinions in the scientific community as to the probability that EMFs cause health problems. The DHS reviewers provided numerical values for their degrees of confidence that risk of various diseases could be increased to some degree by EMF exposure. Other researchers have rarely packaged their judgments in this way, so it is hard to make comparisons. Judging by one such exercise that the DHS reviewers conducted (Neutra, 2001), reasonable scientists can have different ways of interpreting the data resulting in different degrees of certainty.

* Although the majority of scientists assembled to prepare the NIEHS Working Group Report voted for a "possible 2B" classification for these cancers, the lay person's summary submitted by the Director of NIEHS to Congress stated: "ELF-EMF exposure cannot be recognized as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard." (Final Report NIH Publication 99-4493, May 1999)

The three DHS reviewers have been active in the EMF field for more than a decade and are familiar with the opinions and arguments used by the scientists in scientific meetings. Since Reviewer 1 was part of the IARC-EMF review panel and all three reviewers had some participation in the earlier parts of the NIEHS process, they also have some understanding of the process by which selected panels of these individuals arrived at a group determination about EMFs. The reviewers think there are at least two relevant differences between their process and the usual procedures followed by the other groups.

First, the DHS Guidelines require that they consider the inherent tendency of the several streams of evidence to either miss a true effect, or falsely "indict" a putative causal agent. The weight given to those streams of evidence was influenced by this consideration. The standard guidelines involve discussions of whether the adjectives "limited" or "sufficient" best fit the pattern observed in a stream of evidence, and depending on the decision one makes, simple guidelines of how combinations of "limited" and "sufficient" streams of evidence influence whether a "possible," "probable," or "definite" causal status is assigned. While the DHS Guidelines allow null results of animal pathology studies using one ingredient of a mixture to get little weight, the IARC rules involve a simple combination of binary judgments about the animal and epidemiological evidence. The way the DHS reviewers used the Guidelines meant that they did not let the primarily null results from the mechanistic and animal pathology streams of evidence decrease their certainty as much as seems to be the case for reviewers in other panels. The reasons for this have been explained above. Having been less deterred by the null mechanistic and animal pathology, they were also less prone to invoke unspecified confounders and bias as an explanation for the persistent, if not homogeneous, epidemiological findings for certain health endpoints.

The other reason for the discrepancies in the DHS reviewers' IARC classification choices can be traced to differences in the procedures for combining the scientists' judgments. They found several striking differences between the IARC and this evaluation processes:

- The Panel's Composition. The EMF Program's review was carried out by the EMF Program's scientific staff and not by a large panel of experts outside the agency. An outside panel, however, evaluated the document. One could criticize the DHS panel as being too small and not diverse enough, but this is standard procedure for California government agencies. The IARC followed its usual practice of convening outside experts to write drafts, discuss the drafts, and turn them over to staff to finalize. Given the spread of the scientific opinions on the EMF issue, it is safe to say that the outcome of any review is a strong function of the working group members' belief before the review takes place. (The DHS reviewers have striven to make this transparent through the elicitation of the prior beliefs and the "pro and con" discussion.) Two unbiased ways to assemble a working group would be by random selection out of a pool of "qualified" individuals or through a conscious effort to include balanced numbers of individuals known to have opposite points of view. In the first case, the definition of "qualified" could influence the verdict of any sample, and sampling variability could yield a mix of opinions that would vary from sample to sample so that different working groups could reach different conclusions. The second procedure could be an excellent solution, if the evaluation were carried out through extensive debates and discussions, with a shared desire to come to a consensus opinion irrespective of its potential social and economic consequences. This was the original approach used by IARC (Tomatis, private communication). However, the pressure to conclude the evaluation within a short period of time led to abandoning the discussion format in favor of the voting system. This leads to the next important difference.
- The Time Element: The meeting to draft the IARC-EMF monograph (June, 2001) lasted five and a half days. The vast majority of the plenary session time was dedicated to reviewing the draft chapters prepared ahead of time by designated committee members with maybe 10% of the time allowed for discussion of the rationale for reaching conclusions. Whenever a paragraph precipitated a controversial discussion, a common way out was to propose the deletion of the offending paragraph, a proposal that the time-pressured working group members were usually glad to adopt. In contrast to this process, the DHS reviewers spent innumerable hours and days, over a period of years and in consultation with independent consultants, to explain their inferences and resolve or clarify their differences.
- The Format of the Conclusion: IARC aims for a consensus conclusion. Members with more extreme views are strongly encouraged to converge on a middle of the road conclusion. In the California evaluation, if consensus could not be reached (as was the case for some endpoints), each member was allowed to express his or her personal belief. Although two of the DHS reviewers were subordinate to the third, substantial differences remained for some endpoints and are openly revealed in this evaluation.
- IARC's Voting System: The members of the working group were asked to vote separately on animal and human evidence. Although a sizable

minority of the working group believed that there was limited animal evidence indicating a possible cancer risk, their opinion was not carried past that point of the process. Since the majority regarded the animal evidence as "inadequate," when the final vote on the overall evaluation was taken, the option posed to the working group's members were the majority positions, that is, that animal evidence was inadequate and epidemiological evidence for childhood leukemia was limited. According to the guidelines, these two majority positions resulted automatically in a Group 2B classification and Class 2A or Class 1 were not even considered as options to vote on, even if individual reviewers, such as Reviewer 1, might have so voted. The published monograph does not document that the minority view had in fact a higher degree of certainty of the EMF risk than the majority view.

Somewhat similar considerations apply to the NIEHS evaluation. Although the whole process lasted eighteen months, the decision was reached over the course of a week-long meeting, followed by a vote. This meeting was preceded by a series of workshops including discussions and presentations, but not all members of the working group participated in the workshops, and most of the workshop participants were not members of the working group. Therefore, the final conclusion was still the result of a few days intensive meeting, during which much of the time was devoted to revising and finalizing the wording of the final report rather than to writing about points of controversy. The working group report did document the vote count.

Apart from procedural differences, there are also philosophical differences between the various review panels. For example, with regard to adult leukemia, the IARC's evaluation differs from the NIEHS and the California evaluation because of the way epidemiological evidence was considered. Almost all the evidence on adult leukemia comes from occupational studies. The Epidemiology subgroup at the IARC meeting regarded most of these studies as being of poor quality, with within- and between-study inconsistencies. Most of the evaluation centered on the most recent large studies (Sahl, Kelsh & Greenland, 1993), (Savitz & Loomis, 1995), and (Theriault et al., 1994), which contradicted each other. The DHS reviewers' evaluation considered the whole body of studies, residential and occupational. While they acknowledge that many of the studies have limitations, neither they, nor the IARC reviewers, have identified fatal flaws. For example, there is no evidence to suggest that the use of crude exposure assessment surrogates, while virtually certain to influence the quantitative estimate of risk and to frustrate any attempt to explore the dose-response relationship, introduced an upward bias in the reported association. On the contrary, the limitations of the studies may well be responsible for the inconsistencies between them. And while these inconsistencies do exist, they are not as common as the IARC evaluation may suggest. The Kheifets (1997) meta-analysis concludes that the body of epidemiological evidence shows a slight but statistically significant increase in risk. From a binary outcome standpoint, the studies with a relative risk estimate >1 are more than twice as numerous as those with a $RR \leq 1$.

Nonetheless, where the DHS and other reviewer panels agreed to assign a "possible" carcinogen label to an EMF/disease association, it is not easy to infer if there would be agreement on a degree of certainty. According to Dr. Rice, Chief of IARC's Carcinogen Identification and Evaluation Unit (personal communication to Vincent DelPizzo), "If IARC were to say that an exposure is in Group 2A, probably carcinogenic to humans, that would mean that the evidence is just a little short of certainty that the exposure in question has actually caused human cancer. . . Group 2B is the lowest level of identifiable carcinogenic hazard in the IARC system."

Finally, it must be remembered that in DHS's EMF Program, policy recommendations were addressed separately from the risk evaluation. In some other cases, evaluations are part and parcel of a policy recommendation (they may include regulatory recommendations in the conclusion). This may make them more conservative, as it seems to be the case with IARC: "….the IARC Monographs system of carcinogenic hazard evaluations is deliberately a very conservative one. There are many carcinogenic hazards in the human environment that are very real indeed, and control of exposures to those hazards is extremely important for public health. To accomplish this, it is necessary that carcinogenic hazards be correctly identified. We must avoid misdirecting public attention to any exposure of any kind that may be perceived as a hazard, but in fact is a misplaced concern." (Dr. Jerry Rice in a letter to Vincent DelPizzo, Aug. 10, 2001). The cover letter to the NIEHS report to congress concluded with a recommendation for only "passive regulatory action" (NIEHS, 1999). The DHS's three reviewers have packaged their differing degrees of confidence about causality in a way that can be used in the decision analytic models prepared for the program. DHS has pointed out that the policy implications of this range of confidences depends on the policy framework of the decision maker: non-interventionist, utilitarian, virtual-certainty-required, or social justice. The public regulatory process will determine which one or which mixture of these frameworks will apply to govern policy. Thus the DHS risk evaluation is packaged to facilitate decision making but separates risk assessment from risk management. The fact that a reviewer may feel very certain that EMF is a risk factor for a particular disease does not imply that he or she advocates exposure mitigation.

In summary, the differences between the DHS reviewers' judgments and those of other reviewers are partly due to differences in procedure and terminology and partly due to the way those three reviewers weighed the several streams of evidence.

15 Differences Between DHS Reviewers

As noted above, the three DHS reviewers were not able to reach a consensus on all health endpoints. In this section, they explain the reasons behind their respective judgments.

15.1 Reviewer 1 (DelPizzo)

In almost all cases, Reviewer 1's posterior degree of confidence is higher than that of the other two reviewers. There are several reasons for this difference.

a) Different priors—the reviewer is generally more suspicious of man-made environmental pollutants, which have no place in the evolution process.

b) Reliance on the sign test—this reviewer has put much weight in the sign test, a simple, dichotomous test, which measures the probability of several studies erroneously reporting the existence of a risk while no risk truly exists. In many cases the test finds that this probability is extremely small, that is, the results are unlikely to be erroneous. In the reviewer's opinion, this test is particularly suitable to answer the simple question, is there a risk or not? rather than asking what the relative risk is. The results of this test are not changed if the outcome of one or more studies are partly due to bias. Some worst-case scenarios, assuming extraordinary coincidences of chance and bias acting simultaneously in the same direction, do weaken the evidence, but when a condition has been studied by many different investigators, these scenarios do not reduce Reviewer 1's belief by much.

c) Weight given to empirical results—Reviewer 1's prior was limited by the intuitive belief that the energy associated with environmental EMFs is so small that, even if these fields are potentially disruptive, the amount of disruption is insufficient to cause a biological effect. Once Reviewer 1 examined the results of in vivo and in vitro research on EMF exposure, however, he became convinced that biological EFFECTS (as distinct from PATHOLOGY) can result from exposure to levels below those which conventional knowledge considers necessary. That is, if one equates "energy" to "dose," exposure to environmental fields may be regarded as a non-negligible dose. Thus, the argument that kept Reviewer 1's prior low disappears and the possibility of a hazard, when repeatedly reported by independent epidemiological studies, becomes more credible.

15.2 Reviewer 2 (Neutra)

The fact that EMFs are the only agent that this reviewer has encountered for which there are theoretical arguments that no physiological, much less pathological, effect could be possible, did decrease Reviewer 2's prior somewhat. But physics applied to simplified models of biology were not convincing enough to make this prior credibility vanishingly small. This reviewer noted biological effects in mechanistic experiments in the thousands of mG but accepted the arguments that these were probably not relevant to effects below 100 mG. The few experiments that claimed to show an effect below 100 mG (the chick embryo studies and the confirmatory studies of Liburdy's melatonin studies) were considered highly worthy of further study, but not robust enough or free enough of alternative explanations at this point to cancel out the modest initial doubts about the energetic feasibility of residential EMFs to produce biological effects. The animal pathology studies have convinced Reviewer 2 that very-high-intensity pure 60 Hz or 50 Hz sinusoidal magnetic fields do not have a strong enough effect to produce consistent pathological effects in small numbers of the species and strains of animals selected for study. If these species of animals were to respond as humans are described to have done in the epidemiology, this was a predictable result even if pure sinusoidal 60 Hz fields were the active ingredient of the EMF mixture. Humans exposed to hundreds of mG, like electric train engineers, when compared to persons with 24-hour average exposures around 1 mG do not show relative risks consistently above 1.00 much less very high relative risks. Why would animals be expected to do so? Moreover, pure sinusoidal fields may not be a bioactive ingredient of the mixture, and the animal species chosen may not be appropriate models for humans. Reviewer 2 believes that the animal bioassay stream of evidence in this case is thus triply vulnerable to missing a true effect, and the null results do not reduce his confidence in an EMF effect much. The fact that there are epidemiological associations with several different cancer types and with other diseases that have different known risk factors does increase confidence somewhat but, without mechanistic reasons, not a great deal. Any changes from the prior were due to epidemiological evidence. Large studies likely to be free of selection bias carried a lot of weight. Many studies of different design and in different locations showing similar results also carried substantial weight, although Reviewer 2 only interpreted the sign test to indicate whether a meta-analytic or pooled association came from just a few large studies, or from a rather consistent pattern of result from many studies. Reviewer 2 did not think that any of the specific

candidate confounders or biases that had been proposed to date for explaining away the epidemiology had convincing evidence to support it. The fact that most of the associations are not much above the resolving power of epidemiological studies left open the possibility of unspecified combinations of bias, confounding, and chance having produced these associations. This kept Reviewer 2 from having an updated degree of confidence above the certainty zone of "close to the dividing line between believing and not believing" that EMFs increase the risk to some degree.

15.3 Reviewer 3 (Lee)

Reviewer 3 mainly used the human epidemiological evidence to form a posterior degree of confidence. The large number of studies showing consistent results across different study designs, study populations, and exposure assessments, as well as large, well-conducted studies with adequate power to address confounding, bias, dose response, and effects among subgroups contributed strongly in updating the prior degree of confidence. The association of EMF with several types of disease and experimental and animal evidence were minor contributions to the updating process. Specificity, visibility, analogy, and, in general, temporality did not contribute much to the posterior degree of confidence.

16 How The Degrees of Confidence and Range of Uncertainty Could be Used in Policy Analyses

Community and stakeholder policy decisions usually are made from one or more of the following ethical perspectives: "non-interference," which emphasizes individual choice and rights free from the infringement of others and of government; "social justice," which emphasizes the protection of the weak, and rights and duties; "virtual-certainty-required," where protective action is only taken when the vast majority of scientists are virtually certain that there is a problem; and the "utilitarian perspective," which emphasizes results and the most good for the most people at the least cost. Each perspective would have somewhat different requirements for the degree of confidence of causality before initiating action.

The "non-interference" perspective seeks to avoid regulatory impingement and taxes and tends to favor "right to know" warnings and voluntary solutions to problems, regardless of the degree of confidence. The "virtual-certainty-required" framework would tend to require a high degree of confidence with narrow uncertainty bounds on the part of most scientists and a high probability of harm from exposure before acting on an environmental hazard. Indeed, this perspective would favor risk-assessment methods having few false positives, even at the cost of false negatives.

The "social justice" perspective seeks to avoid even the possibility of risk, particularly if the risk and the benefit are imposed on different parties. This perspective would tend to advocate protective action at lower degrees of confidence, wider uncertainties, and lower absolute probabilities of harm given exposure. It would favor risk-assessment approaches with few false negatives, even in the face of false positives. It would focus on the added lifetime risk to the most highly exposed.

The "utilitarian cost/benefit" perspective would evaluate the policy implications of the best estimate of the degree of confidence but would explore the consequences of the lower and upper bounds of the confidence that a hazard exists. It would focus on the burden of societal disease that could be avoided by EMF mitigation. Depending on the relative prevalence of stakeholders who suffer, respectively, from false positives and false negatives, the utilitarian perspective would develop a preference for risk-assessment methodologies. The reviewers would propose that the policy integration document discuss the implications for policy arising from the range of best estimates among the three reviewers and the range of uncertainties expressed. It should also discuss where the three DHS reviewers' degrees of confidence lie in the spectrum of scientific opinion.

17 Evidence of Risk Relevant for Policymakers Mindful of Environmental Justice Issues

It is sometimes alleged that lower SES subjects are more likely to live in areas with stronger environmental EMFs. Salzberg et al. (Salzberg, Farish & DelPizzo, 1992) first explored this hypothesis and found only weak support for it. Bracken et al. (Bracken et al., 1998) reported a strong correlation between some SES indicators (women's occupations, house values) and the very high-current configuration (VHCC) wire code configuration. Hatch (Hatch et al., 2000) found no such association. Two very large data sets collected in the San Francisco Bay Area as part of the study by Lee et al. (Lee et al., 2002) found no evidence of an association between family income and measured EMF exposure. However, there was a weak association between low SES and wire code (Hristova et al., 1997). In a geographic information system (GIS) study as part of the power grid policy project, English et al. (http://www.dhs.ca.gov/ehib/ emf/ pdf/ AppendixG-GIS.PDF) examined the ethnic and income characteristics of census blocks within 500 feet of transmission lines. The proportion of black and Hispanic residents in these corridors was lower than the state average proportion. Zaffanella and Hooper (Zaffanella & Hooper, 2000) found somewhat higher magnetic fields in schools with students of lower socioeconomic status. In summary, the evidence to support the contention that the EMF exposure,

if real, disproportionately affects low SES subjects is not very strong, but there is some suggestive data that decision makers may consider when evaluating policy options.

18 THE EMF MIXTURE

A careful assessment of the electricity-related exposures from power lines, appliances, and occupations would reveal what amounts to a complex mixture including electrical and magnetic fields with their respective frequency, polarization, etc. The reviewers will call these the "aspects" of the mixture.

Each aspect varies from instant to instant to form a time-series of intensities, which can be summarized as a single number by various summary "exposure metrics," which may be more or less biologically active. For example, the exposure metric of ionizing radiation that best predicts biological effects is the simple integral of the exposure-time series. The exposure metric that best predicts the effect of an antibiotic might be the integral of blood levels above some threshold. Other electricity-related correlates of proximity to power lines, internal wiring, and appliances are not part of the fields at all, but might be correlated with them. These include electrically charged and "sticky" air pollution particles; contact currents from stray currents, from plumbing and in the earth, and intermittent shocks. The reviewers will call these the "ingredients" of the mixture.

What aspects, ingredients, or exposure metrics, if any, should we be considering in this risk evaluation?

For a number of years, some researchers believed that if the risk increase were truly due to some component of the EMF mixture then this component must be something captured by the exposure-assessment surrogate known as "wire coding," consisting of classifying residences based on their proximity to visible power lines and on the type of these power lines. Recent new data and reanalysis of old data (Linet et al., 1997), (Greenland et al., 2000) appear to have disposed of this hypothesis convincingly. They have shown that risk is more consistently correlated to measured or calculated TWA magnetic field than to wire coding classification.

This does not mean that the TWA—measured by surrogates such as point-in-time or "spot" measurements, calculations using engineering models and historical line current loads and job exposure matrices—is necessarily the true causal agent. The units, mG or μT, that measure the magnetic field's TWA do not describe the magnetic field (and much less the electric field associated with it) any more than the units marked on the volume dial on a stereo system fully describe the sound coming out of the speakers.

Nevertheless, although the reviewers cannot definitely "rule in" the component(s) of interest, they can rule out some aspects of the fields that are not correlated with TWA field strength. A detailed discussion of this issue can be found in Neutra and DelPizzo (2001). Here, the reviewers include Table VII adapted from that paper, pointing out which of the more commonly proposed metrics are indeed correlated with TWA (indicated by a "**U**") and those which are not (indicated by "No"):

TABLE VII. CORRELATION OR ABSENCE OF CORRELATION BETWEEN EXPOSURE METRICS AND EXPOSURE-ASSESSMENT SURROGATES

EXPOSURE METRIC TO 30-300 HZ MAGNETIC FIELDS	HIGH WIRE CODE	HIGH MEASURED FIELD	HEALTH ENDPOINT	REFERENCE
(1) TWA	**U**	**U**	**U**	many
(2) Length of time with constant field above a threshold	**U**	**U**		
(3) Repeated periods of elevated exposure	**U**	**U**	**U**	(Feychting, Forssen & Floderus, 1997), (Feychting, Pedersen & Svedberg, 1998b). (Lee & McLoed, 1998)
(4) Third harmonic	**U**	?	?	(Kaune, 1994b)
(5) Resonance with static field	No	No	?	(Kaune, 1994b), (Bowman, 1995)
(6) Time above a threshold	**U**	**U**	?	(von Winterfeldt & et. al., 2001)
(7) Polarization	?	?	?	(Burch et al., 2000)
(8) Transients	No	No		(Preece et al., 1999)
(9) Maximum daily exposure	**U**	**U**	**U**	(Li et al., 2002), (Lee et al., 2002)
(10) Average change between measurements	**U**	**U**	**U**	(Lee et al., 2002)
(11) Electric field	Not inside home	Not inside home	?	(Miller et al., 1996), (Coghill et al., 1996)

This table allows the reviewers, at least, to cast doubt on two metrics that are supported by mechanistic arguments, but not (or at least not consistently) by empirical data. These are 1) magnetic field transient, which can induce strong, if brief, electrical currents in the body, and 2) resonance conditions, which may facilitate energy transfer from the field to the living organism.

The table also emphasizes the difficulty of testing the hypothesis of an EMF risk by conducting experimental studies. Studies using an exposure apparatus that delivers an appropriate TWA (but not an appropriate exposure to a hypothetical aspect, ingredient, or exposure metric found in residential or occupational environments) are liable to produce false-negative results. Or they may produce positive results suggesting dose-response relationships different from those that may result from environmental fields.

Reducing TWA exposure will reduce exposure to several other metrics and reduce any risk from TWA or the exposure metrics that are changed with it. However, this is a sufficient but not necessary condition: if TWA is not by itself the causal factor and if we could identify and remove from the EMF mixture the component directly causally associated with the health endpoint, a subject could still be exposed to high TWA and not be at risk. Also, because the correlation coefficient between TWA and these other components of the field are modest to moderate, reducing TWA exposure would not reduce the risk proportionally to the decrease in the average field strength.

The following table compares the values of the magnetic field strength, measured by direct personal measurement or by environmental monitoring (spot or 24-hour measurements). Note that these are not data collected on the same sample, but general information gleaned from the literature (Zaffanella & Kalton, 1998), (Lee et al., 2002) and mathematical modeling.

TABLE VIII COMPARISON OF THE VALUES OF THE MAGNETIC FIELD (MG) STRENGTH MEASURED BY DIRECT PERSONAL MEASUREMENT WITH ENVIRONMENTAL MEASUREMENTS

PERCENTILE POINT OF EACH TYPE OF MEASUREMENT	TWA PERSONAL FIELD	AVERAGE SPOT HOME MEASUREMENT	MEDIAN SPOT HOME MEASUREMENT	MEDIAN 24-HOUR HOME FIELD
99	5.5	6.6	5.8	5.5
95	3.2	3	2.6	2.6
90	2.4	2.1	1.7	1.8
75	1.5	1.1	1	1
50	0.9	0.6	0.5	0.5

The personal TWA is generally higher than the environmental levels, reflecting the contribution that occasional close proximity to localized sources (appliances, wall wires, buried cables) makes to the average personal exposure. However, at the upper end of the distribution, this difference is minimal or non-existent, reflecting the fact that exposure to localized sources is common to all subjects. These localized sources contribute a few tenths of a mG to the personal 24-hour average (TWA).

What determines the "exposed" status of a subject in epidemiological studies (generally defined as a TWA above 2–4 mG) is usually the background environmental exposure, and that is contributed largely by home exposure (where people spend the most time). Certain occupations are an exception to this generalization because work-time exposure is so much higher than home exposure. According to Zaffanella's "1000 homes study" (Zaffanella, 1998), these background fields are due, with almost equal frequency, to proximate power lines and to grounding system fields.

Of course, this conclusion about background fields will change drastically if future research confirms the hypothesis-generating data by Lee (Lee et al., 2002) and Li (Li et al., 2002), indicating that, at least for spontaneous abortion (SAB), the true risk factor is the maximum daily exposure above 14 mG or the average field change between measurements. If maximum exposure, or one very strongly correlated to it, is the appropriate metric, then sources of localized fields (appliances, home wiring) become more important than power lines and ground currents because the latter seldom produce fields of the intensity implicated by the Lee and Li studies.

An additional difficulty that arises in this case is that personal measurements taken at the hip, as is common practice, may introduce errors that are large compared to the instrument error. This is because the field produced by a localized source shows significant variation based on which anatomical site is measured (DelPizzo, 1993),

even though some sources like power lines outside the house may produce a field at locations like the eye and the hip that are virtually identical. We also have no clear evidence by which to determine if the EMFs interact with biological systems at specific target organs. For example, there is some evidence that birds perceive geographic variations of the earth's magnetic field by means of their eyes (Graves, 1981). On the other hand, EMFs might act directly on cells in the marrow or in the uterus. Personal measurements taken at the hip might miss some exposures to the eye, but not exposures to the uterus.

It must be stressed that, although the Li (2002) and Lee (2002) studies are recent, good-quality studies with similar results, they have not yet been replicated. While meriting attention, they do not negate the wealth of data associating 24-hour average field to risk of other diseases.

19 Potential Annual numbers of Deaths Attributable to EMFs

Two recent review articles calculated the proportion of all childhood leukemia cases that might be attributed to the rare highest residential EMF exposures. This was estimated to be around 3%. With about 100 childhood leukemia deaths per year, this would translate to about 3 deaths in California per year attributable to EMFs. The evidence does not permit similar direct calculations for the other reviewed conditions. However, suppose that only 1% of the conditions that were considered in this evaluation (minus those that the three reviewers "strongly believed" were not caused by EMFs) could be attributed to EMF exposure. The numbers of attributable cases could still be in the hundreds per year and comparable to the theoretical burden of ill health that has motivated other environmental regulation (di Bartolomeis, 1994). The annual California deaths from each of these conditions are shown in Table IX. The reader can apply 1% to these numbers to verify the assertion in the previous sentence.

Table IX. 1998 Yearly California Deaths (some fraction of which might be affected by EMFs) *

AGE GROUP	CHILD LEUK.	ADULT LEUK.	CHILD BRAIN	ADULT BRAIN	MALE BREAST	FEMALE BREAST	SPONT. ABORT.+	ALS	ALZ-HEIMER	SUICIDE	ACUTE M.I.
0-19	99	0	79	0	0	0	11,000	0	0	171	2
29 Plus	0	1888	0	1294	30	4095	49,000	434	320	3044	17,236

* From http://www.ehdp.com/vn/ro/av/cau1/eg1/index.htm

+ Note: many would not consider spontaneous abortion as serious as the death of a child or adult.

20 Potential Added Lifetime Risk from High Exposure

Since epidemiology is a blunt research instrument, the theoretical lifetime individual risk that derives from any agent that has an epidemiologically detectable effect will be automatically greater than the lifetime risk of 1/100,000 that triggers many regulatory processes. This means most of the epidemiological associations examined in this document could clearly be of regulatory concern if real.

That being said, with the exception of miscarriage, the theoretical lifetime risks from the highest EMF exposures are such that, depending on the disease and assuming relative risks ranging from 1.2 to 2.0, 93% to 99.9% of even highly exposed individuals would escape contracting the non-miscarriage health conditions studied.

These insights are illustrated in Table X below.

TABLE X. ADDED LIFETIME RISK IMPLIED BY RELATIVE RISKS OF 1.2 OR 2.0 FOR RARE AND COMMON DISEASES

ANNUAL INCIDENCE	DISEASES IN CATEGORY	ADDED ANNUAL RISK FROM: RR =1.2; RR= 2.0	ADDED LIFETIME RISK FROM: RR = 1.2, RR = 2.0	LIFETIME CHANCE OF ESCAPING DISEASE AFTER EXPOSURE
1/100,000	ALS, Male Breast Cancer	0.2/100,000 ; 1/100,000	1.4/10,000; 7/10,000	99.99%; 99.93%
5/100,000	Child Leukemia	1/100,000; 5/100,000	2/10,000; 10/10,000	99.98%; 99.9%
10/100,000	Suicide, Adult Brain, & Leuk.	2/100,000; 10/100,000	14/10,000; 70/10,000	99.9%; 98.3%
100/100,000	Acute Myocardial Infarction	20/100,000; 100/100,000	1.4%; 6.8%	98.6%; 93.2%
1%	Alzheimer's	0.2%; 1%	NA (late onset)	NA
10%	Miscarriage	2%; 10%	NA (occurs during pregnancy)	NA

Note: RR = risk ratio; NA = not applicable

Two new epidemiology studies (Li et al., 2002), (Lee et al., 2002) suggest that a substantial proportion of miscarriages might be caused by EMFs. Miscarriages are common in any case (about 10 out of 100 pregnancies) and the theoretical added risk for an EMF-exposed pregnant woman may be an additional 10 out of 100 pregnancies according to these two studies. If true, this could clearly be of personal and regulatory concern. However, the type of EMF exposure implicated by the new epidemiological studies (short, very high exposures) probably come primarily from being very close to appliances and indoor wiring, and only rarely from power lines. Seventy-five percent of the women in the studies had at least one of these exposures during a day, and even one exposure a day, if typically experienced during pregnancy, seemed to increase the risk of miscarriage. Nonetheless, the vast majority of pregnant women with such exposures did NOT miscarry.

21 POLICY-RELEVANT AREAS FOR FURTHER RESEARCH

One of the major impediments to evaluating the potential bioactivity of a complex mixture is identifying the bioactive components of that mixture. This usually requires finding some kind of bioassay with which to assess the mixture and then successive fractions of it. While some epidemiologists have attempted to evaluate the effects of different aspects of the EMF mixture and some exposure analysts have attempted to characterize the occurrence and intercorrelation of its aspects, important policy-relevant questions still remain.

Experimentalists have rarely used the mixture as it occurs in real life and have focused instead on one or the other aspect of the mixture, usually pure sinusoidal 60 Hz fields at intensities far above those found in residential or blue collar occupational environments. Deeply ingrained experimental research styles and an orientation to explaining mechanisms rather than describing phenomena has meant that investigator-initiated research and even programs that attempted to guide research have rarely been characterized by progressively refined descriptions of dose-response relationships to produce stronger bioeffects.

This has been compounded by the expectation of a quick resolution of the question by those who fund research, as was the case with the New York State program of the mid-1980s, the current California Program, and the recent five year federal EMF–RAPID program. As was discovered after President Nixon's "War on Cancer" in the early 1970s, research progresses slowly and in successive multi-year research cycles, with the results of each cycle governing the direction of the next. It would not be surprising if it took four more five-year research cycles to clarify the EMF issue.

This means that if one were serious about clarifying this issue there would need to be a long-term commitment to steady research funding and funding for intermittent assessments of the state of the science and research directions. Most research peer review groups would favor research where a clear bioeffect was present and credible alternative mechanisms were being explored. Those situations tend to have

a high yield of early definitive results, and such results lead to continued research funding, publications, and research career advancement. The EMF area does not fit this description and from this perspective would receive a low priority for funding from the usual peer review study sections. Indeed, prominent researchers who doubt that there are any bioeffects, much less epidemiological effects, from the residential and occupational EMF mixture, feel there is nothing to find and have recommended that no more funding for this area be provided (Park, 1992).

Clearly the three DHS reviewers disagree with the assessment of the evidence to date and see a number of research areas which are worth pursuing that could influence and focus exposure avoidance strategies, if any. The cost effectiveness of further research has been a topic of the program's policy analysis and will be discussed at greater length in our policy integration document. The cost/benefit analysis of EMF research suggests that there is so much at stake in choosing between "expensive," "inexpensive," and "no mitigation" that more research funding can be easily justified. (http://www.dhs.ca.gov/ehib/emf/pdf/Chapter09-ValueofInformation.pdf)

The highest initial priorities for the reviewers would be to carry out exposure studies in residential settings and the workplace to see if purported aspects of the EMF mixture that would require different mitigation strategies are correlated with magnetic field exposure and could therefore explain their apparent effect. Such aspects include sudden exposures to the 60 Hz fields, such as micro-shocks, stray ground currents, and charged air pollutants. Such exposure studies would make it possible to reanalyze some of the existing worker cohorts to determine if these aspects are associated with diseases.

Rather than further pursuing new studies of rare diseases with long incubation periods, further studies of the more common conditions in which EMFs might have shorter induction periods, such as spontaneous abortion, acute myocardial infarction, and suicide should be given priority. These would be more relevant to a utilitarian policymaker.

On the experimental front, the reviewers suggest giving priority to finding reliable bioeffects below 100 mG and to carefully exploring dose-response relationships and then mechanisms. The balance between investigator-initiated and programmed research, as well as the guidelines that will be used for interpreting results, need to be carefully considered.

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1.0 INTRODUCTION

1.1 HOW TO READ THIS DOCUMENT

This document is not a summary of the facts from the vast literature on the possible health effects of extremely low frequency (ELF) electric and magnetic fields. There have been many such reviews, including some very recent ones (NAS et al., 1997), (Portier & Wolfe, 1998). Therefore, the descriptions reported in the Working Group Report published by the National Institutes of Environmental Health Sciences (NIEHS) will not be reiterated. It is available in print and on the web, although studies published since the deadline for inclusion in the NIEHS document will be described. In reaching the herewithin conclusions, however, the three reviewers will consider all studies.

In preparation for this evaluation, the California Electric and Magnetic Fields (EMF) Program held a two-day epidemiology workshop to discuss some of the most relevant epidemiological findings and methodological issues. The proceedings of that workshop, which were pivotal to some of the conclusions reported here, were published in a peer-reviewed Supplement (5) of the journal *Bioelectromagnetics* on January 22, 2001. Those who had assisted in the drafting of the 1999 NIEHS document were asked to provide updated versions of their contributions to help the reviewers in preparation of brief tabular summaries of the evidence for this document. The reader will find that chapters 1, 2, 3, and 7 cover in somewhat more detail areas covered in the Overview and Rationale of Conclusions. The latter was meant to be a brief summary of the entire document. The other chapters go into detailed discussions of the various streams of evidence and particular disease endpoints.

1.2 WHAT IS NEW IN THIS EVALUATION

NEW EVIDENCE

There have been many adequate reviews, including some very recent ones (NAS et al., 1997); (Portier & Wolfe, 1998); (IARC, 2001). The NIEHS review, in particular, was regarded as the starting point for this evaluation. Their NIEHS Working Group carried out their evaluation in June 1998. Several important studies have been published between the conclusion of the NIEHS Working Group review and this evaluation, including three major studies on childhood leukemia (Green et al., 1999b), (Green et al., 1999a), (McBride et al., 1999), (UKCSS, 1999). The deadline for including studies in this evaluation was June 24, 2000. This is later than the deadline originally mentioned in the Risk Evaluation Guidelines (REGs). Since the Department of Health Services evaluation began later than initially envisaged, the reviewers felt that it was unwise to disregard recently published, and possibly important, studies simply to observe a previously set but otherwise arbitrary date. Only one large study (van Wijngaarden et al., 2000) that dealt with suicide emerged during this extended deadline period.

In addition, the reviewers considered studies sponsored by the California EMF Program (Li et al., 2002), (Lee et al., 2002) and in the Epidemiology Workshop satisfying the criteria for inclusion in this evaluation, as specified in the Guidelines. In this final draft the DHS scientists also discuss articles that were brought to their attention during the public comment period (see Appendix 6 for additional references considered).

The document has features that were not present in the NIEHS document. One of these—presenting a graded degree of certainty of causality—is described below. Also discussed are the aspects that make up the EMF mixture that characterizes the exposure of persons who come near the power grid, the internal wiring of houses, and common household appliances. These are described in Chapter 3. The reviewers stress the notion of "mixture" because different aspects of EMF exposure (e.g., 60-cycle magnetic fields and high frequency transients) would require different actions for abatement. For each of the diseases considered, there are explicit discussions about whether the epidemiological associations observed, if real, would convey a risk from lifetime exposure that would be of regulatory interest. This is a parameter of interest to the social justice policy framework, which focuses on the individual risks of the most highly exposed. In Chapter 21 at 21.5, the baseline mortality for conditions considered possibly associated with EMFs are discussed. The reviewers ask if the attributable burden of mortality from even a very small fraction of that baseline would be of regulatory interest when compared to the mortality burden thought to be avoided by regulation of other agents. The attributable burdens of mortality or morbidity are parameters of interest to the utilitarian policy framework, which aims at the most good for the most people at the least cost. The document also attends to any evidence suggesting inequitable exposure or vulnerability to EMFs. This is relevant to the environmental justice policy framework, which is concerned with unfair distributions of risk.

Each health condition considered had at least two epidemiological studies in which there was a statistical association with some surrogate for EMF exposure. The list of conditions is similar to that discussed in the NIEHS document and includes:

- Adult and childhood leukemia
- Adult and childhood brain cancer
- Male and female breast cancer
- EMF as a “broad spectrum” carcinogen for all cancers
- Miscarriage
- Other reproductive and developmental conditions
- Amyotrophic lateral sclerosis (Lou Gehrig’s Disease)
- Alzheimer’s disease
- Acute myocardial infarction
- Suicide
- Other adverse non-cancer health outcomes (depression, electrical sensitivity)

1.3 QUALITATIVE BAYES OR DEGREE OF CERTAINTY APPROACH TO EVALUATION

The DHS scientists found the usual process of describing the pattern of evidence in some detail and then expressing an opinion (without explaining the rationale for that opinion) to be insufficiently transparent. Accordingly, they supplement the usual International Agency for Research into Cancer (IARC) procedure with an additional form of presentation and an additional form of judging whether EMFs are a cause of disease. The following table shows the questions that were systematically addressed. For definitions of epidemiological terms in the table see pages 20-22 (Sections 12.1.1 -12.1.3).

TABLE 1.1 QUESTIONS RELEVANT TO DEVELOPING A DEGREE OF CERTAINTY ABOUT CAUSALITY

EXPLANATIONS OF A STATISTICAL ASSOCIATION OTHER THAN A CAUSAL ONE
Chance: How likely is it that the combined association from all the studies of EMF and disease is due to chance alone?
*Bias: How convinced are the reviewers that EMFs rather than a study flaw that can be **specified and demonstrated** caused this evidentiary pattern? If no specified and demonstrated bias explains it, how convinced are they that EMFs caused these associations rather than **unspecified** flaws?*
*Confounding: How convinced are the reviewers that these disease associations are due to EMFs rather than to another **specified and demonstrated** risk factor associated with EMF exposure? If not due to a specified risk factor, how convinced are they that they are due to EMFs rather than to **unspecified** risk factors?*
*Combined effect: How convinced are the reviewers that these disease associations are due to EMFs rather than to a combined effect of chance and specified or **unspecified** sources of bias and confounders?*
ATTRIBUTES SIMILAR TO HILL'S (HILL, 1965) THAT ARE SOMETIMES USED BY EPIDEMIOLOGISTS TO EVALUATE THE CREDIBILITY OF A HYPOTHESIS WHEN NO DIRECT EVIDENCE OF CONFOUNDING OR BIAS EXISTS
Strength of association: How likely is it that the meta-analytic association is strong enough to be causal rather than due to unspecified minor study flaws or confounders?
Consistency: Do most of the studies suggest some added risk from EMFs? How likely is it that the proportion of studies with risk ratios above or below 1.0 arose from chance alone?
Homogeneity: If a large proportion of the studies have risk ratios that are either above or below 1.0, is their magnitude similar (homogeneous) or is the size of the observed effect quite variable (heterogeneous)?
Dose response: How clear is it that disease risk increases steadily with dose? What would be expected under causality? Under chance, bias, or confounding?
Coherence/Visibility: How coherent is the story told by the pattern of associations within studies? If a surrogate measure shows an association, does a better measurement strengthen that association? Is the association stronger in groups where it is predicted? What would be expected under causality? Under chance, bias, or confounding? How convinced are the reviewers that the magnitude of epidemiological results is consistent with temporal or geographic trends?
Experimental evidence: How convincing are the experimental pathology studies supporting the epidemiological evidence? What would be expected under causality, bias, chance, or confounding?
Plausibility: How convincing is the mechanistic research on plausible biological mechanisms leading from exposure to this disease? What would be expected under causality, chance, bias, or confounding? How influential are other experimental studies (both in vivo and in vitro) that speak to the ability of EMFs to produce effects at low dose?
Analogy: How good an analogy can the reviewers find with similar agents that have been shown to lead to similar diseases? What would be expected under causality, chance, bias, or confounding?
Temporality: How convinced are the reviewers that EMF exposure precedes onset of disease and that disease status did not lead to a change in exposure?
Specificity and other disease associations: How predominantly are EMFs associated with one disease or subtypes of several diseases? What would the reviewers expect under causality, chance, bias, or confounding? How much is their confidence in EMF causality for disease X influenced by their confidence that EMFs cause disease Y?

As a heuristic device, and following Huticinson and Lane (Hutchinson & Lane, 1980), the REGs suggested that these questions about the pattern of evidence be posed so that one could say the pattern is more likely under the hypothesis that EMFs contributed to the cause of that health condition or more likely under the hypothesis that chance, bias, or confounding produced the pattern. This allows the reviewers to provide the reader a rationale for the relative weight given mechanistic, animal pathology, and epidemiological evidence, and to understand which parts of the evidence suggest causality and which speak against causality.

The DHS reviewers coined the term "Qualitative Bayes Approach" to characterize a form of verbally justifying judgments about hazard that paid attention to the insights of Thomas Bayes, an 18th-century mathematician. His insights would suggest starting with some initial degree of certainty that any given agent is capable of being harmful based on knowledge about agents in general. Evidence is then accumulated on this specific agent and this changes the degree of suspicion or certainty.

Imagine a prehistoric hunter deciding whether to try some jungle fruit he has never seen before. He has an initial degree of suspicion high enough that he does not partake right away. He takes some fruit home and feeds it successively to several types of captured birds. As each species seems to survive, it seems less and less likely that the fruit would be harmful to humans. But since the leaves of the tree bearing that fruit resemble those from a tree that bears a poisonous fruit (causing the initial suspicion to be very high) the hunter's specific experiments might still leave him fairly suspicious and lead him to cruelly feed the fruit to a captive from another tribe. Only if the captive survived would his initial suspicions be allayed. This example illustrates Thomas Bayes's two key insights: As evidence builds we update our degree of certainty of harm, but at any point in time, that updated degree of certainty also depends on how suspicious we were initially. This idea is expressed mathematically by a simple formula.

Initial Odds * Relative Likelihood of Evidence = Updated Odds

The first term of the Bayes formula is the prior odds, that is, the odds that a given hypothesis is thought to merit *a priori*, before examining the evidence. In this document it is called the "prior" because it is not based on subsequent research.

The second term, the "relative likelihood," is a multiplier, calculated (or, in this case, qualitatively discussed) after scientific evidence has been collected and evaluated. The term "relative likelihood" is most properly restricted to the case where one compares the statistical likelihood of a result under one specific hypothesis relative to that under another hypothesis, usually the null. It expresses the likelihood of the observed pattern of evidence if EMFs do indeed cause disease, divided by the likelihood of that pattern if EMFs do not cause disease. The third term, the posterior, is the product of the first two and represents the odds of the risk being true after the prior has been modified by our evaluation of the evidence.

It has been pointed out (Royall, 1997) that policy-relevant evidence evaluation involves at least two very different questions, which often are confused. In the EMF context, these two questions are: (1) Does the evidence developed specifically about EMFs support the "hazard" hypothesis more than the "no-hazard" hypothesis?; and (2) How probable is it that EMFs are a hazard? Royall makes the case that the first question can be answered by inspecting the statistical relative likelihood or Bayes Factor to see if it is greater than 1.0 and, if so, by how much. Others (Lindley, 2000) would argue that non-experimental examples require consideration of biases and confounding and not a mere consideration of the relative likelihood of non-chance vs. chance. So, when the reviewers talk heuristically about the strength of the evidence as a question separate from Question 2, below, they mean their overall assessment of the relative likelihood of the evidence after considering bias, confounding, and chance. The reviewers use this construction even though it would not be easy to quantify and they do not attempt to do so as a separate step.

The second question requires considering both the prior and the strength of evidence. As noted, if the prior is very small, the usual run-of-the-mill strength of evidence will not be sufficient to convince us that the posterior probability of an EMF hazard is large.

Because of the difficulty of translating complex evidence into numbers, the reviewers only use the ideas behind the formula as a way of explaining how certain or uncertain they were to begin with and to explain the basis for the weights they gave a particular stream of evidence in order to update our degree of certainty. The Bayesian perspective used by the California reviewers recognizes that a reassuring pattern of evidence from a stream of evidence that often misses a harmful effect does not allay one's suspicion much, even though an alarming pattern of evidence from that same stream of evidence might increase suspicion a lot. Going back to the hunter-gatherer example: if birds sometimes survive eating fruits that are lethal to humans, then reassuring evidence from bird experiments would not allay suspicion as much as the death of the birds after eating the fruit would increase our suspicion. In the terminology of probability, the relative likelihood conveyed by a positive or negative result depends on the false-positive rate and false-negative rate characteristic of that stream of evidence. The

mathematical basis for this insight is discussed in the REGs (www.dhs.ca.gov/ehib/emf). It resulted in realizing that any stream of evidence, judged by the extent to which it usually produced false-positive and/or false-negative results, could be classified into four possible types: 1) capable of strengthening OR weakening one's certainty, 2) predominantly capable of strengthening certainty (like the bird feeding example given above), 3) predominantly capable of weakening certainty and, 4) uninformative, neither capable of strengthening nor weakening one's confidence. While this structured discussion helped organize the reviewers' judgments, it did not involve a mathematical combination of weights as would be the case in a quantitative Bayes evaluation. It should be noted that the Hill's attributes are like the bird feeding example. If they are present they strengthen confidence, but if they are absent, confidence falls only a little.

In the "Qualitative Bayes Approach," the DHS reviewers elicited their own expert judgment about the *a priori* (initial) probability of hazard after a special training session on how to avoid common errors of probabilistic estimation. It was important to be explicit about the prior probability because some physicists were arguing on the basis of physical theory applied to simplified biological models of the cell, that any biological effect from residential EMFs was impossible and thus had a vanishingly small initial credibility. This meant that they would require extraordinarily strong specific evidence to change their initial impression. Previous risk assessments have not explicitly considered this issue.

The discussion then turns to the patterns of specific EMF evidence in biophysical, mechanistic, animal pathology, and epidemiological streams of evidence. Obviously, if all four streams of evidence pointed toward or away from an EMF effect, the reviewers' job would be easy. But what if some streams of evidence are supportive and some are not? What weight should be given each stream of evidence? It was in the effort to address this problem that discussions of the inherent proclivity to give false positive and negative results came into play. This discussion was guided by a series of pre-agreed-upon questions described in the table above. The discussion included pro, con, and summary arguments. An example of such arguments are presented in the next table:

TABLE 1.2 EXAMPLE OF PRO, CON, AND SUMMARY ARGUMENT

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all the associations (relative risks) are above 1.00 or statistically significant.	(F1) The narrow confidence limits in the meta- analytic summaries and the low likelihood of this pattern of evidence by chance leans away from chance as an explanation.	(C1) A non-chance explanation must be sought.

Considering this kind of structured discussion helped organize the reviewers' judgments, after they weighed all the information in the usual way, although it did not involve a mathematical combination of weights as would be the case in a quantitative Bayes evaluation. After consideration of this carefully structured discussion of the evidence (considering how much more—or less—likely the pattern of evidence would be if the risk hypothesis were true compared to the likelihood of that evidence if EMFs were safe), the reviewers expressed an expert judgment on the posterior probability of a causal relationship.

1.4 QUALITATIVE BAYES RISK EVALUATION COMPARED TO TRADITIONAL AND QUANTITATIVE BAYES RISK EVALUATIONS

The traditional risk assessment has a section in which a judgment is given as to whether the agent being evaluated is capable of causing cancer or some other adverse health effect. This is called the "hazard identification." The typical presentation is heavy in describing the relevant evidence and rather light in explaining the rationale for the conclusion. Often the weight, given mechanistic, animal pathology, and epidemiological streams of evidence, depends on a review

panel's interpretation of adjectives which best describe the pattern of evidence. For example is the pattern of evidence "sufficient" or should it be called "limited"? Can confounding and bias be "reasonably" discounted? Then there are pre-agreed-upon rules for combining the streams of evidence. Limited animal evidence plus limited epidemiological evidence results in one rank, sufficient animal evidence plus limited epidemiological evidence leads to another rank, and so forth. The combinatorial rules are straightforward, but the rationale for deciding that a stream of evidence is "limited" is not clearly defined and is subjective.

A completely quantitative Bayesian approach of the sort proposed by McColl et al. (McColl et al., 1996), or by Lindley (Lindley, 2000), would require assigning many quantitative parameters to a complex Bayesian Net model which would mathematically combine the subjectively assigned parameters to produce a posterior degree of certainty of causality. To the reviewers' knowledge, this kind of model has never been applied to any environmental agent and the DHS reviewers' stakeholders urged them to opt for transparency rather than mathematical elegance.

In response to the third draft, the Electric Power Research Institute contracted with Professor Sander Greenland in late 2001 to prepare a quantitative Bayesian model based on the epidemiological evidence for childhood leukemia. Since his will be the only extant quantitative Bayesian analysis, the reviewers contrast its proposed approach to their own. His model will provide a posterior dose-response curve based on a prior dose-response curve, the pooled epidemiological data, and prior estimates of selection bias and non-differential measurement bias. The all-important biophysical, mechanistic, and animal pathology streams of evidence will not be part of Greenland's model, although they could influence the prior dose-response curve in a subjective way. Calculations from Greenland's model would allow one to provide a probability that the posterior slope of the dose-response curve is not flat, that is, that there is some causal effect.

The following table compares the Qualitative Bayes evaluation to the traditional and to Greenland's Quantitative Bayes approach to risk evaluation as to a number of characteristics.

TABLE 1.3 COMPARISON OF USUAL RISK ASSESSMENT METHOD TO QUALITATIVE AND QUANTITATIVE BAYES METHODS

CHARACTERISTIC	USUAL METHOD	QUAL. BAYES	QUANT. BAYES
Evaluates all streams of evidence?	Sometimes	Yes	Focuses on epidemiology, other streams influence prior
Elicits prior probability?	No	Yes	Prior dose-response curve
Compares likelihood of each element of the evidence under the hazard and non-hazard hypotheses?	No	Qualitatively	Quantitatively with many of the parameters subjectively elicited
Pro, con, and summary arguments to make rationale transparent?	No, most risk assessments are skimpy in justifying hazard categories assigned	Yes	Not unless a supplementary document were to accompany the model
Combines relative likelihoods mathematically to derive posterior?	No	No	Yes, but non-epidemiological evidence is folded into the prior subjectively
Elicits an expert posterior probability after considering all elements of the evidence?	No	Yes	No
Displays judgments of various judges separately?	Usually strives for semblance of consensus	Yes	Technically possible for different experts to elicit their own parameters
Frames intermediate degrees of certainty as "not a proven hazard?"	Often	No, reveals posterior probability	No, reveals posterior probability

Both the Qualitative Bayes and the Quantitative Bayes evaluations can provide a posterior degree of certainty that the epidemiological associations are causal, which, if in the range from 10 to 90 out of 100, will not seem trivial to the general public and will stimulate policy discussions. The statements, “possible,” “there is no proven hazard,” or “there is no consistent evidence,” often used for this range of degrees of confidence, will not stimulate such discussions. Thus, both the Qualitative Bayes and Quantitative Bayes methods pose risk communication “problems” for those who believe that society should not begin policy discussions until most scientists are virtually certain that a hazard exists. The traditional hazard identifications would pose the same “problem” if they routinely used more nuanced categories of hazard assessment that distinguished between, say, a certainty level of 11/100 and one of 89/100. As now framed they pose a risk communication “problem” for those who believe that policy discussions should begin even before a hazard is firmly established.

Compared to traditional qualitative evaluations, the Qualitative Bayesian approach makes the evaluation more transparent, but it still accommodates different opinions. The DHS reviewers have no doubt that critics of their conclusions could use the Qualitative Bayes format to make their points. Some of the physicists who believe that they have a theory to prove that no residential EMF effect is possible would use priors so low that their posterior degrees of certainty would be low as well; the toxicologists who believe reassuring animal tests prove that EMFs are safe would make a case that the animal study results decrease their degree of certainty of a hazard to a level below their initial degree of certainty. In a contentious area such as EMFs, the reviewers doubt very much that any of the

three styles of risk evaluation discussed in the table would force a consensus among subject matter experts who weigh and interpret the several streams of evidence differently. Even in the Quantitative Bayes model experts will use different priors and will elicit different subjective relative likelihood parameters for items like bias and confounding, for which there is no direct evidence. In the traditional method, experts will disagree on whether a stream of evidence warrants the adjective “limited” or “sufficient,” and in the Qualitative Bayes approach experts will disagree on “how much more likely” the pattern of evidence is under the causal and non-causal hypotheses. But the reasons for these different judgments will be more transparent in the Qualitative Bayes style of risk evaluation and we believe that this is desirable in controversial areas.

1.5 WHO DID THE EVALUATION AND WHAT FORM DID THE CONCLUSIONS TAKE?

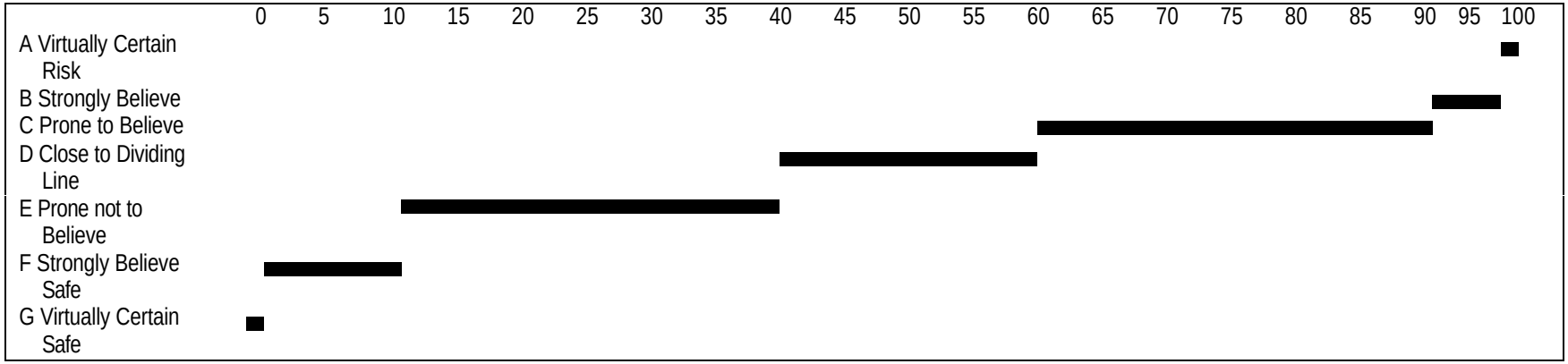
On behalf of the California Public Utilities Commission (CPUC), three scientists who work for the DHS were asked to review the studies about possible health problems from electric and magnetic fields (EMFs) from power lines, wiring in buildings, some jobs, and appliances. The CPUC request for review did not include radio frequency EMFs from cell phones and radio towers. Reviewer 1, Vincent DelPizzo, Ph.D., is a physicist and epidemiologist; Reviewer 2, Raymond Richard Neutra, M.D., Dr.P.H., is a physician epidemiologist; and Reviewer 3, Geraldine Lee, Ph.D., is an epidemiologist with training in genetics. All three have published original research in the EMF area and have followed the field for many years. To integrate and extend their body of knowledge, the EMF Program contracted with specialists in biophysics, statistics, and animal experimentation to prepare a background in critical literature review in their respective fields to make sure that the literature review was up to date through June 2000 (P Gailey Ph.D., G Sherman Ph.D., W Rogers Ph.D., and A Martin Ph.D.). The first three were involved with the writing of the 1998 NIEHS report. Furthermore, for each chapter of the review, another DHS epidemiologist or toxicologist was asked to read the original literature and consulted extensively with whichever of the three core reviewers was writing that chapter. This ensured that the writer based his/her evaluation on an understanding of the evidence that was as objective and consistent as possible. All three reviewers worked for the EMF program for at least five years and to some extent they influenced each other’s thinking through their constant interaction and the review of each other’s chapters. All three did their reviews according to the guidelines that had been developed earlier and approved by the program’s Science Advisory Panel (SAP). The Guidelines specified that the conclusions about any hazard should be done using two systems. The first was developed by IARC and has been used by NIEHS. It rates an agent as a "definite," "probable," "possible," or 'not a" carcinogen, or specifies that the evidence is “inadequate” to rate the agent. In addition, the California Guidelines specified that in order to accommodate the probability-based computer models of the program’s policy projects each of the DHS reviewers would individually assign a number between 0 and 100 to denote their degree of certainty that epidemiological associations between EMFs and certain diseases were causal in nature. The Guidelines, which were modified with advice from public comment and the SAP and the DHS reviewers, attached pre-agreed-upon English language phrases to various ranges of this degree of certainty. These are presented below in Table 1.4.

If all three judges had best judgments above 50 out of 100, but that fell in different categories in Table 1.4 judges were said to be "inclined to believe" that EMFs increased the risk of that disease to some degree.

If they found themselves in different categories below that point, they were said to be “inclined not to believe" that EMFs increased the risk of that disease to any degree.

TABLE 1.4 EVERYDAY ENGLISH PHRASES TO DESCRIBE DEGREES OF CERTAINTY OF CAUSALITY (GRAPH ILLUSTRATES THE RANGE OF CERTAINTY NUMBERS TO WHICH THE PHRASES PERTAIN)

ARE THE HIGHEST EMFS AT HOME OR AT WORK SAFE, OR DO HIGH EMFS INCREASE THE RISK OF ..... TO A DEGREE DETECTABLE BY EPIDEMIOLOGY?	DEGREE OF CERTAINTY ON A SCALE OF 1 TO 100
Virtually certain that they increase the risk to some degree	>99.5
Strongly believe that they increase the risk to some degree	90 to 99.5
Prone to believe that they increase the risk to some degree	60 to 90
Close to the dividing line between believing or not believing that EMFs increase the risk to some degree	40 to 60
Prone to believe that they do not increase the risk to any degree	10 to 40
Strongly believe that they do not increase the risk to any degree	0.5 to 10
Virtually certain that they do not increase the risk to any degree	< 0.5



1.6 DOES PHYSICAL THEORY MAKE AN EVALUATION UNNECESSARY?

A number of scientists (mainly physicists) have expressed the opinion that the hypothesis that environmental EMFs are hazardous is intrinsically implausible and, therefore, all empirical evidence supporting it must be regarded as artifactual. In the Bayesian language, the prior—if not truly zero—is so vanishingly small that any realistic value of the relative likelihood conveyed by the evidence will inevitably fail to produce large posterior odds. Therefore, in their opinion, society should stop paying attention to this issue altogether. The DHS reviewers do not agree with this position. Because they did not find that the theoretical arguments were strong enough to dismiss the hypothesis out of hand, they proceeded with the evaluation of the evidence according to the REGs. Nonetheless, the reviewers do consider this and other relevant arguments for large and small prior degrees of confidence that EMFs might cause disease.

2.0 THE INITIAL OR "PRIOR" DEGREE OF CONFIDENCE OF A POSSIBLE EMF HAZARD

2.1 TO WHAT HYPOTHESES DO THE DHS SCIENTISTS' PRIOR PROBABILITIES REFER?

As mentioned above, developing a prior probability is unavoidably subjective and an issue of hot debate among statisticians. Although the reviewers' priors were not used as a mechanical multiplier to derive a posterior, presenting the priors does reveal explicitly the assumptions of the reviewers and allows the reader to see how much the EMF-specific evidence has moved the three reviewers from their *a priori* degree of confidence. In particular, the reviewers wanted to address explicitly whether the biophysical arguments make their prior vanishingly small and how their prior for EMFs compares to that for other environmental agents.

The posterior degrees of confidence, on the other hand, were elicited directly, after a structured consideration of the EMF-specific evidence. The three core reviewers did their best to separate out what could have been known or discussed in 1979 before the publication of Wertheimer and Leeper's first paper on alleged power line effects and use only that prior knowledge to form their prior degrees of confidence. For example, the extensive dialogue on the biophysical credibility of a noticeable physical induction of molecular changes from residential EMFs emerged after 1979. However, it was based on knowledge available before 1979 and could have taken place then, so it was considered relevant to the prior. EMF-specific epidemiological, mechanistic, and animal pathology results were excluded from discussion.

The three reviewers also discussed environmental agents in general and tried to anchor and compare their EMF priors to their "general" priors. In this way they tried to avoid having EMF-specific information influence their priors. Unless the reviewers did this, the priors affected by the EMF-specific information would be falsely inflated and there would be a falsely smaller difference between the priors and the independently elicited posteriors based on EMF-specific information.

After taking a workshop on probability elicitation, the reviewers developed an initial prior and then challenged each other as to the rationales for their respective priors. The main lines of argument are reproduced below. The three reviewers first asked themselves:

> How probable is it that the EMF mixture (comparing the 95th percentile or above to the 1st percentile or below) of residential exposure in the United States is capable of altering the risk of one or more types of cancer or other disease with a relative risk between X and Y? These relative risks should be detectable by epidemiology.

Ideally, one would like to answer this question for a series of relative risks, ranging from those suggesting a protective effect (Relative Risk < 0.95) to those with virtually no effect, (RR = 0.95–1.05), and including levels of increasing risk (RR = 1.06 –1.19), (RR = 1.2–1.95), (RR =1.95–2.95), (RR = 2.95–4.95), and (RR $\geq$ 5). That is, one would like to draw a distribution of prior probabilities for all possible relative risks conveyed by the 95th percentile or above exposure within a typical residential setting relative to the lowest risk exposure. A histogram of these probabilities would have an area of 1.0.

By necessity, the reviewers have not specified exactly what should be contrasted, that is, what aspect of the mixture of the EMF exposure (e.g. what frequency), what summary exposure metric (e.g., time-weighted average (TWA)), or what levels of that metric (e.g., 2 milliGauss (mG) vs. 0 mG). The reviewers have been vague in the same sense than an epidemiologist might be vague about aspects of red wine (alcohol content, grape type, aging, sediment) dosages and dosing patterns when she asks:

> "How probable is it *a priori* that red wine consumed in the usual amounts might alter the risk of cardiovascular disease with relative risks ranging from X to Y?"

Thus, the reviewers conceptualize this general prior probability distribution as if it related to exposures to the whole EMF mixture.

By querying one's prior beliefs, one can begin to anchor the graph of probabilities in various ways:

> How much of the distribution is concentrated around a RR between 0.99 and 1.01, because a) there is really no effect at all, or b) any effect, whether beneficial or harmful, would be virtually negligible?

> Is the graph symmetrical, that is, is it equally likely that EMFs increase or decrease the rate of disease?

> Where does the distribution "start" and "stop"? That is, given what we know about temporal patterns of disease after the introduction of electricity, are

we comfortable assigning non-negligible probabilities to very protective or very deleterious relative risks? Could the usual range of EMF exposure have increased or cut the disease rate by a factor of 100? 50? 25? 5?

Assuming that the epidemiologically detectable RR is about 1.2, is the probability of an EMF effect above this limit vanishingly small? If so, that anchors the graph even further. If not, what does the curve look like above RR=1.2?

2.2 What Do Trends in National Statistics Do To Bound the Upper Limit of An EMF Effect?

With a few notable exceptions (see discussion below of childhood leukemia), a large percentage increase in non-infectious diseases during the century that electricity was gradually introduced across the United States and in the world has not been documented. This fact can serve to establish an upper bound for the possible risk from EMFs for the many diseases whose incidence did not increase.

Environmental agents tend to have a skewed distribution of exposure, with most people at the lower levels of exposure and a thin "tail" of people at the highest exposures. This means that comparing people above the 95th percentile of exposure to people below that level is a comparison with a group that is mostly comprised of people with very low exposures.

Environmental epidemiology rarely has the ability to detect a dose-response pattern more refined than a kind of step function with some risk at the very highest levels of exposure, such as the 95th percentile, when compared to all other levels of exposure or to the lowest percentiles of exposure. If EMFs produce detectable effects, it would not be surprising if that pattern were to emerge.

How high would the RR conveyed by the 95th percentile have to be before it would substantially affect the overall rate of disease? One can answer this by calculating something called the Population Attributable Risk Percent (PAR%), the percentage fall in the overall rate of a disease of interest if EMF "exposure" contributing to that disease rate were removed.

It can be expressed as:

$$PAR\% = 100 * \{ (PrU + PrE * RR) - 1 \} / (PrU + PrE * RR)$$

Where PrU = probability of being unexposed

Pr E =probability of being exposed

RR = relative risk conveyed by exposure.

Figure 2.1.1 shows PAR% as a function of the relative risk conveyed by the 95th percentile.

If the 95th percentile conveys a barely detectable relative risk of 1.2 relative to persons exposed below that level, the PAR% is a few percentage points. If it conveys a relative risk of 2, the PAR% is about 5%. Once it conveys a 5-fold relative risk, it accounts for 20% of the overall rate—a detectable effect. It must convey a RR of 21 for EMFs to account for 50% of the current overall rate. This would be the point at which removing the 95th percentile exposure would cut the overall disease rate in half. So, the reviewers' *a priori* confidence in relative risks above 5 or below 1/5 is quite low; but it could be higher for values between these two values because such effects would not be easily noticed.

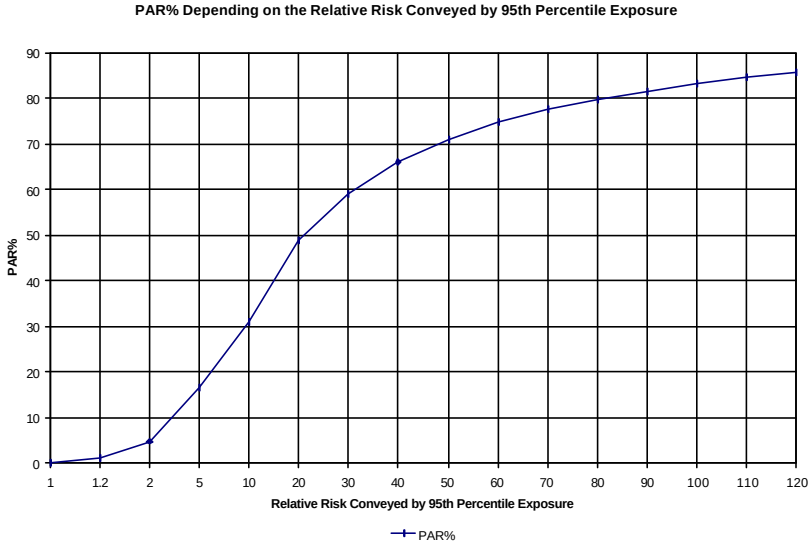


Figure 2.1.1

What if EMFs were very unusual for environmental agents and showed a step function of risk at quite low exposures, say the 25th percentile of exposure? Figure 2.1.2 shows the PAR% as a function of the RR conveyed by the 25th

percentile of exposure. A RR of 2 now produces an obvious 40% impact on any disease that is routinely tracked, and a RR of 5 now produces an 80% impact.

So, for diseases that are tracked by vital statistics or special registries and have not changed much, we can say that it is unlikely that EMFs have even modest effects in the lower ranges of exposure. But, if they behave like many other environmental agents, and only display effects at the upper percentiles of exposure, they could convey a RR between 1.2 and 5 without producing obvious impact on overall rates as the use of electricity spread.

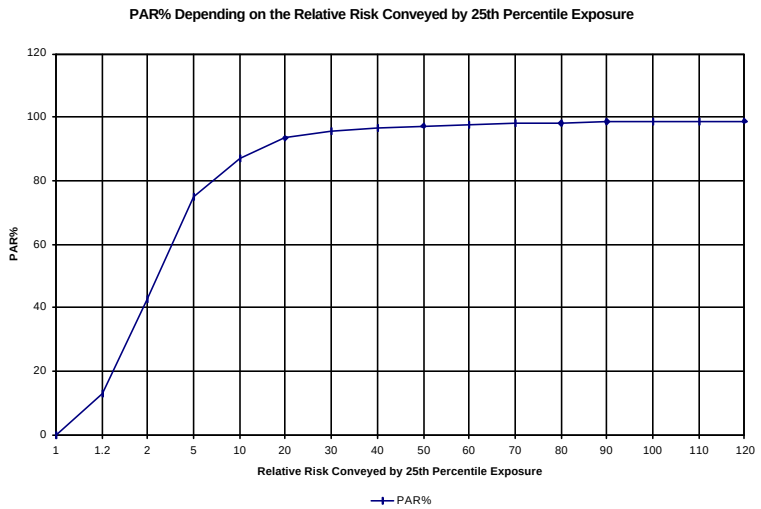


Figure 2.1.2

2.3 The Special Case of Childhood Leukemia

Milham (Milham & Ossiander, 2001) drew attention to something that Court Brown and Doll (Brown & Doll, 1961) had pointed out more than forty years ago, that an increased risk of leukemia mortality for 2- to 4-year-old children first appeared in the 1920s and increased in intensity in the 1940s. Thus some factor(s)—perhaps electricity, perhaps accuracy in diagnosis—in those modernized locations caused the registration of toddler leukemia deaths to increase threefold. The evidence from Court Brown, Doll, and others that childhood leukemia mortality registration had indeed increased during the early 20th century increased the prior probability of a moderately large EMF effect, at least for childhood leukemia. This meant that the prior probability of a moderate effect for childhood leukemia was larger than for other diseases.

2.4 Arriving at a Prior Degree of Certainty

As explained above, the prior represents the credibility of the hypothesis before hypothesis-testing research was undertaken. It is based only on past experience in analogous situations and on general scientific knowledge. Therefore, the reviewers exclude from this original consideration any epidemiology, experimentation, or exposure research that has been specifically targeted at the power-system EMF hypothesis. The reviewers include in their consideration theoretical estimates of a threshold for environmental EMF impact on biological systems as calculated using basic biological and physical theory because, in principle, these theoretical arguments could have occurred at any time in the recent past, devoid as they are of any empirical input. The reviewers summarize, below, arguments that would tend to increase or decrease one's initial degree of confidence that exposures could influence risk.

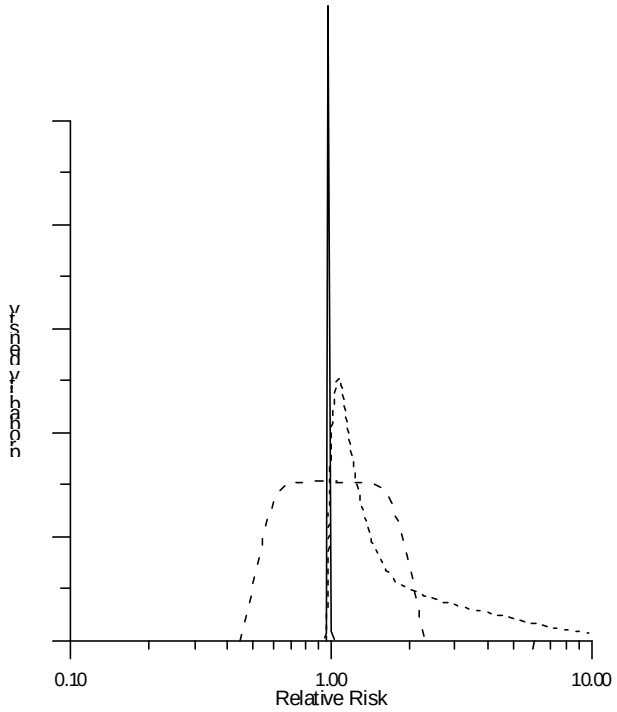


Figure 2.1.3

The DHS reviewers developed arguments in favor and against three possibilities (Figure 2.1.3):

1) A probability distribution of the prior that is symmetrical and has a large variance, suggesting that beneficial and harmful effects are equally likely (indicated by long dashes).

2) A probability distribution of the prior that is tightly clustered around a relative risk of 1, essentially no effect (indicated by a solid line).

3) A probability distribution of the prior strongly skewed toward relative risks of a harmful nature (indicated by short dashes).

In discussing the distribution of the *a priori* probability of risk, the reviewers refer to 50–60 Hz EMFs as an "extraneous" environmental agent. They define an extraneous agent as one that either is totally extraneous to the evolutionary environment or is present in abnormal concentrations and forms (e.g., lead, refined from the mineral galena, its natural form, and introduced in industrial products).

An extraneous agent is not to be confused with an impurity. Drinking water is full of components other than H_2O, but most of these were present over the billions of years life has evolved on Earth. The question, "What percentage of impurities found in today's water supplies should people be concerned about?" may well have a different answer from, "What percentage of impurities in today's water that were not there during evolutionary times should people be concerned about?"

2.4.1 Arguments for A Probability Distribution of the Prior That is Symmetrical and has a Large Variance

Argument

In the absence of evidence, one should keep an open mind and allow that, although extreme protective effects or extreme risks are very unlikely, because the consequences would have become apparent without targeted research, moderate protective effects or moderate risks are both possible and equally likely.

Rebuttal

Agents that are beneficial for the whole, or at least the vast majority of the population (e.g., fresh fruit) are so because the human body has evolved to make use of what is available in the environment. Many environmentally extraneous agents are also beneficial (e.g., mineral supplements) but only to those individuals who need their specific properties. Although we add fluoride to drinking water and iodine to table salt, we do so in concentrations similar to those found in nature in some (but not all) water sources and in marine salt. The reviewers cannot think of a single factor that is totally extraneous, environmentally, and that people would consider adding to the water supply or disperse in the environment trusting that it would benefit at least some section of the population without harming other sections.

2.4.2 Arguments for a Distribution of the Initial Degree of Confidence Tightly Clustered Around a Relative Risk of 1 (No Effect)

Argument

Environmental EMF levels induce fields and currents that are orders of magnitude lower than endogenous fields and currents in living organisms. It is true that some animals can perceive very weak electric and/or magnetic fields, but these require highly specialized organs, which these animals evolved to take advantage of variations in the geomagnetic field. Precisely because EMFs in the extremely low frequency range (50–60 Hz) are man-made, there was no reason or opportunity for the body to develop a detector of electric or magnetic fields at these frequencies.

Such organs, in species where they are found, are relatively large and complex. There is no reason to believe that such an organ in humans could be so simple and small as to be so far undetected.

Therefore, theory indicates that EMFs can have no biological effect and therefore no pathological effect. Notice that the ignorance about a possible physical induction mechanism for residential-intensity EMFs is qualitatively different from the ignorance we have about the exact physicochemical mechanisms for chemical carcinogens or the exact physical interaction with an asbestos fiber. In the EMF case, what little IS known suggests that no effect should be happening and we cannot build a physico-biological model that predicts a biological effect at ambient levels. With other agents, a variety of plausible mechanisms are known, but it is not known if one of them is at work.

Even assuming that EMFs can be perceived above noise and that a coupling mechanism exists, the amount of energy transferred to the body would be so small that any effect must be trivial and easily tolerated. The effects of residential exposures to other agents have rarely been detectable by epidemiological methods.

For other physical agents that are known to cause harm, the mechanism by which physical energy initiates a cascade of chemical or biological events is understood. One physical mechanism by which electromagnetic radiation could cause cancer is the breaking of molecular bonds if the photon energy is sufficiently high. Other adverse effects (e.g., radio frequency EMF (RF) burns) are due to the heating of tissue and the induction of relatively large currents. None of these mechanisms occurs with exposure to environmental 50–60 Hz EMFs at residential or even blue collar exposure levels. No other mechanism has been identified which could lead from biological change (even if biological change were possible) to physiological or pathological results that would cause us to believe there would be an effect.

For these reasons the prior for any effect except, at most, very small ones should be virtually zero.

Rebuttal

Modern science is based on observation and experimentation. Theory cannot "prove" anything. It can only explain or predict observation. The physio-biological models that predict no effect is possible are sophisticated on the physics side but may be incomplete on the biology side.

Man-made 50–60 Hz fields are extremely regular: macroscopic changes in intensity and direction are negligible on the time-scale of the sinusoidal oscillations. Because of their time coherence (e.g., the regularity of the frequency) they might be distinguished from random noise, using a comparable time reference. This would not necessarily require a resonance but simply a time marker against which the regularity of these fields could be verified.

Because of their space coherence (e.g., the fact that the crests and troughs of these waves reach all parts of the body at the same time) billions of cells are stimulated simultaneously. These weak but numerous stimuli may add together to produce a detectable signal.

Although the human body had no evolutionary incentive to develop a detector to use 50–60 Hz EMFs, it is possible that these man-made frequencies are perceived as a perturbation of the status quo. By analogy, a radio set is not designed to detect electromagnetic interference from an appliance but does so, with a resulting adverse effect to the radio's proper function.

The way the human body may detect these oscillating, extremely regular signals bears no relationship to the way magnetic organs in some animals detect static fields. The shape and size of these organs is not necessarily relevant to predict the shape and size of a 50–60 Hz detector.

The only well-understood effects of electromagnetic radiation are those deriving from the breaking of atomic and molecular bonds, the heating of tissue, and the induction of electrical currents. Nevertheless, there was vast, if controversial, scientific literature even before 1979 (the time when the Wertheimer and Leeper study was published) that argued there were observed health effects from radio frequency EMFs, for which there was no mechanistic explanation. [For a critical summary, see Steneck, "The Microwave Debate."] EMFs are not unique in this respect. Many carcinogens and reproductive toxicants act by unknown mechanisms. For example, the physical-induction mechanisms responsible for the effects of ultra-violet (UV) light are not fully understood either.

It is not known if energy is the appropriate measure of dose. Radio signals reaching a radio antenna a have very low energy level but are adequate to make the radio work. A weak stimulus may be all that is required to trigger a stronger, secondary effect.

Discussion and Conclusion

Since the inception of modern science, the role of theory has been not to prevail over observation, but rather to explain and predict it. Both in ancient and modern times, there are numerous examples of theories being proven wrong and models being proven inadequate. One cannot put too much trust in the theory-based belief that EMFs cannot be distinguished from noise and, therefore, cannot produce biological or pathological effects.

2.4.3 Arguments In Favor of a Distribution of Prior Probabilities Strongly Skewed Toward Relative Risks of a Harmful Nature

One should be suspicious of extraneous environmental factors. Living organisms are complex entities that, over billions of years, developed opportunistically to maximize the benefits and minimize the damages of the agents making up the environment in which they exist. They have had no time to evolve specific defense mechanisms (e.g., specific detoxifying enzymes) against extraneous agents. Moreover, in the case of something so totally artificial as 50–60 Hz EMFs, they do not even have general repair mechanisms (such as detoxifying enzymes developed for a naturally occurring different, but chemically similar, agent) or simple aversion reflexes, such as blinking or coughing.

Electric currents play a vital role in normal physiological functions. EMFs induce electric currents and therefore have the potential to seriously disrupt a vast range of biological functions.

Even if low on a physical scale of measure, environmental levels of EMFs at 50–60 Hz are potentially a massive biological dose, representing a many-order-of-magnitude increase over the virtually insignificant levels existing in the natural environment.

In the absence of specific evidence as to dose, it is reasonable to assume that the probability of an adverse effect is higher for a small risk than for a large one, and that it becomes vanishingly small for values of the risk so large as to make it inconsistent with the information gleaned by environmental health monitoring (RR 5, according to standard calculations). Therefore, a distribution of prior probabilities positively skewed should be accepted, with a mode close to, but greater than, 1.

Rebuttal

It seems unreasonable that all extraneous agents would be harmful, particularly at low ambient levels. Using the criterion that at least 1 of 4 standard bioassays was positive (male and female rats and mice), Fung et al. (Fung et al., 1993) summarized the carcinogenicity of 379 chemicals as 68%, 37 "natural agents" as 40%, and 126 agents chosen primarily on volume of use as 21%. So "natural" agents were not less carcinogenic than agents chosen at random.

One ought to think quantitatively about detection limits and dose. Just because aspirin is capable of treating headaches does not mean that one aspirin tablet added to the city's reservoir will cure all the headaches in town. That 21% of chemical agents chosen primarily on the volume of use can produce cancer in laboratory animals at the highest tolerated dose does not mean that very low doses of the same agent in the environment will produce ***epidemiologically detectable*** cancer. Perhaps none of these chemicals has a threshold of effect, but each is increasing the risk to some small degree, even though not enough for an epidemiologist to detect. A very small proportion of the 21% would produce effects from low environmental exposures that could be detected by epidemiologists, and this is equally true for "natural" and "extraneous" agents.

2.5 Conclusion of the Core Evaluators

Reviewer 1

On the basis of the arguments for a high or a low prior for biological effects, Reviewer 1 believes that the probability that environmental EMFs are beneficial is very small because of the extraordinary coincidence that would be required for a complex organism to benefit from something that was totally absent during its evolutionary development. The probability that extraneous electrical signals leave an organism that depends on electrical signals for its proper functioning totally unperturbed also is very small. The question is one of dose and size of effect. If the dose and the resulting response are small and easily tolerated (not repaired, because Reviewer 1 has no basis to believe that repair mechanisms against an unknown and totally alien agent may have evolved by accident), then pathological results could be seen only in a very few subjects who, either by chance or extraordinary vulnerability, are not able to tolerate these small effects. (This is analogous to saying that exposure to a common cold virus carries a very small

risk of death). Reviewer 1 believes that this scenario has a very high probability. However, this probability is not close to unity because the dose may be considered in relative terms. In this case, the reviewers are justified in believing that an increase from virtually zero to several mG represents a massive increase in dose that is not easily tolerated. In broad terms, Reviewer 1 believes that the *a priori* probability that EMF has little or no effect is large (about 85%) and that the probability of a beneficial effect is considerably smaller (say, about 3%) than that of a moderate (RR < 5) risk (about 12%).

Reviewer 2

Reviewer 2 was not much swayed by arguments linking physical principles to simplified biological models which predicted that no biological effect and no pathological effect would be possible from residential and occupational exposures to the EMF mixture. The EMF mixture was, thus, only slightly less likely to cause harm than any other randomly chosen agent about which one initially has little specific information. The initial lack of mechanistic information or relevant animal pathology evidence was similar to that of all members of the class of agents about which little is known. And effects of regulatory concern could have been occurring without being noticed if, like other environmental agents, the risk were barely detectable by epidemiology and confined to the upper percentiles of exposure. It seemed reasonable that extraneous agents were somewhat more probable to produce harm than agents prevalent in the environment during the course of evolution, but Reviewer 2 thought that even such agents as these were more likely to produce no detectable effect at all. The fact that electrical and magnetic phenomena are involved in normal physiology also argued somewhat for the possibility that the EMF mixture might have biological or pathological effects. But even if Fung et al. (Fung et al., 1993) are correct, that agents chosen at random have a 20% chance of producing a noticeable pathological effect at high dose and some effect at ambient doses, perhaps a quarter of those (say 5%, range 1%–20%) produce effects at low doses that epidemiologists can see with relative risks (say, between 1.2 and 5.0) or their reciprocal on the protective side. More of that 5% (3 or 4%) would be on the harmful (RR > 1.2) rather than the beneficial (RR < 0.8) side, on the basis of the "extraneous agent" arguments.

This is tantamount to saying that the probability of no epidemiologically detectable effect at any dose would range from 80% to 99%, with a best estimate at 95%.

The prior probability of relative risks above 5.0 or below 0.2 seemed extremely small.

Reviewer 3

Reviewer 3 believed that environmental (residential and occupational) EMFs are exogenous agents, for all practical purposes, nonessential for normal human function. This is because they are man made and added by human activity resulting from an increase in electricity use correlated with industrialization. Hence, the probability of a prior protective nature of EMFs is very small. Reviewer 3 believed that environmental EMFs convey some health risk, since they are composed of a mixture of a variety of components, where any one or several of the components may interact with a number of biological processes and result in an adverse health effect. The probability of any effect greater than a relative risk of 1.0 is 17% (median value) with a range of 5% to 37%, with a very small probability of relative risks above 5. These distributions are based on the fact that 1) most diseases are multifactorial in nature, 2) adverse health effects associated with environmental agents may be subtle and have long induction periods, and 3) information about the relevant biological EMF agent(s) and their associated dose are not known.

3.0 THE EMF MIXTURE

A careful assessment of the electricity-related exposures from power lines, appliances, and occupations would reveal what amounts to a complex mixture with many aspects, such as EMFs with their respective frequency, polarization, etc. In this report these will be called the "aspects" of the mixture. Each aspect varies from instant to instant to form a time series of intensities that can be summarized as a single number by various summary "exposure metrics," which may be more or less biologically active. For example, the exposure metric of ionizing radiation that best predicts biological effects is the simple integral of the exposure time series. The exposure metric that best predicts the effect of an antibiotic might be the integral of blood levels above some threshold. Other electricity-related correlates of proximity to power lines, internal wiring, and appliances are not part of the fields at all, but might be correlated with them. These include contact currents from stray currents on plumbing and in the earth, and intermittent shocks. These will be called the "ingredients" of the mixture.

What aspects, ingredients, or exposure metrics, if any, should be considered in this risk evaluation?

EMFs associated with electric power are time-varying vectorial quantities. Since the fields alternate between symmetrical positive and negative values, their simple time average is zero. However, the energy associated with these fields is proportional to the ***square*** of their amplitude, therefore the field strength (often called ***intensity***) is expressed by the average of the square root of the square of the field (root mean square or ***rms***). The basic measure of human exposure to EMFs is the time-averaged rms of the intensity. In some studies, short-term measurements of the field taken in various environments were multiplied by a weight proportional to the time a subject spent in each of those environments and then averaged, hence the commonly used acronym TWA (time-weighted average) to indicate average rms of the field. A crude surrogate to assess exposure to average field is the so-called "wire coding," consisting of classifying residences based on their proximity to visible power lines and on the type of these power lines. For a number of years, some researchers believed that if the risk increase were truly due to some component of the EMF mixture that this component must be something other than the time-weighted average (something unintentionally captured by wire coding). Recent new data and reanalysis of old data (Linet et al., 1997), (Greenland et al., 2000) appear to have convincingly disposed of this hypothesis.

This does not mean that the other common metric used in epidemiological studies, the TWA measured by surrogates (e.g., point-in-time or "spot" measurements), calculations using engineering models and historical line current loads, and job exposure matrices) is necessarily the true causal agent. The units, mG or μT (1 μT = 10 mG), that measure the magnetic field's TWA do not describe the magnetic field (and much less the electric field associated with it) any more than the units marked on the volume dial on a stereo system describe the sound coming out of the speakers. Nevertheless, although the reviewers cannot definitely "rule in" the component(s) of interest, they can rule out some aspects of the fields which are not correlated with TWA field strength. Neutra and DelPizzo have a detailed discussion of this issue (Neutra & DelPizzo, 2001). Included here is a table adapted from that paper, pointing out which of the more commonly proposed metrics are indeed correlated to TWA and which are not (note that not all proposed metrics can be traced to the published literature, although they may have been discussed at professional meetings):

TABLE 3.1.1

EXPOSURE METRIC TO 30-300 HZ MAGNETIC FIELDS	HIGH WIRE CODE	HIGH MEASURED FIELD	HEALTH ENDPOINT	REFERENCE
(1) TWA	**U**	**U**	**U**	many
(2) Length of time with constant field above a threshold	**U**	**U**		
(3) Repeated periods of elevated exposure	**U**	**U**	**U**	(Feychting et al., 1997) (Feychting et al., 1998b) (Lee & McLoed, 1998)
(4) Third harmonic	**U**	?	?	(Kaune, 1994b)
(5) Resonance with static field	No	No	?	(Kaune, 1994b) (Bowman et al., 1995)
(6) Time above a threshold	**U**	**U**	?	(von Winterfeldt & et. al., 2001)
(7) Polarization	?	?	?	(Burch et al., 2000)
(8) Transients	No	No	?	(Preece et al., 1999)
(9) Maximum daily exposure	**U**	**U**	**U**	(Li et al., 2002) (Lee et al., 2002)
(10) Average change between measurements	**U**	**U**	**U**	(Lee et al., 2000)
(11) Electric field	Not inside home	Not inside home	?	(Miller et al., 1996) (Coghill et al., 1996)

This table allows the reviewers at least to rule out two metrics that are supported by mechanistic arguments, but not (or at least not consistently) by empirical data: 1) magnetic field transient, which can induce strong, if brief, electrical currents in the body; and 2) resonance conditions, which may facilitate energy transfer from the field to the living organism.

The table also emphasizes the difficulty of testing the hypothesis of an EMF risk by conducting experimental studies. Studies using an exposure apparatus that delivers an appropriate TWA (but not an appropriate exposure to a hypothetical aspect, ingredient, or exposure metric found in residential or occupational environments) are liable to produce false-negative results. Alternatively, they may produce positive results which suggest dose-response relationships different from those that may result from environmental fields.

Reducing TWA exposure will reduce exposure to several other metrics and reduce any risk from TWA or the exposure metrics that are changed with it, although this is

a sufficient, but not necessary condition. If TWA is not by itself the causal factor and if it could be identified and removed from the EMF mixture, the component directly causally associated with the health endpoint, a subject could still be exposed to strong average fields and not be at risk. Also, because the correlation between TWA and these other components of the field are modest to moderate, reducing TWA exposure, while reducing the risk, will not reduce it proportionally to the decrease in the average field strength.

The following table compares the values of the magnetic field strength (in mG) measured by direct personal measurement or by environmental monitoring (spot or 24-hour measurements).

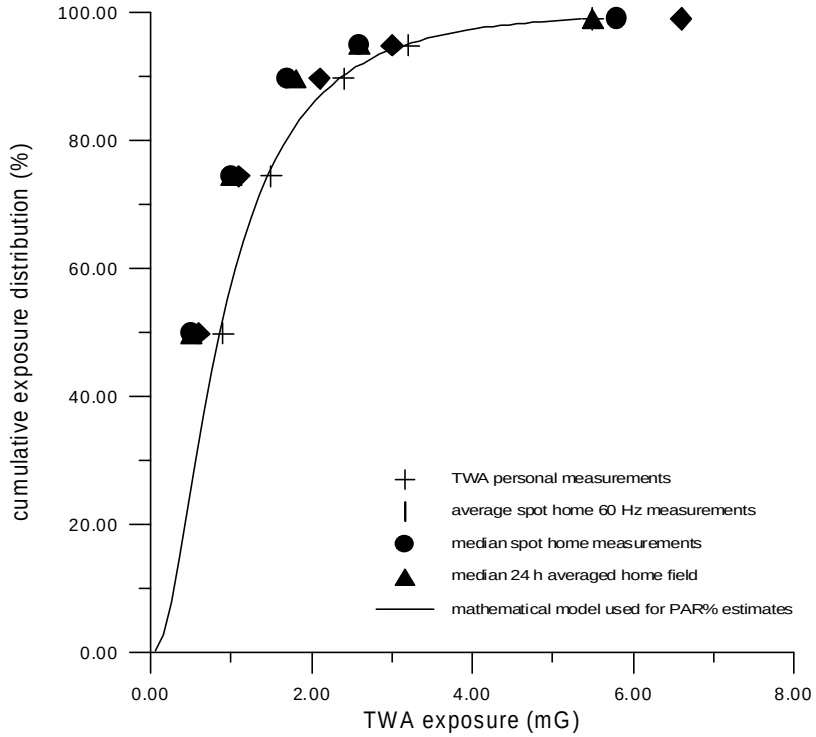
Note that these are not data collected on the same sample, but general information gleaned from the literature (Zaffanella, Savitz & Greenland, 1998), (Zaffanella, 1993), (Lee et al., 2000) and mathematical modeling.

TABLE 3.1.2

PERCENTILE POINT	TWA PERSONAL FIELD	AVERAGE SPOT HOME MEASUREMENT (60 Hz)	MEDIAN SPOT HOME MEASUREMENT	MEDIAN 24- H HOME FIELD
99	5.5	6.6	5.8	5.5
95	3.2	3	2.6	2.6
90	2.4	2.1	1.7	1.8
75	1.5	1.1	1	1
50	0.9	0.6	0.5	0.5

Figure 3.1.1 plots these data over a mathematical fit.

Figure 3.1.1



The personal TWA generally is higher than the environmental levels, reflecting the contribution that occasional close proximity to localized sources (appliances, wall wires, buried cables) makes to the average personal exposure. However, at the upper end of the distribution, this difference is minimal or non-existent, reflecting the fact that exposure to localized sources is common to all subjects averaging some tenths of an mG. What determines the "exposed" status of a subject in epidemiological studies (generally defined as a TWA above 2-4 mG) is usually the background environmental exposure and that is heavily contributed by home exposure (where people spend the most time). Certain occupations are an exception to this generalization because work-time exposure is so much higher than home exposure.

According to Zaffanella's "1000 homes study" (1995), these background fields are due, with almost equal frequency, to proximate power lines and to grounding system fields.

Of course, this conclusion will change drastically if future research confirms the hypothesis-generating data by Lee (2000) and Li (2000), indicating that, at least for spontaneous abortion (SAB), the true risk factor is the maximum daily exposure above 14 mG or the average field change between measurements. If maximum exposure is the appropriate metric, or one very strongly correlated to it, sources of localized fields (appliances, home wiring) become more important than power lines and ground currents because the latter seldom produce fields of the intensity implicated by the Lee and Li studies. An additional difficulty that will arise in this case is that personal measurements taken at the hip, as is common practice, may introduce errors that are large compared to the instrument error. This is because the field produced by a localized source often is very different when measured at different anatomical sites (DelPizzo, 1993) and because there is no clear evidence by which to determine if the EMFs interact with biological systems at specific target organs.

It must be stressed, however, that although these are recent, good-quality studies, they represent isolated findings which merit attention but do not negate the wealth of data associating average field to risk of other diseases.

4.0 BIOPHYSICAL ISSUES

4.1 BIOPHYSICAL LITERATURE

See the NIEHS review and Appendix B. The NIEHS Working Group (1999) has reviewed relevant biophysical discussions where pro and con arguments are summarized below.

(IMPORTANT NOTE: Table 4.1.1. and all the following similar tables are meant to be as comprehensive as possible. The reviewers have strived to include ALL conceivable arguments that can be raised in favor or against the hypothesis of causality, whether based on data or on speculation. Inclusion of an argument does not necessarily mean that that argument is supported by any of the reviewers. The reviewers' judgment is expressed only in the third column, "COMMENT AND SUMMARY.")

TABLE 4.1.1 BIOPHYSICAL PRO AND CON ARGUMENTS

BIOPHYSICAL PRO AND CON ARGUMENTS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
General		
(A1) All biological models of hypothesized mechanisms (e.g., magnetite) show that no effects are possible at environmental levels.	(F1) One cannot anticipate all the possible biological structures and configurations occurring within the body at the molecular, cellular, and organ levels. The physics of these models may be correct, but the biological assumptions are simple and perhaps incomplete. Thus it is impossible to predict what is and is not possible.	(C1) A credible biophysical-mechanism hypothesis would boost the level of confidence tremendously, but absence of one cannot be used to dismiss empirical epidemiological evidence.
(A2) Forces and energies involved in biochemical processes are far stronger than those induced in humans by environmental fields.	(F2) Power frequency fields exhibit spatial and temporal coherence that may make them discernable above the random endogenous noise.	(C2) This argument has already been considered in setting the prior; therefore, it cannot be used to modify it.

BIOPHYSICAL PRO AND CON ARGUMENTS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A3) The resonance mechanisms are not supported by common sense argument. They assume molecules or atoms without surrounding molecules. No resonance model has been replicated reliably in multiple laboratories. (A3a) The theories led to epidemiological validation (Bowman et al., 1995), (Kaune, 1994b), (Kaune et al., 2002) with conflicting results.	(F3) Several models have been proposed that may well be viable considering the fact that biological processes depend on continuous energy input and therefore cannot be adequately described by models based on equilibrium thermodynamics. Several of these models (e.g., cyclotron resonance and parametric resonance) are supported by some in vitro data. (F3a) Some analyses suggest a weak agreement between Kaune and Bowman. Better personal exposure monitoring may show an effect.	(C3) Having a clear or even simplified, but uncontroverted, mechanism would strongly increase the posterior. However, given the complexity of the characteristics of the exposure, the nature of biological processes, and the ill-understood etiologies of the diseases associated with EMF exposure, the fact that these mechanisms are still tentative and controversial cannot be used as an argument against causality. (C3a) While it is possible that brief flashes of resonance could occur when the right combination of alternating (AC) and steady (DC) fields are encountered, given the demonstrated variability of both fields in the residential environment, it is hard to believe that the associations seen to date, which based on measurements taken in one location, could be strongly correlated with personal exposures. In any case, resonance conditions are not associated with wire code or high TWA magnetic fields and thus do not explain their associations with disease.
(A4) The field itself grows, collapses, and then grows in the opposite direction and collapses 50-60 times a second. So, the average field is always zero. Therefore, for basic symmetry principles, effects of 50-60 Hz EMF should vary as the square of the intensity. The reviewers have an upper benchmark for biological effects from which they can infer the shape of the lower end of the theoretically proper dose response, which is based on the square of the field, [the phenomenon of phosphenes (flashes of light) induced by magnetic fields at the Tesla level]. The human epidemiology does not follow the predicted shape and thus must be due to bias or confounding.	(F4) Many materials (including cell membranes) exhibit nonlinear electrical properties; therefore symmetry arguments do not apply. In interaction where the time scale is short relative to the period of the applied signal, the above arguments for a B-squared dependence are not relevant. For example, a neuron that fires rhythmically at 100 Hz would experience only part of a 60 Hz cycle before firing. The average value of this part of cycle is not zero. Even if the initial interaction depends on the square of the field, there is no reason to believe that in the complex chain of events between this first step and the manifestation of a disease, this square field relationship should be retained. A physical agent may interact in more ways than one. The phosphene phenomenon may not be the proper anchor for a carcinogenic or reproductive	(C4) Prediction and evaluation of evidence is fine when one understands the system being evaluated, which is usually the case in physics. There is too much scientists do not understand to give weight to predictions about dose response based on simple physical principles.

BIOPHYSICAL PRO AND CON ARGUMENTS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
	health process.	
(A5) Attempts to use theory to predict effects have not been productive.	(F5) Most of the biophysical theorizing has not reflected close collaboration with experimentalists.	(C5) Until there are accepted robust effects at levels below 100 mG, where current theories suggest no effects are possible, there can be no evidence on which to try out theories.
(A6) The strategy of physics, to predict results from first principles and then test them, is time tested and successful. It predicts that EMF effects are impossible at residential levels of exposure.	(F6a) To use theory to predict empirical observation is only ONE of the strategies of physics and not the mainstay of modern science, in which observation is the ultimate test of truth. (F6b) Over the two decades of EMF research, the calculated threshold for EMF interaction has decreased as the biological component of the models has become more sophisticated. This argues that these thresholds cannot yet be accepted as accurate.	(C6) Theory can guide experimentation when the system is sufficiently understood. The changing predictions remind the reviewers how little this system is understood.
(A7) There are no published robust experimental effects seen in multiple laboratories, at levels below 40-100 mG, which is what theory predicted.		(C7) The chicken embryo literature shows statistically significant effects in the 40–100 mG range, which have been dismissed because the effect was not larger than the variation between historical controls. This is an additional evidentiary condition imposed by regulatory agencies to avoid false positives. The reviewers do not totally ignore this evidence.
		(C8) The demand that experimental mechanistic effects be detectable at residential levels of exposure is a stringent requirement that many recognized chemical pathogens would not be able to meet.

4.2 CONCLUSIONS

While biophysical arguments seem to have strongly decreased the confidence of potential health effects of some scientists (primarily physicists), these arguments did not influence to any great degree the initial degree of confidence or the updated degree of confidence of the review team. The fact that chicken embryo experiments appear to offer some evidence contrary to the theoretical predictions increases our skepticism in theoretical models. Overall, the prior of the review team was little changed by biophysical arguments.

5.0 MECHANISTIC STUDIES

5.1 BODY OF EVIDENCE

The mechanistic body of evidence is extensive and is characterized by many isolated experiments using a variety of exposure conditions. The DHS reviewers and those in the NIHES Working Group did not find a pattern of evidence providing much clarification. In as much as the evidence is not easy to summarize concisely, the reader is referred to the NIEHS Working Group's review.

Nevertheless, the DHS reviewers felt that studies on chicken embryo developments under magnetic field exposure show a somewhat consistent pattern of results than may deserve further investigation. For a summary of these studies see Appendix Five.

5.2 PRO AND CON ARGUMENTS

TABLE 5.2.1 GENOTOXICITY AND REGULATION OF GENE EXPRESSION

AGAINST CAUSALITY	FOR CAUSALITY	COMMENT AND SUMMARY
(A1) There is no consistent pattern supporting genotoxicity.	(F1) If an effect is limited to a susceptible section of the general population, the small number of animals used in these studies may include few or NO susceptible subjects. This is a distinct possibility: Scarfi et al. (Scarfi et al., 1997) show increased micronuclei formation in lymphocytes from patients with Turner's syndrome (only one X chromosome) when the cells are exposed to pulsed but not to sinusoidal magnetic fields. No effect of these treatments is seen in lymphocytes from normal patients. The response of lymphocytes from Turner syndrome patients demonstrates the existence of at least one genetic subpopulation with greater sensitivity to specific types of EMF exposure. There may be other sensitive subpopulations. This problem is not encountered in epidemiological case-control studies or in sufficiently large cohort studies.	(C1) The evidence indicates that EMFs cannot be a cancer initiator, but is not relevant to the hypothesis that EMF is a risk factor at some stage of cancer OTHER than initiation.
(A2) Some positive results have been irreproducible even within the original laboratory.		(C2) The possibility that EMFs act only on a subset of the general population casts more doubts on the probative value of negative animal experiments.

AGAINST CAUSALITY	FOR CAUSALITY	COMMENT AND SUMMARY
(A3) There is overwhelming negative evidence against DNA damage and chromosomal effects.		(C3) True, but the risk of developing cancer does not depend only on the ability of damaging DNA.
(A4) There are consistently negative results of mutagenesis below 0.1–1 mT.		
(A5) Any reported effect resulted from exposure to fields is orders of magnitudes above environmental levels.		

TABLE 5.2.2 SIGNAL TRANSDUCTION

AGAINST CAUSALITY	FOR CAUSALITY	COMMENT AND SUMMARY
(A1) Most of the positive results come form single laboratories and have not been independently replicated.	(F1) Results indicate that magnetic fields ≥ 0.1 mT and electric fields ≥ 1mV/m have effects on a number of signal transduction-related pathways in mammalian cells.	(C1) It is not clear how these results influence the interpretation of epidemiology.
(A2) The physiological significance of blocking of antiproliferative effects of melatonin or Tamoxifen, published by three laboratories (Liburdy et al., 1993), (Blackman et al., 2001), (Ishido et al., 2001) is unknown. The effect is very weak.	(F2) The blocking of antiproliferative effect of melatonin at 1.2 μT has been published by three labs. This suggests the possibility of bioeffects at intensities where biophysical theory suggests that no bioeffect would be expected.	(C2) Any replicated biological effect at exposure levels comparable to those in the environment increases the credibility of the hypothesis. Moreover, effects on cell proliferation are relevant to cancer and reproductive health. These findings need to be replicated and published from other labs.
(A3) There is no clear pattern of effects.		(C3) Failure to find cell physiological responses to high intensity or near residential intensity fields is unsupportive of the hazard hypothesis. But there is the usual problem of testing a complex mixture on special cell preparations so that the sensitivity of the test is not great. Many agents will not cause effects observable in the laboratory at ambient levels of concentration. Those agents often have linear dose response so that high doses produce obvious effects. Epidemiological evidence suggests that this may not be true for EMFs.
(A4) Positive results have been achieved only with prolonged exposure to strong (>50 uT) fields.		

5.3 CONCLUSIONS

Overall, the picture is mixed and does not affect the DHS reviewers' confidence level much.

The blocking of antiproliferative effect of melatonin at 1.2 uT, that has been published by three independent labs, increases the level of certainty, but not by much. The lack of replicated in vitro reactions to pure 60 Hz fields at near ambient levels and the lack of an understanding of a chain of mechanisms leading from exposure to pathology is an evidentiary deficiency, but this stream of evidence often is prone to false negatives. If positive results are present, they increase confidence a lot, but their absence decreases it only a little.

6.0 ANIMAL PATHOLOGY AND PHYSIOLOGY

6.1 THE EVIDENCE

Tables 6.1.1–6.1.20 summarize the literature reviewed for this evaluation in addition to what was reviewed by the NIEHS Working Group. The DHS scientists re-reviewed certain critical studies in the light of newer studies.

The pro and con arguments are presented in Tables 6.2.1-6.2.18.

Summary Tables for In Vivo Bioeffects Review: California EMF Program

TABLE 6.1.1 CHEMICALLY INITIATED BREAST CANCER IN RATS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Beniashvili et al., 1991)	young female rats; groups of 50	20 μT (?); 50 Hz	For either 0.5 or 3.0 hrs per day for up to 158 days; some groups received nitrosomethyl urea (NMU) as a single *i.v.* injection of 50 mg/kg	palpation of tumors & histology	Exposure to a 50 Hz MF increases incidence of mammary gland tumors, decreases latent period for tumor development, & increases incidence of malignant tumors.
(Loscher et al., 1993)	young female Sprague-Dawley (SD) rats; groups of 99	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	Magnetic field (MF) exposure promotes chemically initiated mammary tumorgenicity.
(Mevissen et al., 1993)	young female SD rats; groups of 36 or 99	exposed = 30 μT, sham = 0.7 μT& control = ambient; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	The authors offer the tentative conclusion that MF exposure can act as a promoter or co-promoter of breast cancer.
(Loscher et al., 1994)	young female SD rats; groups of 36 or 99	exposed = 30 μT, sham = 0.7 μT & control = ambient; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors & histology	Under the conditions examined, MF exposure does not promote chemically initiated mammary tumorgenicity.
(Baum et al., 1995)	young female SD rats; groups of 99	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	histology data for exp't of Loscher et al. (Loscher et al., 1993)	MF exposure did not increase incidence but did accelerate tumor development.
(Loscher et al., 1994)	female SD rats; 36 or 99 per group	sham-exposed, 0.7 μT, 10 μT, 50 μT, or 100 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	# tumor data from several previous exp'ts; not based on histology	There is a strong, linear dose-response relationship.

TABLE 6.1.1 DMBA & BREAST CANCER IN RATS (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Mevissen et al., 1996a)	female SD rats; 99 per group	exposed = 10 μT; shams = 0.01μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	The authors do not emphasize lack of differences between groups in this exp't. They concentrate on lack of melatonin effects in this exp't & increased tumors in other exp'ts.
(Mevissen et al., 1996b)	female SD rats; 99 per group	exposed = 50 μT; shams = 0.05μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	Exposure to 50 μT exerts a clearly detectable, dose-dependent co-promotional effect on DMBA-initiated tumorgenicity without affecting melatonin.
(Anisimov, Popovich & Zabezhinski, 1997)	outbred female rats, groups of 20 - 50	not well described; 50 Hz, 160 A/m in coils of box solenoids	presumably c. 24 hrs/day for up to c. 1 year; some groups received 50 mg/kg NMU; groups held in 24-hr light, 24-hr dark or 12:12 light:dark	tumors by palpation, plus histopathology	MF increases breast cancer: light increases & dark inhibits breast cancer.
(Loscher, Mevissen & Haussler, 1997)	young female SD rats; 99 per group	exposed = 100 μT & sham-exposed = 0.1 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	# tumors; data from previous exp'ts	MF promotional effect is affected by season of year.
(Ekstrom, Mild & Homberg, 1998)	young female SD rats; groups of 60	exposed = 0.25 & 0.5 mT; 50 Hz	c. 20 hrs/day for 25 wks; MF was "intermittent" (15 sec on & 15 sec off); DMBA = 7 mg	tumors assessed by palpation; no histology	MF exposure had no promotional effect on tumor development.
(Mevissen et al., 1998)	young female SD rats; 99 per group	exposed = 100 μT & sham-exposed = 0.1 μT; 50 Hz, horizontal sham-exposed & 100 μT; 50 Hz	c. 24 hrs/day for 13 wks; DMBA = 20 mg	tumors assessed by palpation & visualized at autopsy but no histopathology	Exposure to 100 μT had a clear promotional effect on tumor development, replicating a previous observation.
(Anderson et al., 1999)	young female SD rats; 100 per group	sham-exposed, 100 μT @ 50 Hz, 500 μT @ 50 Hz, 100 μT @ 60 Hz	18.5 hrs/day for 13 wks; DMBA = 20 mg	# tumors palpated, plus histology	This exp't provides no evidence that MF exposure promotes tumor or carcinoma development.
		sham-exposed, 100 μT @ 50 Hz, 500 μT @ 50 Hz			

TABLE 6.1.1 DMBA & BREAST CANCER IN RATS (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Boorman et al., 1999a)	young female SD rats; 100 per group	sham-exposed, 100 μT @ 50 Hz, 500 μT @ 50 Hz, 100 μT @ 60 Hz	18.5 hrs/day for 26 wks; DMBA = 10 mg	# tumors, etc.; complete histology	No evidence that MF exposure promotes tumor development.
(Thun-Battersby, Mevissen & Loscher, 1999)	young female SD rats; groups of 99	sham exposed & 100 μT; 50 Hz, horizontal	c. 24 hrs/day for 27 wks; DMBA = 10 mg	% tumors @ 13 wks & % tumors @ autopsy; histology completed	The data indicate that MF exposure promotes tumor development.

TABLE 6.1.2 LEUKEMIA OR LYMPHOMA

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Reif, Lower & Ogilvie, 1995)	pet dogs	MF measured in yard & house	epidemiology study of real-world exposure	cases = dogs with lymphoma & controls = dogs with other forms of cancer	As with humans, there is a weak association between lymphoma & MF exposure.
(Fam & Mikhail, 1996)	CFW mice; exposed = 92 & control = 41	25 μT @ 60 Hz; controls at 0.5 μT; horizontal	continuous for 3 generations; natural light plus 12:12 L:D	premalignant, early lymphoma or advanced lymphoma in 3rd generation	Multi-generation exposure to very strong MF induces lymphoma.
(McCormick et al., 1998)	PIM mice; 30 per group	sham-exposed (0.1 μT), 2 μT, 20 μT, 0.1 μT (contin.) or 0.1 μT (on/off); 60 Hz, linearly polarized, transient-free	18.5 hrs/day for 23 wks; ENU-initiated	lymphoma incidence & latency	MF does not induce cancer in genetically susceptible mice.
	TSG-p53 mice; 30 per group	sham-exposed or 1 mT (contin.)	18.5 hrs/day for 23 wks; genetically "initiated"		
(Morris et al., 1999)	male Fischer 344 rats; 108 per group, 18 animals assessed at 5, 6, 7, 8, 9, & 11 wks	sham-exposed 2 μT @ 60 Hz 1 μT @ 60 Hz horizontal	20 hrs/day; all subjects were LGL-initiated; one group received ^{60}Co @ 5 Gy	hematology, spleen growth, & LGL infiltration of liver & spleen	MF exposure does not promote leukemia in rats.

TABLE 6.1.3 SKIN CANCER

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kumlin et al., 1998a)	female transgenic (K2) mice & non-transgenic littermates; four groups of 43 or 44	shams = < 0.05 μT, continuous = 100 μT, intermittent = 1.3, 13 & 130 μT for 20 min each, followed by "0" for 2 hrs; 50 Hz	exposure was for 10.5 months; UV light at 1 MED given 3 times/wk	tumor incidence	MF exposure modestly increased tumor development.
(Sasser et al., 1998)	SENCAR mice; 56 per group	sham-exposed 2 mT @ 60 Hz	6 hrs/day for 5 days/wk for 23 wks	% with tumors # tumors per animal	MF exposure does not initiate cancer.

TABLE 6.1.4 BRAIN CANCER

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Mandeville et al., 2000)	female F344 rats; 50 per group; 8 groups, including 2 internal controls & 1 positive control	sham (< 0.02 μT), 2, 20, 200 or 2,000 μT; 60 Hz	20 hrs/day for 420 days; animals received *in utero* exposure to NMU; positive control group received TPA	histology for tumors in central & peripheral portions of nervous system	MF exposure does not promote NMU-initiated brain tumors.

TABLE 6.1.5 LONG-TERM TOXICOLOGY BIOASSAYS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Boorman et al., 1999b)	female & male Fischer 344 rats; 100 per group	sham-exposed, 2 μT, 200 μT, 1 μT (contin.), or 1 μT (1 hr on/off); 60 Hz, horizontal	18.5 hrs/day for 2 years	histology of all tissues	Lifetime MF exposure does not cause toxicity, including cancer. Thyroid C-cell adenomas & carcinomas regarded as an anomaly.
(McCormick et al., 1999)	female & male B6C3F1 mice; 100 per group	sham-exposed, 2 μT, 200 μT, 1 μT (continuous), or 1 μT (1 hr on/off); 60 Hz, linearly polarized, transient free	18.5 hrs/day for 2 years	histology of all tissues	Lifetime MF exposure does not cause toxicity, including cancer.

TABLE 6.1.6 REPRODUCTION & DEVELOPMENT

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kubinyi et al., 1998)	pregnant CFLP mice; progeny followed to postnatal day 24; 240 adult females & 240 adult males exposed	100 μT, 50 Hz, vertical	exposed on days 2-18 of gestation for 7 hrs per day; adults exposed for 17 days	survival plus body & organ weights	MF exposure does not affect these measures.
(Svedenstal & Johanson, 1998)	young male CBA/Ca mice; 2 groups of 12 (6 wks of age at start) & 2 groups of 6 (4 wks of age at start)	sham exposed = ambient (0.1 - 0.7 μT); MF-exposed = 5 μT; 50 Hz	54 hrs	^{125}IUdR incorporation; counts for whole body & for 12 specific organs	MF exposure does not affect cell proliferation.
(Ryan et al., 1998)	male & female SD rats; 40 per group	sham-exposed, 2 μT, 200 μT, 1 μT (continuous), or 1 μT (1 hr on & 1 hr off); linearly polarized, transient free, 60 Hz	18.5 hrs/day; F_0 exposed for 18 wks; & F_1 exposed for 29 days	many measures in F_0, F_1, & F_2 generations	MF exposure does not cause reproductive or developmental effects.

TABLE 6.1.7 HEMATOLOGY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Bonhomme-Faivre, Mace & Bezie, 1998b)	Swiss mice; 6 wks of age at start; 2 groups of 12	monthly average = 5 μT & diurnal cycle = 3.2-6.8 μT; controls with ambient MF (< 0.1 μT)	exposed for 350 days in cages on floor in a laboratory directly above the main service bus bars of a 13 kV transformer	many hematological measures sampled at 20, 43, 63, 90, & 350 days	E/MF exposure produces diverse hematologic changes that differ with duration of exposure.
(Burchard, Nguyen & Block, 1999)	Holstein cows; multiparous, non-lactating (n = 8); & ovariectomized heifers (n = 7)	10 kV/m & 30 μT; 60Hz, vertical EF & horizontal MF	exposure was for 30 days for c. 22 hrs/day; data were collected during pre-exposure & post-exposure periods; indwelling catheters were used to sample cerebrospinal fluid	concentrations of 9 ions in both plasma & cerebrospinal fluid	MF exposure produced changes in concentrations of five ions.
(Svedenstal & Johanson, 1998)	CBA/S mice; males & females used in 1st exp't; males used in remaining 4 exp'ts; animals usually 20-30 days of age at start, except exp't 2 animals = 84 days of age	exposed = 5 μT (rms, 14 μT peak-peak) & controls = 0.7-9.1 μT; 50 Hz	in 5 exp'ts, exposure was for various durations; exp't 1 = 240 days, exp't 2 = 140 days, exp't 3 = 60 days, exp't 4 = 96 hrs, exp't 5 = 90 days	numbers & types of leukocytes & erythrocytes	MF exposure does not exert strong effects on erythrocyte & leukocyte formation.

TABLE 6.1.8 IMMUNOLOGY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Haussler et al., 1999)	young, female SD rats; data from groups of 5-9	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	sham- or MF-exposed for 14 wks, following 20 mg DMBA treatment; c. 24 hrs/day	IL-1 & IL-2 expression	MF exposure does not affect IL-meditated stimulation of lymphocytes *ex vivo*.
			sham- or MF-exposed for 1 day, 1 wk or 2 wks; c. 24 hrs/day		
(Komeva et al., 1999)	adult male CBA mice; 3 groups of 100	22 μT, 50 Hz	1 hr/day for 5 days; measurements made 1, 24 or 96 hrs after end of MF exposure	thymus weight & numbers of colony-forming units in spleen & bone marrow	Exposure to 50 Hz MF can affect natural defense mechanisms of the body.
			marrow from MF exposed animals injected into mice previously exposed to lethal dose of X-rays (9 Gy)		
(Thun-Battersby, Westermann & Loscher, 1999)	young female SD rats; groups of 6 - 8	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	3 days, 14 days, or 13 wks; c. 24 hrs/day	many common measures of B & T lymphocyte type & function	MF exposure does not affect the mechanisms involved in control of lymphocyte homeostasis.

TABLE 6.1.9 BONE GROWTH

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL COMMENTS
(Landry et al., 1997)	young male Fischer rats; six groups of 30	exposed = 100 μT & shams = < 1 μT; 60 Hz	continuous for 24 or 72 hrs	osteoblast concentration, distance between proliferating cells, & % callus in defect	Bone growth is enhanced by 60 Hz MF; effect is on differentiation rather than proliferation.
(Vera, Picazo & Royuela, 1999)	OF1 mouse; second generation exposed to sexual maturity; four groups of 30	exposed = 15 μT & unexposed animals "exposed to only geomagnetic fields in the room", 50 Hz, horizontal	continuous, *in utero* to 12 (females) or 14 wks (males) of age	26 densitometric & mechanical variables	MF exposure does not significantly affect measures of bone growth.

TABLE 6.1.10 STRESS PROTEINS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(DiCarlo, Farrell & Litovitz, 1998)	chicken embryo (developmental stage 24); 451 control, 66 heat-shocked, & 506 MF-exposed	sham (< 0.5 μT), 4, 6, 8 or 10 μT; 60 Hz; all MF-exposed data were combined	20 min of MF exposure @ 37.8^{0}C; another group was heated to 43^{0}C for 20 min without MF exposure; produce anoxia & then observe survival	% survival during a variable-duration period after a variable-duration period of anoxia	Acute MF exposure increases survival & this is a simple model to demonstrate MF bioeffects.
(DiCarlo & Litovitz, 1999)	White Leghorn chicken embryos (developmental stage 24) from two flocks; n per condition = 63 - 148	sham (< 0.5 μT) or 8 μT, 60 Hz	expose for 20 - 120 min; produce anoxia & then observe survival	% survival during a variable-duration period after a variable-duration period of anoxia	Genetic differences can modify an MF-induced biologic effect.
(DiCarlo, Farrell & Litovitz, 1999)	chicken embryo (developmental stage 24); 957 eggs used in 80 exp'ts	sham (< 0.5 μT), 8 μT, & 8 μT + "noise" MF; 60 Hz	two MF groups for 20 min @ 37.8^{0}C; plus sham control group, plus 4th group heated to 43 ^{0}C for 20 min; produce anoxia & then observe survival	% survival during a variable-duration period after a variable-duration period of anoxia	Addition of a noncoherent MF cancels the effect of a coherent MF.

TABLE 6.1.11 ORNITHINE DECARBOXYLASE ACTIVITY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kumlin et al., 1998a)	female transgenic (K2) mice & non-transgenic littermates; four groups of 43 or 44	shams = < 0.05 μT, continuous = 100 μT, intermittent = 1.3, 13 & 130 μT for 20 min each, followed by "0" for 2 hrs; 50 Hz, vertical	exposure was for 10.5 months; UV light at 1 MED 3 times/wk	ODC activity at end of chronic exp't (in which increased skin cancer had occurred)	MF exposure produced no measurable effects on ODC activity.
(Kumlin et al., 1998b)	female K2 mice; 4 groups of 15	100 μT, 50 Hz, vertical; continuous or intermittent (1.3, 13, 130 & 0 μT), plus sham-exposed	duration = 10.5 months; UV only, UV + continuous MF, & UV + intermittent MF	ODC activity plus putrescine, spermidine, & spermine concentrations of skin	No ODC effects apparent at end of chronic exp't.
	female K2 mice; 3 groups of 12	100 μT, 50 Hz, vertical; sham, continuous MF, & intermittent MF	as above; but only 24 hrs of exposure		Acute MF exposure affects epidermal polyamine synthesis; putrescine is elevated & ODC activity is down-regulated.
(Svedenstal & Johanson, 1998)	male CBA mice; one exp't (4 wks of age) with 12 exposed & 12 control, & a 2nd exp't (6 wks of age) with 6 exposed & 6 control	exposed = 5 μT & shams = 0.1 - 0.7 μT; 50 Hz, vertical	continuous exposure for 54 hrs	cell proliferation measured with radiolabeled (^{125}I) deoxyuridine in 11 organs & whole body	Cell proliferation was not affected by MF exposure.

TABLE 6.1.11 ORNITHINE DECARBOXYLASE ACTIVITY (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(DiGiovanni et al., 1999)	SENCAR mice; 24 subjects per each of 8 groups; for statistical comparisons, n = 3 or 4 per group	sham-exposed ("minimal stray" MF) or 2 mT; 60 Hz	6 hrs/day for 5 days/wk; DMBA-initiated & TPA-promoted animals were assessed at 1, 2 & 5 wks; TPA doses = 0, 0.85, 1.70 or 3.40 nmol.	epidermal thickness & labeling, ODC activity, & protein kinase C activity	MF exposure does not promote measured biomarkers of skin cancer.
(Mevissen, Haussler & Loscher, 1999)	female SD rats; 50 - 52 days of age at start of exp't; in 3 exp'ts, groups sizes were 6 to 12	exposed = 100 μT & shams = 0.1 μT (stray MF); 50 Hz, horizontal	exposure for c. 22 hrs/day for periods of 1, 2, 8, or 13 wks; two near-replicate exp'ts were completed; a 3rd exp't subdivided the thoracic mammary complex into cranial & middle portions	ODC activity in mammary glands	Increases in ODC were observed after 2 wks of exposure, especially in cranial complex.

TABLE 6.1.12 ENZYME ACTIVITY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kubinyi et al., 1998)	pregnant CFLP mice; progeny followed to postnatal day 24; adult males also studied; 240 female & 240 males	exposed = 100 μT; 50 Hz, vertical; controls not clearly described	exposed on days 2-18 of gestation for 7 hrs per day; thus adults exposed for 17 days	activity of enzyme tRNA synthetase in brain & liver or adults & weanlings	Males showed slightly reduced activity in liver & females showed slightly increased activity in brain.
(Kula et al., 1998)	rats	18 μT, 50 Hz	8 hrs/day for 8 wks	activities of 4 connective tissue enzymes	Metabolism of connective tissue enzymes is affected by MF exposure.
(Singh, Khanduja & Mittal, 1998)	mice	2 or 10 μT @ 50 Hz	**Have not received a copy of the paper.**	activity of a total of 5 enzymes, some phase I & some phase II enzymes	Phase I enzyme activity is increased, leading to reduced glutathione concentrations.
(Singh, Kaur & Khanduja, 1999)	6 young male Swiss mice	50 Hz, 2 μT	8 hrs/day for 8 wks; data from wks 0, 4, 6, & 8	respiratory excretion of $^{14}CO_2$ from radiolabeled nitrosodiethylamine	Enhanced enzyme activity occurs, which could be a protective response.
(Singh et al., 1999)	young male Swiss mice; 3 groups of 6	sham, 2 μT & 10 μT; 50 Hz	8 hrs/day for 8 wks	activities of 4 antioxidant defense enzymes in red blood cells, liver & lung; plus lipid peroxidation in liver & lung	Antioxidant defense enzymes are stimulated by MF exposure; effects are most apparent at 2 μT suggesting an amplitude "window."

TABLE 6.1.13 OTHER ENDPOINTS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Picazo et al., 1995a)	female OF1 mice at 14 wks of age; 2 groups of 30	15 μT, 50 Hz, horizontal; MF conditions for controls not described	2nd generation with "chronic" exposure	water content, atomic absorption (Ca, Mg, Ni, Zn & Fe) or emission (Na & K) spectrophotometry & descriptive histology	Calcium content was decreased in MF-exposed animals. Variations in fiber morphology, similar to those common in myopathies or early dystrophies, occurred in exposed animals.
(Hurych et al., 1996)	male Wistar rat; groups of 9 or 10 for biochemistry & cytology; groups of 5 for histology	10 μT, 50 Hz; MF conditions for controls not described	1 hr/day, 5 days/wk for 4 months; animals also received weekly pulmonary exposure to fibrogenic & nuisance dusts & to $CdCl_2$	analysis of bronchoalveolar lavage fluid & lung tissue	MF exposure does not damage cell membranes but does decrease collagen synthesis in response to fibrogenic particles.
(Rencova, Jerabek & Volf, 1997)	young-adult female Wistar rats; 7 per group	10 μT @ 50 Hz; "parallel vector"; control condition not described	5 different exp'ts were completed	retention of ^{210}Po or ^{234}Th in nine tissues	Numerous differences occurred between MF-exposed & control groups. Results appear to depend upon experimental conditions & isotope.

TABLE 6.1.14 MELATONIN

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Anisimov et al., 1997)	outbred female rats; groups of 20 to 50	box solenoids at 160 A/m; 50 Hz	presumably c. 24 hrs/day for up to 390 days; some groups received 50 mg/kg NMU; groups held in 24-hr light, 24-hr dark or 12:12 light:dark	serum melatonin	MF exposure does not appear to greatly affect melatonin. Light affects melatonin & NMU reduces melatonin.
(Burchard, Nguyen & Block, 1998a)	lactating Holstein cows; n = 16	horizontal 30 μT & vertical 10 kV/m; 60 Hz	within-subject, counter-balanced (ABA & BAB) exposures for three 28-day periods	plasma melatonin concentrations in samples collected every 0.5 hour for 14 hrs	MF exposure does not affect nocturnal melatonin concentration.
(Loscher, Mevissen & Lerchl, 1998)	young female SD rats; group sizes c. 10	100 μT, 50 Hz, horizontal	7 exp'ts: exposures of 1 day, & 1, 2, 4, 8, & 13 wks, with some internal replication efforts	plasma melatonin concentration at 3, 4, 5, &/or 6 hrs after onset of darkness	Exposure to 50 Hz MF does not reliably reduce melatonin.
(Mevissen et al., 1998)	female SD rats; 99 per group	sham-exposed (0.1 μT) & MF-exposed (100 μT); 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	serum melatonin after 12 wks of exposure	MF exposure does not reduce melatonin in this exp't; reasons for inconsistency in MF effects on melatonin are not known.
(Picazo et al., 1998)	40 male OF1 mice assessed at sexual maturity (3 months)	control & 15 μT, 50 Hz	continuous exposure into 3rd generation	plasma melatonin concentrations	Cumulative MF exposure causes loss of diurnal melatonin rhythm.
(Reiter, 1998)	SD rat	sham (< 0.2 μT) & 100 μT; 60 Hz	9 exp'ts with exposures of 15 or 60 min, single exp'ts with 3, 4, or 6 hrs of exposure; 5 exp'ts with 12 hrs of exposure	pineal & blood melatonin concentrations; NAT activity	MF exposure does not affect melatonin.

TABLE 6.1.14 MELATONIN (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Bakos et al., 1999)	male Wistar rats; groups of 5 or 6	exposed = 100 μT & controls = 1 μT; 50 Hz, horizontal, parallel or perpendicular to magnetic north	MF exposure for 24 hrs on 3rd day of 5-day exp't	urinary excretion of 6-sulphatoxymelatonin	MF exposure under these conditions does not affect melatonin.
(Heikkinen, Kumlin & Laitenen, 1999)	female CBA/S mice; 526 days of age; groups of 24	50 Hz, vertical, regularly varying (20 min at 1.3, 13 & 130 μT); shams were kept in an unenergized coil	24 hrs/day for 1.5 years	urinary melatonin excretion	At the end of near-lifetime MF exposure, there were no effects on melatonin.
(Selmaoui & Touitou, 1999)	young (9 wks) & old (23 months) male Wistar rats; groups of 6	Exposed = 100 μT (50 Hz) & controls = ambient	18 hrs/day for 1 wk	pineal melatonin plus SNAT & HIOMT activity	MF exposure reduced melatonin in young rats but not in older rats.
(Wilson, Matt & Morris, 1999)	Siberian (Djungarian) hamsters; males (4 - 6 months); group sizes = c. 20 animals	0.1 mT (most exp'ts) or 0.5 mT (one exp't); shams < 0.1 μT; 60 Hz, horizontal	four different exp'ts; 15 min to 42 days of exposure; short- & long-day conditions	pineal melatonin	60 Hz MF reduce melatonin.

TABLE 6.1.15 OTHER HORMONES

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Picazo et al., 1995b)	female of1 mice; 2nd exposed generation	control & 15 μT; 50 Hz	apparently continuous	quantitative light microscopy & descriptive electron microscopy	No statistically significant differences, but 30% of exposed animals showed signs of adrenal hyperfunction.
(Romo et al., 1997)	female mice	control & 15 μT; 50 Hz	apparently continuous	adrenal gland	Presumably effects were found.
(Bonhomme-Faivre et al., 1998b)	Swiss mice; 6 wks of age at start; 2 groups of 12	monthly average = 5 μT; diurnal cycle = 3.2-6.8 μT. Controls, housed in another room, had ambient MF < 0.1 μT; 50 Hz	exposed for 350 days in cages on floor in a laboratory directly above the main service bus bars & of a 13 kV transformer	cortisol measured at 90 & 190 days	Cortisol concentrations were reduced at 190 days.
(Burchard, Nguyen & Block, 1998b)	Holstein cows, 16 non-pregnant & lactating	10 kV/m vertical & 30 μT horizontal; 60 Hz	using a counter-balanced design, exposure was for either 1 or 2 estrous cycles, which were 24-27 days in duration; exposure was for c. 21 hrs/day	plasma progesterone, including area under the curve	Plasma progesterone (mean & AUC) did not differ significantly with exposure, but estrous cycle length was increased by 15% during MF exposure.
(Wilson et al., 1999)	Siberian (Djungarian) hamsters; males (4-6 months), group sizes c. 20	exposed = 0.5 μT (one exp't) or 0.1 μT (most exp'ts); shams < 0.1 μT; 60 Hz, horizontal	4 different exp'ts; 15 min to 42 days of exposure; short- & long-day conditions	Plasma prolactin, body, & organ weights	MF exposure can affect neuroendocrine system.

TABLE 6.1.16 BEHAVIOR

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Vojtisek et al., 1996)	adult female Wistar rats: untreated control group = 12, sham-exposed group = 12, MF exposed group = 16	10 mT, 50 Hz; methods are not described	1 hour, twice weekly for 3 months; intra-tracheal administration with manganese solution; no MF & no Mn group, Mn & no MF group, & MF + Mn group	functional observation battery including over 30 endpoints	MF exposure affects various behavioral measures.
(Sienkiewicz, Haylock & Saunders, 1998)	adult male C57BL/6J mice; groups of 6 - 8	exposed = 7.5 μT, 75 μT, 0.75 μT, or 7.5 μT @ 50 Hz; sham-exposed c 50 μT	45 min of exposure immediately before daily behavioral testing for 10 days	level of performance (% correct) in 10 daily training sessions in an 8-arm radial maze	Exposure immediately before testing reduced acquisition in the 0.75 & 7.5 μT groups.
		exposed = 0.75 μT @ 50 Hz; sham-exposed = < 50 μT	45 min of exposure ending 45 min before daily behavioral testing for 10 days		With a delay of 45 min, MF exposure had no effect on acquisition.
		exposed = 7.5 μT, 75 μT, or 0.75 μT @ 50 Hz; sham-exposed 50 μT	45 min of exposure after daily behavioral testing for 10 days		Exposure following daily sessions produced no effects on acquisition.
(Stern & Laties, 1998)	mature Long-Evans rats; 3 female & 4 male	homogeneous, vertical 60 Hz EF of 100 kV/m	49 EF operant sessions of 50 min; 103 other sessions involved light exposure; & c. 150 other sessions involved no potentially aversive stimulus	ratio of responses on two levers, one turning the stimulus "off" & one turning it "on"	The time spent responding on the lever associated with EF- or light- onset was reduced 5-10%; similar to light, EF exposure can be weakly aversive.

TABLE 6.1.17 NEUROTRANSMITTERS & OPIODS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Burchard et al., 1998c)	Holstein cows; n = 8	10 kV/m vertical & 30 μT horizontal; 60 Hz	pre-exposure, exposure, & post-exposure periods 30 days in duration	concentrations of seven neurotransmitter-related metabolites in cerebrospinal fluid	Quinolinic acid increased, suggesting EMF exposure produced a weakening of the blood brain barrier.
(Kavaliers, Wiebe & Ossenkopp, 1998)	young CF1 male mice; groups of 10	exposed = horizontal, 141 μT (peak, not rms), shams = ambient MF (< 0.4 μT peak); 60 Hz	inject with analgesia-producing drug, expose for 30 min, & conduct hot plate test	analgesia, measured as latency to licking of foot	MF exposure reduces analgesia.
			inject with analgesia-producing, inject with Ca-channel blocking drug, expose for 30 min, & conduct hot plate test		MF exposure reduces analgesia; calcium channel blocks the effect.

TABLE 6.1.18 NEUROCHEMISTRY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Vojtisek et al., 1996)	adult female Wistar rats: untreated control group = 12, sham-exposed group = 12, MF exposed group = 16	10 μT, 50 Hz; exposure methods are not described	1 hour, twice weekly for 3 months; intra-tracheal administration with manganese solution; no MF & no Mn group, Mn & no MF group, & MF + Mn group	Mn content of brain, lungs, liver, & kidney	MF exposure increased brain Mn content.
(Lai & Carino, 1998)	adult male SD rats; 8 groups of 6-8	2 mT & sham exposed (14 μT); 60 Hz	expose for 1 hour & assay; pre-treat with vehicle or 1 of 2 opiate receptor agonists	sodium-dependent high-affinity choline uptake in frontal cortex & hippocampus	MF exposure reduces uptake, but both drugs blocked the effect.
(Lai & Carino, 1999)	adult male SD rats; 8 groups of 7-16	0.01, 0.1, 0.5, 1.0, 1.5 or 2.0 mT; 60 Hz; sham-exposed controls in "bucked" (canceled) coils	30, 45, 60, or 90 min	cholinergic activity (high affinity choline uptake) in frontal cortex & hippocampus	Immediately after exposure, cholinergic activity in two brain regions is reduced; there is a interaction of flux density & exposure time.
(Singh & Lai, 1998)	adult male SD rats; n = 8 per treatment condition	exposed = 0.5 mT & sham-exposed controls in "bucked" coils	expose for 2 hrs & wait 4 hrs	single strand breaks in brain cells by comet assay	Acute MF exposure damages DNA of brain cells, probably through free radical processes.

TABLE 6.1.19 ELECTROPHYSIOLOGY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Vojtisek et al., 1996)	adult female Wistar rats: untreated control group = 12, sham-exposed group = 12, MF exposed group = 16	10 μT, 50 Hz; exposure methods are not described	1 hour, twice weekly for 3 months; intratracheal administration with manganese solution; no MF & no Mn group, Mn & no MF group, & MF + Mn group	visual evoked potentials (P1 latency)	MF exposure did not significantly affect VEP latency.
(Potschka, Thun-Battersby & Loscher, 1998)	young adult female Wistar rats; 1 group of 9	sham-exposed at ambient (0.03 - 0.04 μT) when MF- exposed group at 1 μT; sham exposed at 0.1 μT when MF-exposed at 100 μT; 50 Hz, horizontal	acute exp't involved 1 hour at 1 μT, 1 hr at 100 μT, & 2 hr at 100 μT; rats were fully kindled before MF exposure	brain stimulation, through electrodes implanted in the amygdala, was used to study kindling & seizures; several parameters measured on multiple occasions	Acute exposure had no effect on any of 4 parameters.
	young adult female Wistar rats; 2 groups of 10		exposed at 1 μT for 1 wk followed by 100 μT for 7 wks; MF or sham exposure for c. 22 hrs/day		Chronic exposure to MF exerts a weak inhibitory effects on three seizure parameters.
(Vorobyov et al., 1998)	male Wistar rats; 5 exp'ts, usually with 3 rats per exp't	48 Hz, 21 μT & 0 Hz, 21 μT (3rd harmonic for calcium cyclotron resonance)	pre-exposure, exposure & post-exposure periods, each 30 min in duration; also morphine treatments given	38 measures of EEG power, expressed as percent change from previous condition	Weak MF can influence spontaneous electrical brain activity.

TABLE 6.1.20 INVERTEBRATES

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Jenrow, Smith & Liboff, 1995)	*Dugesia tigrina* (planaria); no fewer than 8 replicate exp'ts; minimum n = 192	1, 10, 40, 51 or 78 μT; 60 Hz, horizontal	23 hrs/day for 12 days	% abnormal following period for regeneration of severed head	MF exposure causes abnormal development in regenerating planaria.
(Hemmersbach, Becker & Stockem, 1997)	three species of ciliates, including wild-type & mutant *Paramecium* (with abnormal calcium channels)	2 μT, 50 Hz	30 min	swimming speed & linearity measured with image-processing software	MF exposure alters swimming, increasing speed & reducing linearity, by affecting cell membrane transport mechanisms for calcium.
(Kavaliers, Choleris & Prato, 1998)	land snail (*Cepaea nemoralis*); groups of 10	141 μT (peak); 60 Hz, horizontal; sham-exposed in coils without current	15 min exposure; an enkephalinase inhibitor was used; nitric oxide mechanisms were investigated using agonist & antagonist	antinociception measured as latency of foot withdrawal on hotplate	The inhibitory effects of MF exposure on opiod analgesia involve nitric oxide.
(Kikuchi et al., 1998)	fruit fly (*Drosophila melanogaster*)	0.5 μT or 5 μT; controls < 1 μT; 50 Hz, horizontal	lifetime for 40 generations	genetic indices of mildly deleterious & lethal mutations, plus viability decreasing rate	MF exposure at very high MF flux density is not mutagenic.
(Tipping et al., 1999)	3rd instar fruit fly (*Drosophila melanogaster*) larvae; triplicate assays from 100 mg	larvae reared in either "ambient" or shielded (0.004 μT) conditions; MF was 8 μT, 50 Hz	half received 20-min MF exposures in the shielded space, & half received shielded exposures	membrane probe binding of three genes, *Cobia*, *Histone 1.9*, & *HSP 70a*	MF-exposure reduced gene transcripts in larvae reared in shielded environment but not in larvae reared in ambient environment.
(Junkersdorf, Bauer & Gutzeit, 2000)	nematode (*C. elegans*); two different transgenic strains were used; one included gene for hsp16, & other included gene for hsp70	0, 50, 100, or 150μT; 50 Hz	60, 120, or 180 min at 29 or 30° C, depending upon strain	lacZ gene used as a reporter: for 1st strain, β-galactosidase staining of the roller phenotype was used; for the 2nd, β-galactosidase activity was measured photometrically	MF exposure enhances the production of heat shock proteins elicited by mild thermal stress.

6.2 PRO AND CON ARGUMENTS

TABLE 6.2.1

RODENT BREAST CANCER PROMOTION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Replications of the hypothesis-generating studies by Losher group were unsuccessful. They were conducted in two independent reputable labs, following good laboratory practice. Any statistically significant association noted suggested a *protective* effect.	(F1) Losher and his group have consistently reported increased tumorigenesis, if not necessarily carcinogenesis, in DMBA treated rats.	(C1) Unsuccessful replications cannot claim to refute the hypothesis-generating study if the protocol and the conditions are different. Losher's results stand unrefuted but also unreplicated.
	(F2) Attempts to replicate them did not follow the Losher protocol. In particular, the rate of tumors in the sham exposed rats (initiated with DMBA from a different supplier) was so high (>90%) as to mask any reasonable increase due to EMF exposure.	
	(F3) The "protective" associations refer to the number and/or size of tumors in diseased animals, not to the percentage of animals who developed tumors, which was not very high in both the exposed and sham group.	

TABLE 6.2.2

LEUKEMIA AND LYMPHOMA		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A set of chronic exposure experiments showed no effects.	(F1) Experiments conducted using the traditional NTP protocol of testing for chemical carcinogenicity rely on the assumption that the risk resulting from exposure to levels well above those found in the environment carries a proportionally high risk and, therefore, sufficient power can be obtained with small sample sizes.	(C1) A null result of a test which may not be a sensitive indicator of the human carcinogenicity of a complex mixture does not pull down confidence as much as a supportive result would increase confidence.
(A2) If proponents accept the positive Losher results, they cannot argue that a pure sinusoidal 60 Hz wave is not the right exposure parameter to test.	(F2) The epidemiological evidence on EMF exposure suggests no additional risk above levels of 8-10 mG and, therefore, these studies would not have sufficient power.	(C2) If one believes Loscher's positive breast cancer results, one cannot invoke "wrong ingredient" or "insufficient power" arguments.
	(F3) Exposure conditions in the laboratory do not mimic the complex mixture of EMF parameters found in the environment.	(C3) All experiments designed to test for cancer initiation are irrelevant to the present evaluation.

TABLE 6.2.3

SKIN CANCER		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Seven out of ten studies provide no evidence for carcinogenicity.	(F1) See leukemia discussion.	(C1) See leukemia discussion.

TABLE 6.2.4

LONG-TERM CARCINOGEN BIOASSAYS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Three 1-2 year bioassay experiments conducted according to "the gold standard" of NTP procedures developed during decades of testing for chemical carcinogenicity showed no support for the hypothesis.	(F1) One study showed equivocal results at one tumor site (C-cell adenomas and carcinomas of the thyroid in male rats). The author regarded this study as "equivocal."	(C1) See leukemia discussion.
(A2) If proponents accept the positive Losher breast cancer results, they cannot argue that other carcinogenicity bioassays do not have sufficient statistical power.	(F2) Animal bioassays have not always detected human carcinogens at first (cigarette smoke, asbestos, arsenic, and benzene are examples).	
	(F3) Exposure to EMF without prior initiation cannot test the most commonly held belief that EMFs are not initiators, but act at later stages of cancer.	
	(F4) The Losher breast cancer studies were promotion studies: the animals were initiated with a chemical carcinogen while in the standard toxicology tests they are not. Therefore, the statistical power requirements are quite different.	

TABLE 6.2.5

LIVER CANCER		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Two studies of chemically initiated liver cancer revealed no effect of EMF exposure.	(F1) See leukemia discussion.	(C1) See leukemia discussion.

TABLE 6.2.6

REPRODUCTION AND DEVELOPMENT		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Eight studies on mammals (rodents) showed no effect on embryo development.	(F1) One study on hamsters reported changes in spermatogenetic cell populations.	(C1) Although the reproductive effects on chicken embryos are not considered relevant to humans by regulatory toxicology, and although not sufficiently "robust" for regulatory purposes, they help overcome the belief, based on the theoretical models, that no effect can take place at these levels (50-100 mG).
(A2) The effects on chicken embryos are not relevant to humans.	(F2) Several studies on chicken embryos show consistent effects with one strain of chicken. The importance of these studies is twofold: (F2a) Even if not relevant to produce reproductive effects in mammals, they show that EMF may have biological effects in living organisms, negating the prediction of theoretical models and the claim that *in vitro* results are due to artifacts. (F2b) It highlights how susceptible these experiments are to parameter choice (in this case chicken strain).	(C2) The evidence of differential response by different strains of chicken opens the possibility of species differences in susceptibility to EMF effects.
(A3) The null mammal results take precedence.		(C3) The null mammalian results could be due to species differences, but this evidence decreases confidence somewhat.
(A4) The effects on chicken embryos are not robust in that they are not larger than fluctuations between control groups in different laboratories and, though statistically significant in several laboratories, should be ignored.		(C4) If one believes the chicken results, one cannot invoke "wrong ingredient" or "insufficient power" arguments.
(A5) Chicken embryo studies did not evaluate results at a sufficiently stable and advanced stage.	(F5) The chicken results increase confidence somewhat.	

TABLE 6.2.7

PHYSIOLOGY – HEMATOLOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The pattern of results is consistent with no effect.	(F1) Although the pattern of results is not statistically significant, most of the major studies (5 out of 8) showed an effect on red cell, white cell, or ion concentrations in blood. Therefore the evidence, if not convincing, is suggestive of an effect.	(C1) Given the multiple parameters investigated, the likelihood of this pattern of results by chance is larger than the likelihood if EMFs caused a particular effect.
		(C2) The failure to affect a physiological parameter does not much sway confidence in a pathological effect.

TABLE 6.2.8

IMMUNOLOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The pattern of results is consistent with no effect.	(F1) The majority of studies (6 out of 8) report an effect. Even when the analysis is restricted to the more recent studies, there is no consistent negative outcome.	(C1) The results are inconclusive.

TABLE 6.2.9

BONE REPAIR		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is evidence that EMF is effective in accelerating bone repair, but the intensities used are well above those of interest in the context of environmental exposure. The exact mechanism is not understood.		(C1) This is not a health hazard and is not evaluated here.

TABLE 6.2.10

STRESS PROTEINS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) All data come from the same group. There is no clear dose response. The effects are largely limited to one strain of chicken embryos.	(F1) These data provide easily verifiable evidence that EMF exposure, at levels below those for which well-understood mechanisms can be invoked, induce stress response. The fact that the effect is strain sensitive is consistent with the finding of the hen-house type experiments.	(C1) These results advance a viable mechanistic theory involving the concepts of a minimum sensing interval and signal coherence. However, at present, they are not sufficiently established to have more than a weak positive effect on the degree of confidence.

TABLE 6.2.11

ENZYME ACTIVITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear evidence of an effect in vivo. All positive results are from exposure to very strong fields. The direction of the effect (decreased ODC activity) is opposite to increased activity reported in vivo.		(C1) Once again, this strain of evidence is not a very sensitive indicator of pathology. The reviewers cannot rule out that predominantly negative results are not due to the choice of experimental conditions.

TABLE 6.2.12

MELATONIN		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The literature is evenly divided between studies reporting an effect and those that do not.	(F1) The experiments failing to show an effect do not explain away the results of those which do. On the other hand, there are many possible explanations for the negative results. Several of the positive findings were obtained with low-level exposures, below the threshold predicted by theoretical models.	(C1) Although it would be desirable to deal with a more consistent body of evidence, there is sufficient unrefuted evidence of an effect. However, whether or not this is related to a pathological endpoint is unclear.
		(C2) The fact that these effects have been reported at levels where theoreticians predicted that no effect should be observed is a strong reason to doubt these theoretical models and the argument that these fields, even if perceived, are too weak to produce noticeable effects.

TABLE 6.2.13

OTHER HORMONES		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no clear relationship between the weak effects reported and pathological endpoints.	(F1) Most studies show an effect. Endocrine dysfunctions are known to be causally related to several types of cancer and other health effects.	(C1) Overall, the results provide moderate evidence that EMFs affect the endocrine system *in vivo*, although most of these were obtained at exposure levels higher than those found in the environment (although below the theoretical thresholds).

TABLE 6.2.14

NEUROPHYSIOLOGY – BEHAVIOR		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear relation to cancer and other adverse health effects.	(F1) Consistent evidence of effects on the operation of the central nervous systems at levels only moderately above environmental ones.	(C1) Although often overlooked and not strongly indicative of a hazard, this is the most consistent set of experimental data.

TABLE 6.2.15

NEUROTRANSMITTERS AND OPIOIDS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear relation to cancer and other adverse health effects.	(F1) Consistent evidence of an effect.	(C1) Effects reported at the mT level, 1,000 times higher than the highest environmental fields.

TABLE 6.2.16

NEUROCHEMISTRY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear relation to cancer and other adverse health effects.	(F1) Three recent studies concur in showing that EMF exposure induces changes in brain function.	(C1) CNS effects might have pathological implications, but link is unclear.
(A2) Effects reported in the high microtesla range, well above environmental levels.		

TABLE 6.2.17

ELECTROPHYSIOLOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Effects reported at a level much higher than the highest environmental fields.	(F1) There is a small, but persuasive body of literature indicating that power-frequency EMFs interact acutely with the CNS to produce functional changes.	(C1) CNS effects might have pathological implications, but link is unclear.
(A2) Some effects are arguably beneficial, rather than hazardous.		
(A3) Other studies report no effects or scattered effects, possibly resulting from multiple comparisons.		

TABLE 6.2.18

6.38 INVERTEBRATES		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Strong MF were not found to be mutagenic in fruit flies exposed for 40 generations.	(F1) The hypothesis is that MF are a risk factor for cancer, a multifactorial disease. Proving that they are not the initiator does not weaken the hypothesis.	
(A2) These are mostly older studies without a specific hypothesis to test.	(F2) Other studies report a variety of adverse effects on invertebrates.	

6.3 CONCLUSIONS

Overall, the animal studies can be divided into three categories: 1) those showing no effect and having statistical power to show one; 2) those that do not significantly weaken the hypothesis because there are many possible explanations for a negative result, including lack of statistical power and use of inappropriate exposure metrics and modalities; 3) those showing an effect at mT levels, which may be important for future research, but is not relevant to the present evaluation.

Those showing an effect at near-environmental levels argue against accepting the theoretical models predicting a very high threshold for any effect to occur. These increase the reviewers level of confidence in a causal association, irrespective of whether or not the effect is obviously related to cancer. Included in this category are the data on neurological effects, the chicken embryo studies, and the Losher mammary tumor results.

Given the significant differences in the conduct of these mammary tumor replication studies (Anderson et al., 2000), compared to the original research (most notably the different and very high rate of cancer in the control group, possibly traceable to the use of different suppliers for the initiator and animals), the reviewers cannot place much weight on the failure to replicate these studies until they understand the explanation of the different results (Anderson, Kelman & Weigel, 1987).

Overall, the animal pathology studies are predominantly, but not entirely, negative. However, in the case of the EMF mixture the reviewers believe that, given the many difficulties of experimental design and conduct of animal pathology studies, that a pattern of many false-negative results was quite possible, even if the effect were to be real. This is because of the problems of choosing the right species to test, the special problem of power as judged from the expected dose response from the epidemiology, and the issue of choosing the right aspect of the mixture to test. Reviewers 1 and 3 had their confidence increased slightly by the mammary tumor and chicken evidence. Reviewer 2 was not moved one way or the other, but felt that the chicken studies and mammary tumor studies needed to be pursued toward clarification.

7.0 GENERIC ISSUES ON EPIDEMIOLOGICAL EVIDENCE

In the DHS Risk Evaluation Guidelines (see Appendix 2) the three reviewers proposed to organize their pro and con arguments around a series of pre-specified questions relevant to developing a degree of confidence as to whether epidemiological associations were causal in nature. Because these factual issues are also relevant to policy, they developed questions relevant to the status of research assessing dose-response relationships, any unequal vulnerability to EMFs, or an unequal distribution of exposure. The questions in the Guidelines are summarized by the questions in the following two tables, and these are repeated for each endpoint specifically considered. Having pre-specified questions such as these assures a systematic evaluation.

Following the scheme of IARC, the reviewers first asked (see Table 7.1) if the associations observed could be due to chance, bias, or confounding. If not, they systematically examined attributes of the evidence which might incline us to attribute the association to causation.

As the reviewers went through the specific diseases using these standard questions, they realized that some of them always involved the same pro and con arguments and that they always came down on one side of the argument, regardless of the disease being considered. They decided to deal with those questions in this section and only mention them in the summary tables for the respective diseases.

TABLE 7.1 QUESTIONS RELEVANT TO CAUSALITY

EXPLANATIONS OF A STATISTICAL ASSOCIATION OTHER THAN A CAUSAL ONE
Chance: How likely is it that the combined association from all the studies of EMF and disease is due to chance alone?
*Bias: How convinced are the reviewers that EMFs rather than a study flaw that can be **specified and demonstrated** caused this evidentiary pattern? If no specified and demonstrated bias explains it, how convinced are they that EMFs caused these associations rather than **unspecified** flaws?*
*Confounding: How convinced are the reviewers that these disease associations are due to EMFs rather than to another **specified and demonstrated** risk factor associated with EMF exposure? If not due to a specified risk factor, how convinced are they that they are due to EMFs rather than to **unspecified** risk factors?*
*Combined effect: How convinced are the reviewers that these disease associations are due to EMFs rather than to a combined effect of chance and specified or **unspecified** sources of bias and confounders?*
ATTRIBUTES SIMILAR TO HILL'S (Hill, 1965) THAT ARE SOMETIMES USED BY EPIDEMIOLOGISTS TO EVALUATE THE CREDIBILITY OF A HYPOTHESIS WHEN NO DIRECT EVIDENCE OF CONFOUNDING OR BIAS EXISTS
Strength of association: How likely is it that the meta-analytic association is strong enough to be causal rather than due to unspecified minor study flaws or confounders?
Consistency: Do most of the studies suggest some added risk from EMFs? How likely is it that the proportion of studies with risk ratios above or below 1.0 arose from chance alone?
Homogeneity: If a large proportion of the studies have risk ratios that are either above or below 1.0, is their magnitude similar (homogeneous) or is the size of the observed effect quite variable (heterogeneous)?
Dose response: How clear is it that disease risk increases steadily with dose? What would be expected under causality? Under chance, bias, or confounding?
Coherence/visibility: How coherent is the story told by the pattern of associations within studies? If a surrogate measure shows an association, does a better measurement strengthen that association? Is the association stronger in groups where it is predicted? What would be expected under causality? Under chance, bias, or confounding? How

convinced are the reviewers that the magnitude of epidemiological results is consistent with temporal or geographic trends?
Experimental evidence: How convincing are the experimental pathology studies supporting the epidemiological evidence? What would be expected under causality, bias, chance, or confounding?
Plausibility: How convincing is the mechanistic research on plausible biological mechanisms leading from exposure to this disease? What would be expected under causality, chance, bias, or confounding? How influential are other experimental studies (both in vivo and in vitro) that speak to the ability of EMFs to produce effects at low dose?
Analogy: How good an analogy can the reviewers find with similar agents that have been shown to lead to similar diseases? What would be expected under causality, chance, bias, or confounding?
Temporality: How convinced are the reviewers that EMF exposure precedes onset of disease and that disease status did not lead to a change in exposure?
Specificity and other disease associations: How predominantly are EMFs associated with one disease or subtypes of several diseases? What would the reviewers expect under causality, chance, bias, or confounding? How much is their confidence in EMF causality for disease X influenced by their confidence that EMFs cause disease Y?

The reviewers next asked (see Table 7.2) questions relevant to dose response and policy, including factual questions relevant to the environmental justice policy perspective and questions about the current state of science in the area. In many cases, however, the evidence is insufficient to provide an answer.

TABLE 7.2 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

How confident are the reviewers that a specific exposure metric or aspect, other than 60 Hz TWA magnetic field, is associated with this disease?
How confident are the reviewers of evidence for threshold or plateau?
How confident are the reviewers of evidence for biological windows of vulnerability?
How confident are the reviewers of a consistent induction period or required duration of exposure?
How does EMF compare to other risk factors for this disease, as to added risk to the total population and to highly exposed people?
How does the observed relative risk compare to that which would generate a 1/1000 or 1/100,000 theoretical lifetime risk?
How confident are the reviewers of evidence for racial, gender, or class differences in exposure or vulnerability? (This is relevant to environmental justice.)

State-of-science questions.

How much room for improvement in quality or size is there in the best existing studies?
How many new studies are in the pipeline and how capable are they of changing the reviewers assessments?
How likely is it that further studies could resolve controversies?

7.2 Approaches to Weighing Streams of Evidence

The reader will notice that, following Hutchison and Lane (Hutchinson, 1980), the three reviewers have phrased these questions so that they would be answered in a graded fashion rather than in a "yes" or "no." They have been worded so that when the reviewers answer with a larger likelihood or degree of confidence, this means that the strength of evidence for causality has increased. This is helpful in thinking about the weight to be given to the answer and in avoiding the pitfall of simply adding "yes" and "no" answers. Following Hutchison and Lane's recommendation of "etiological balancing," many of these questions can be conceptualized by comparing the likelihood of the pattern of evidence (if EMFs really caused the disease in question) to the likelihood of the same evidentiary pattern, if only chance, bias, or confounding had produced the pattern of evidence. So, when the reviewers ask themselves about bias, they couch it as their convictions about EMF causality relative to their convictions about the presence of specified or unspecified study biases. An exception is the question about chance, where the conventional question is posed about the likelihood of the pattern of evidence under the null hypothesis.

In DHS's Risk Evaluation Guidelines, the reviewers pointed out that the *size* of the relative likelihood conveyed by supportive or unsupportive patterns of evidence depended on 1) how good that stream of evidence was in detecting a cause, if it usually detected a harmful agent (sensitivity); and 2) how good that stream of evidence was in not falsely implicating an agent (specificity). The reviewers pointed out that unsupportive patterns of evidence from a stream of evidence that often missed detecting a cause did not pull their confidence down very much, and that supportive patterns of evidence from a stream of evidence that often falsely implicated agents would not pull confidence up much. (See pages 48–52 of Appendix 2.)

As a heuristic, the reviewers can think of the size of these relative likelihoods as the weights given to the different streams of evidence. For example, the question, "How clear is it that risk increases steadily with dose?" could be rephrased as, "How much more or less likely is the observed dose response pattern if EMFs caused disease X than if chance, bias, or confounding had produced this pattern?" Suppose that, in studies where few subjects have high exposures, an inconsistent dose-response pattern might be expected under the EMF hypothesis, and that this is somewhat more likely to be seen than if only chance, bias, and confounding were at work. This pattern of evidence would then increase confidence somewhat, and the heuristic relative likelihood would be a number bigger than one.

Of course, the answers to these questions cannot be mechanically considered in isolation. Certain combinations of answers influence the reviewers degree of confidence more than the isolated answers would predict. For example, one might be quite sure of a minor bias at work in all of the studies, but if the those studies all reported relative risks of 20 with tight confidence limits, concerns about bias would not weigh as highly as would be the case if the studies all reported relative risks of 1.1. That is why the reviewers had to consider the pro and con answers to the structured questions and then come to an integrated judgment about what the evidence suggested, rather than assigning scores and mechanically multiplying them or adding them up.

7.3 General Points About the Causality – Relevant Questions

The reviewers found that some of the questions were harder to formulate in the relative likelihood mode. So, in this section, they have explained how they approached those questions.

Chance

The question about chance simply asks how probable the observed, or a more extreme, pattern of evidence is under the null hypothesis of "no association." If it is quite probable (say 6 times out of 100) under the null hypothesis, then conventional thinking dismisses the pattern of evidence as being due to chance. The DHS reviewers ask this question of the pattern of relative risks and of meta-analytic estimates of effect because IARC specifically considers this. Since it is conventional to do so, decision makers may choose to pay attention to how likely the evidence is under the chance hypothesis. A pattern unlikely under the null hypothesis could be interpreted as follows: "If these were randomized experiments without the possibility of bias or confounding, the statistical associations found would not be expected to occur by chance in 5 or fewer experiments out of 100 replications, if there was really no effect." Of course, epidemiological studies are not experiments. It would be unethical and impractical to experimentally subject large numbers of humans to potentially harmful agents. This leads to the consideration of bias and confounding.

Bias

Any source of error in collecting the data may introduce a bias, which is a reason why the apparent result might not be the truth. A very common bias results from errors in assessing the true exposure of the subjects to the agent of interest, in this case EMFs. Provided exposure of cancer cases and healthy controls is not

assessed differently, this bias on average results in an underestimate of the risk, if one exists. When comparing the health risk of subjects exposed above one value to that of subjects below that value, non-differential misclassification of exposure* would not, on average, show an association if one does not truly exist. However, it may inflate the risk of intermediate exposure subjects and thus frustrate attempts to estimate a dose-response function. In most of the EMF studies, measurements were not taken for a long enough duration during the induction period of the disease to avoid this kind of misclassification. And there is even some argument about whether the right aspect of the EMF mixture has been measured. The three reviewers concluded that all of this may have led to an underestimate of any true effect of high versus low exposures and may have frustrated the ability to develop an appropriate dose-response curve.

Of the many errors that can creep into epidemiological studies, one in particular has been a source of argument with regard to a subset of the EMF epidemiological studies. The reviewers refer to “selection bias” in some of the case control studies. A case control study is analyzed by comparing a series of cases with a disease to a series of healthy subjects as to their EMF exposure. If the cases display a higher proportion of high EMF exposure than the controls, this suggests a causal effect of EMFs. If, however, the probability of being selected for study is influenced both by whether one has the disease AND whether one had a high EMF exposure, then an apparent difference will appear between the cases and the healthy controls, which is the result of this biased selection and the result does not reflect any true effect of EMFs on the disease. One way to recruit healthy subjects is random telephone contact. This method excludes subjects of lower socio-economic status (SES), who may not have a telephone. Experience has shown that healthy controls of lower SES are sometimes less likely to participate in epidemiological studies than upper class subjects. In some studies, lower class subjects are more likely to live in neighborhoods with nearby power lines (Bracken et al., 1998). Since cancer patients of all social classes are easier to recruit (through a cancer registry) and more likely to be interested in participating, the effects of non-representative control selection may distort the comparisons between cases and controls and, therefore, the study results. In the case of EMF, it is claimed that the fact that there are more subjects living close to power lines among the cancer patients than among the healthy controls could be due to the fact that low SES subjects are more likely to live close to power lines and they are underrepresented in the control group. This issue of possible selection bias in case control studies is a particular issue for the North American case control studies on childhood leukemia. Hatch (Hatch et al., 2000) indicate that the association between childhood acute lymphoblastic leukemia (ALL) and front door magnetic fields greater than 3 mG was 1.9 (1.1-3.27) among full participants in their study but fell to 1.6 (0.98-2.61) when 147 partial participants were included. Although this difference was well within sampling variability, she suggested that it might be evidence of the presence of a selection bias which might be even more extreme if non-participants had their front doors measured and had been included in the analysis. Hatch (Hatch et al., 2000) concluded that "while confounding alone is unlikely to be an important source of bias....selection bias may be more of a concern...in case-control studies." The Scandinavian studies relied on cancer registries and lists of citizens and did not require permission of the subjects so that selection bias was not a problem. Ahlbom (2001) has shown that the results of the two groups of studies are not much different. The pooled analysis of all the studies he dealt with showed a relative risk for exposures above 4 mG as 2.0 (1.3-3.1), while the results after excluding the US studies was 1.7 (1.0-2.8). That is, the confidence interval of the two risk estimates overlap, indicating that there may or may not be some over-estimate of the effect of living near power lines in the American studies, but that even if these are excluded, the association remains statistically significant. In the pooled analysis by Greenland et al. (2001), there was an effect of power line proximity (“wire code”), as well as an effect of measured magnetic fields. This might indicate some selection bias for power line proximity. Nonetheless, magnetic fields come only partially from power lines. Internal wiring and currents on plumbing form an important source (Zaffanella & Kalton, 1998). The only evidence we know of that examines personal EMF exposure from all sources and its relation to social class (Lee GM & Li D-K, personal communication) does not suggest differences in personal EMF exposure in different social classes. The evidence linking EMFs and adult leukemia, adult brain cancer, Lou Gehrig’s Disease, and Li’s prospective miscarriage study come largely from study designs where selection bias is not possible (studies where rosters of healthy workers or subjects of high and low exposure are followed until death or health outcomes are determined from available records without requiring subject cooperation). Thus, although selection bias may have distorted the associations between EMF and childhood leukemia in some of the studies, the three reviewers did not believe that it totally explained the childhood leukemia findings and selection bias was not even an issue in the bulk of the studies related to adult leukemia, adult brain cancer, ALS, or in one of the two recent studies on EMF and miscarriage.

CONFOUNDING

The term “confounding” is derived from the Latin “confundere,” to melt together. Epidemiologists use the term when the impact of two risk factors “melt together” and

* "non-differential misclassification of exposure" is said to occur when errors of measurement occur equally in cases of disease and in healthy controls.

must be disentangled. If heavy alcohol consumption and smoking are both known to cause esophageal cancer, and people who drink also tend to smoke, then the effect of drinking will confound the effect of smoking and vice versa. Therefore, one must correct for this confounding in the way the data are analyzed. Sometimes the non-effect of a factor which conveys no risk at all is confounded with the true effect of another factor. For example, it has been suggested that people who live near power lines also live on busy streets with lots of traffic and air pollution. This argument suggests that the effect of air pollution on childhood leukemia was confounded with the non-effect of the power lines, and the power lines were falsely implicated instead of the air pollution. Two conditions must pertain for an agent to be a strong confounder of the EMF effect on the various diseases discussed in this report. That agent must be strongly correlated with EMF exposure and it must have an effect on the studied disease that is even stronger than the apparent effect of EMF. If it is weakly correlated with EMF exposure it must have an effect on disease that is very strong indeed if it is to make EMF falsely appear to have an effect. Langholz (Langholz, 2001) has examined the candidate confounders for childhood leukemia and their association with wire code. He concluded that while something connected with the age of home was a possibility, factors like traffic density, ethnicity, and smoking were not likely confounders. Indeed, not all studies of traffic and childhood leukemia suggest it as a risk factor (Reynolds et al., 2001), but a recent study of traffic and power line proximity and childhood leukemia (Pearson et al., 2000) did suggest that there might be a joint effect. Hatch (Hatch et al., 2000) examined a variety of socioeconomic, and other confounders, and concluded that together, or alone, measured confounders would distort the association with ALL by less than 15%. Hatch also found no association between residential mobility, magnetic fields, or leukemia unlike Jones (Jones et al., 1993).

Electric shocks have been invoked to explain the relation between high-exposure jobs in the utility industry and ALS (Ahlbom, 2001), (NRPB, 2001a). If this were confirmed, they might also be invoked to explain the adult leukemia and brain cancer associations on the as yet unproven assumption that shocks could somehow cause cancer. However, the literature linking shock to ALS, unlike much of the literature linking high-EMF exposure jobs to ALS, depends on subjects remembering shocks. They are thus more vulnerable to recall bias than the EMF studies. Some of the studies suggest a protective, not a harmful, effect (Cruz et al., 1999), (Kondo & Tsubaki, 1981), (Gunnarson et al., 1992) and the size of the harmful effects of shock are less than the high EMF job effect (Deapen & Henderson, 1986), (Savettieri et al., 1991). No published study has demonstrated a correlation between shocks and high-EMF exposure jobs. Studies are underway to see if grounding currents are associated with measured magnetic fields and power line proximity. The three reviewers felt that the evidence for the confounders that had been proposed for EMF exposure did not have strong support and therefore their degree of confidence was not decreased by the pattern of evidence.

COMBINED EFFECT OF CHANCE, BIAS, AND CONFOUNDING

Although each of these possibilities by itself is unlikely to explain the association between EMF and cancer, is it possible that a combination of the three may be responsible for an artefactual finding? The DHS reviewers considered this possibility and concluded that this is not a credible explanation when many studies of different design have reported similar results. It is not impossible that individual studies may be have their result completely explained by an extraordinary coincidence in which independent unlikely events occur simultaneously. However, for many diseases considered here the general pattern of results is not critically dependent on accepting each individual study as reliable. For example, in the case of childhood leukemia, it has been repeatedly shown that, even if a few studies are excluded, the results of meta-analyses, pooled analyses, or sign tests are not significantly altered.

In conclusion, the DHS reviewers, to different degrees, concluded that chance, bias, and confounding are not probable explanations for the reported associations when they have been reported repeatedly by independent investigators. In addition, the DHS reviewers considered other criteria, notably Hill's criteria for causality, keeping in mind that these are not to be considered as strict rules to follow. Apart from consistency, which, as noted above made them doubt the non-causal explanation for a few endpoints, none of the Hill's attributes, when applied to the pattern of evidence, influenced their degree of certainty by much.

The DHS reviewers recognize the size of the associations between EMF exposure and the various diseases studied are not so far above the resolution power of the studies that confounding and bias could be definitively ruled out as explanations. They recognized that there was rarely an orderly progression of increased risk within studies and that the effects reported for groups with dramatically high exposures like electric train operators did not display dramatically high risks when compared to those with low or moderate exposures. There are also examples where the statistical results are not completely coherent. However, these evidentiary tests are prone to giving false-negative results due to non-differential measurement error and sample size problems. Also, EMFs may have societally important effects that are nonetheless truly close to the detection of epidemiology. Finally, an agent may act in an "on/off" fashion and would not produce a steadily increased effect. These patterns of evidence therefore lowered confidence some, but not a lot.

STRENGTH OF ASSOCIATION

As the apparent relative risk conveyed by EMF exposure gets further and further away from 1.00, the likelihood of the pattern occurring under chance gets smaller and smaller. Prior experience with research studies suggests that, if specific evidence for particular bias or confounding is not present, the probability of unidentified bias or confounding falsely producing an apparently harmful or beneficial association gets smaller and smaller as the association moves away from the null value of RR = 1.0. This means that the likelihood of the evidence under causality RELATIVE to the likelihood of the evidence under bias, confounding, or chance gets bigger and bigger as the relative risk departs from 1.0. However, the posterior probability does not necessarily become greater as the relative risk increases. For example, all three core reviewers had a vanishingly small prior probability that residential EMFs could increase the risk of various diseases 100-fold because this would already have been noticed. If there were an epidemiologically detectable effect, they thought it would be found in the range of relative risks between 1.2 and 5. So, if the reviewers observed a relative risk of 100 in a particular study, their posterior would be less than if they observed a relative risk of 2.00. Some of the core reviewers took the position that a small RR simply did not support the causal hypothesis very strongly but did not go against the causal hypothesis. Other core reviewers gave somewhat more weight to the bias considerations if the pooled RR for the various studies was close to 1.0.

CONSISTENCY

"Consistency" refers to the consistency of the results with the hypothesis of an EMF risk (the reviewers refer to the consistency between studies as "homogeneity"—see below). This concept is useful if the body of evidence consists of a fair number of studies. The reviewers ask if the proportion of studies with risk ratios falling above a relative risk of 1.0 could easily be due to chance, by calculating the cumulative binomial probability of the observed number of risk ratios above a RR of 1.0. If they are nearly equally distributed above and below a RR of 1.0, then the results are not consistent. If all or most are above or are below a RR of 1.0, then the results are consistent. Consistency is hard to evaluate when there are only a few studies. Suppose the body of evidence contained only one large and one small study, each showing a RR above 1.0, and one small study showing a RR slightly below 1.0. The meta-analysis in this case might suggest a statistically significant association above a RR of 1.0. In that case, the pattern of the three risk ratios might easily seem to be randomly inconsistent because of the small number of studies, even though 66% of the studies were above a RR of 1.0. The reviewers recognize that for endpoints in which all the studies had been subjected to a meta-analysis or pooled analysis, a more elegant way to assess what is referred to as "consistency" and "homogeneity" would be to analyze the components of variance around the summary measure of association. This kind of information was not usually available to the reviewers and they attended to the proportion of relative risks above and below unity, as an approximate way of characterizing the evidence.

HOMOGENEITY

Even if the relative risks in a series of studies were consistently above a RR of 1.0, their sizes might not be homogeneous. For example, women with a particular gene might have a large risk of a birth defect from smoking while women without that gene might have a much smaller effect. This would produce a pattern of relative risks between the smoking habit and the birth defect that was consistent but not homogeneous.

EXPERIMENTAL EVIDENCE (ANIMAL PATHOLOGY)

The reviewers agreed that, with few exceptions, animal pathology studies based on high exposures to certain aspects of the EMF mixture showed no effects. There were three reasons why the reviewers believed that animal bioassays of single ingredients of the EMF mixture might be prone to missing a true effect:

a) Finding the right animal species to test: While the reviewers recognized that most agents found to cause cancer in humans also cause cancer in some (but not all) animal species, they were also cognizant that there are known human carcinogens, such as cigarette smoke, alcoholic beverages, benzene, and arsenic for which no animal model existed for many decades.

b) Testing one ingredient of a mixture: The reviewers all questioned whether the bioassay of one element of a mixture could be sensitive enough to detect problems in the entire mixture. For example, many reassuring assays on the carcinogenicity of caffeine would not reassure them about the carcinogenicity of coffee. The animal pathology studies to date have been on pure steady 60 Hz fields not on the mixture of ingredients found near power lines or appliances.

c) Assuming that high intensities of magnetic fields produce larger effects than moderate fields do: The reviewers also questioned the sensitivity of a bioassay involving a small number of animals and assuming a monotonically increasing risk from low to high dose, when the epidemiological studies that prompted the bioassays did not suggest an ever-increasing response.

The epidemiology suggests there is either no effect at all (Tynes, Jynge & Vistnes, 1994a) or no more effect at 250 mG (Minder & Pfluger, 2001) than 3 mG in children (Greenland et al., 2000), or 24 hr TWA of 7 mG in highly exposed utility workers (Kheifets et al., 1997b), (Kheifets, 2001). One would not expect rodents at 1000 mG to demonstrate a large enough effect to be detected in a conventionally sized laboratory experiment with a few hundred animals.

Accordingly, the lack of response in most animal pathology studies did not lower the degree of certainty by much. Reviewers 1 and 3 had their degree of confidence increased somewhat by repeated but unreplicated results from one German laboratory (Mevissen et al., 1996b) and isolated results from two laboratories in the former Soviet Republics (Anisimov et al., 1996), (Beniashvili et al., 1991), which showed co-promotional effects on breast tumors. None of the reviewers were much influenced by the statistically significant increase in thyroid cancers in one of the bioassays (Boorman et al., 1999b), even though it had not appeared in control series of previous bioassays and was thus a very unlikely occurrence. This effect showed up in only one sex of rats and not in mice and thus did not pass conventional toxicological criteria for animal carcinogenicity.

BIOLOGICAL PLAUSIBILITY (MECHANISTIC STUDIES)

In setting their prior (initial degree of confidence), the reviewers already have discussed theoretical models based on general physics and biological knowledge, predicting that the threshold of possible influence above endogenous currents is higher than the environmental levels implicated by the epidemiological studies. They cannot, therefore, use this argument again with regard to new EMF-specific evidence. Various attempts were carried out as part of targeted EMF research to devise more refined models for the purpose of supporting or rejecting the hypothesis of an EMF risk. These are discussed in the section on mechanisms and therefore will not be re-evaluated each time the epidemiology of a specific endpoint is reviewed. The core evaluators thought that a lack of a definitive mechanistic explanation of how EMFs could induce biological change, or a chain of biological events leading to pathology, did not pull confidence down below its initial value. But neither did the chicken studies nor melatonin inhibition cell studies add much, if any, weight of evidence. They were, however, considered high priority for further study since they were relevant to the possibility of bioeffects at "low" levels of exposure.

ANALOGY

If a chemical with a particular structure causes cancer, one can argue by analogy that a similar chemical might have the same effect. The reviewers agree that analogy does not help much with the EMF issue. Many causal agents have no analogous situation to reason from, when first encountered, so the absence of an analogous agent does not pull their confidence down as much as the presence of a good analogous agent would pull them up. This situation does not vary from disease to disease.

TEMPORALITY

If one compared unemployment rates in the general population to those among prevalent cases of rheumatoid arthritis, one would see a higher unemployment among the arthritics. One would not conclude that unemployment causes arthritis because the above-mentioned study design has not ensured that the reviewers could rule out the possibility that the arthritis preceded the unemployment. The criterion of temporality simply requires that study designs rule out that kind of confusion. If they do not, then grave doubts would arise about the evidence. Confusions about temporality are not an issue in the EMF epidemiological study designs included in this evaluation. In an abundance of caution, the reviewers discuss and dismiss this issue in one of the miscarriage studies.

SPECIFICITY AND EVIDENCE FROM OTHER DISEASES

There is a tendency to believe specific associations between an agent and one disease or subtype of disease more than associations with more than one disease. This probably is because the likelihood of chance, bias, or confounding producing a false association with one specific disease or one subtype of, for example, cancer, is smaller than the likelihood of false associations with cancer type 1, 2, 3, or 4. But even with genotoxic carcinogens, more than one cancer may result from exposure. If an agent causes disease by perturbing the immune or endocrine system, the effects could be non-specific. The AIDS virus is associated with Kaposi's sarcoma in some cities and with lymphoma in others, apparently depending on the varying presence of other risk factors. EMFs are physical agents that reach all parts of the body and are not thought to work through traditional genotoxic mechanisms, if, indeed, they have a pathological effect. EMF associations have NOT been characterized by great specificity as to disease type or subtype. One's confidence in causality for disease X might be increased by one's confidence in causality for disease Y, particularly if they share common mechanisms or other features.

The core team members either gave no weight to lack of specificity or found that it increased the credibility (see the core team members' individual conclusions after each endpoint's evaluation).

COHERENCE/VISIBILITY

Sometimes the existence of one association logically suggests that another association also should hold true. When that happens, it is said that the evidence is coherent. For example, if maximum magnetic fields were associated with disease X, and electric blankets expose users to high maximum fields, then one would expect electric blankets to be associated with disease X. If sub-groups of the population are known to be more vulnerable to environmental insults, and EMFs are more strongly associated with disease X in the vulnerable group than in the non-vulnerable group, that, too, is an example of internal coherence.

While the discussion of the internal coherence of studies varied from endpoint to endpoint, the discussion of what is called "visibility" was valid for all diseases tracked by disease registries or reliably traceable through hospitalization records or death certificates.

When electrification came, initially to cities and then rural areas of the United States in the first half of the 20th century, each area went from zero to low average exposures and then to higher average exposures as electricity progressed from mere lighting to heating, cooking, and other uses. The reviewers would argue that personal exposure eventually may have fallen to somewhat lower exposures as affluence brought larger lot sizes, more underground lines, and less knob and tube wiring. But some have argued that the incidence of disease should have increased dramatically and linearly with increased production of electricity even though electricity use, as measured at the electric meter in a home or by kilowatts sold, is not necessarily associated with personal exposure to magnetic fields.

Some argue that, since we all are exposed to magnetic fields higher than those that preceded the introduction of electricity, there should be a change in disease rates over time and from places with more or less consumption of electricity. This assumes that even low levels of exposure cause substantial increases in risk. For the most part, the epidemiological associations have been with the top 5% or 10% of the exposed population. In Chapter 2 the reviewers provided calculations for the impact of various RRs conveyed by 95th percentile exposures. With relative risks below 3.00 this can be shown to produce less than a 15% fluctuation in the overall rate of disease. This size of an effect would be hard to disentangle from changes in other causes of the diseases in question. The reviewers discuss this in more detail in the chapters on childhood leukemia and spontaneous abortion, where there are associations between residential EMFs and disease. For spontaneous abortions and perhaps other diseases which are not routinely recorded and which usually are dealt with on an outpatient basis, larger impacts might have gone unnoticed. For the other diseases the reviewers take the generic position that the modest associations described might exist without being noticed as geographical or temporal fluctuations. They discuss the findings of Milham et al. (2002) with regard to electrification and childhood leukemia mortality in the chapter on that disease.

7.4 QUESTIONS RELEVANT TO POLICY

DOSE-RESPONSE QUESTIONS

Except for childhood leukemia and spontaneous abortion, there is not a sufficient evidentiary base or data to even speculate on the issues of thresholds, plateaus, special metrics, windows, and biological windows of vulnerability. The discussions of these topics are restricted primarily to the evidence from these two diseases.

RACIAL AND CLASS DIFFERENCES IN EXPOSURE AND VULNERABILITY

Policy perspectives that pay attention to environmental justice require evidence on special vulnerabilities or exposures. The reviewers discuss this in the chapter on exposure. With the exception of the two recent miscarriage studies sponsored by DHS, which found no racial or social class special vulnerability to EMFs, none of the papers they read presented data on potential differential impacts of EMFs on different races, ethnicities, or social class. This is noted in the summary tables.

HOW DOES THE OBSERVED RELATIVE RISK COMPARE TO THAT WHICH WOULD GENERATE A 1/100,000 OR 1/1000 LIFETIME ADDED RISK

Some regulatory frameworks consider as negligible (*de minimis*) those risks which would accumulate less than 1/100,000 added lifetime risk from 70 years of residential exposure or 1/1,000 during 40 years of occupational exposure. As an approximation, the reviewers took the crude mortality or incidence of the disease in question and applied the relative risk to obtain the annual theoretical incidence or mortality among "exposed" persons. They subtracted this number from 1.0 to obtain the probability of escaping that disease in one year. For 70 years of residential exposure, they raised that number to the 70th power to obtain the probability of escaping a particular disease in a lifetime. They then subtracted that from 1 to obtain the probability of contracting or dying from the disease in a 70-year lifetime. This was compared to the baseline lifetime probability of contracting or dying from that disease. A similar calculation was made for childhood cancer, but using 20 years, and for occupational cancers, using 40 years.

Epidemiological studies rarely have the resolution power to detect RRs less than 1.2 reliably. As a general rule, if the baseline incidence was equal to or greater than 1 per 100,000 per year, the reviewers determined that a RR of 1.2 or larger conveyed more than a 1/100,000 theoretical lifetime risk from 20 or 70 years of exposure. A baseline rate of 11/100,000 per year or greater was required if a 1.2 fold risk were to accumulate a 1/1,000 theoretical lifetime risk during 40 years of occupational life. This meant that all the agents would be of environmental regulatory concern if detectable by epidemiology. With a few exceptions (ALS, male breast cancer, adult brain cancer), they would be of regulatory concern in the workplace as well.

SIZE OF EMF RELATIVE RISKS AND ATTRIBUTABLE FRACTIONS COMPARED TO OTHER RISK FACTORS

Epidemiologists sometimes evaluate the "importance" of a factor by comparing the relative risk conveyed by the highest exposures and the proportion of the baseline rate due to this factor (the attributable fraction or PAR%) to those of other known factors. By these standards, cigarette smoking is large and exposure to other people who smoke is small when one considers lung cancer. The PAR% describes the expected percentage fall in the overall rate of the disease if the "exposure" were removed. It is a measure of effectiveness. But, at least in the utilitarian policy framework, it is cost effectiveness, not effectiveness, that guides priority setting. For example, highway speed accounts for most vehicular injury fatalities, but the economic and political cost of enforcing a 25 mile-per-hour speed limit (or even a 55 mile-per-hour speed limit) on the freeway makes that strategy less cost effective than enforcing the use of seatbelts. Nonetheless, since the PAR% is a criterion often used, the reviewers address it in the structured questions.

7.5 WHY CANCER CLUSTER LITERATURE IS NOT REVIEWED

Although public and media attention to the EMF issue has been stimulated in great part by reports of cancer clusters near power lines or transformer stations, as well as radio frequency and radar transmitters, the DHS reviewers have not (nor have the NIEHS, NAS, and WHO) included a review of these reports. The reason is that this stream of evidence for EMFs carries little weight. Even if EMFs increase the risk of certain cancers, the proportion of neighborhoods displaying a cancer cluster above what was expected would be low (the test is not "sensitive"). For example, in Sweden, Feychting and Ahlbom (Feychting & Ahlbom, 1993) identified all childhood cancers that had occurred over many decades within 300 meters of the thousands of miles of transmission lines. By accumulating all this information they identified an excess number of childhood leukemia cases within 50 meters of the line. The excess was a handful of cases spread along the many miles of transmission line which ran through inhabited areas. There were not enough cases in those many decades to form a cluster that any neighborhood group would have noticed.

But cluster evidence generates false positives, that is, it is not "specific." This can be predicted by the laws of probability. Since the California Cancer Registry routinely tracks 50 kinds of cancer, the chance that any one suburban city block will escape a statistically significant ($p = .01$) elevation of all these 50 cancers is 0.99 to the 50^{th} power or 60%. That means there is a 40% probability that at least one of those 50 cancers will be found in excess. Inasmuch as the approximately 10 million California households are grouped in a few 100,000 blocks and about 2% of those blocks are near enough to transmission lines to influence the magnetic field levels (Lee et al., 2000), 40% of a few thousand blocks near transmission lines would be found to have at least one of those 50 kinds of cancer, by chance alone (Neutra, 1990).

If one wanted to examine clusters as a legitimate test of the EMF hypothesis, one would examine the 1,000 or so city blocks near transmission lines and compare the number of cancer clusters on them to the number on a 1,000 blocks of similar socioeconomic status but away from transmission lines. The vast majority of the clusters would be from the 40% of blocks with chance clusters and a few extra clusters might be detected if the nearby lines were a causative agent. The strategy of Feychting (1993) is a better strategy because it pays attention to all the cancers, not just the ones which occur in clusters. It is for this reason that the reviewers restrict their examination to well-designed epidemiological studies.

7.6 HEURISTIC FOR UPDATING THE DEGREE OF CONFIDENCE IN CAUSALITY

The ideal way to develop a posterior degree of confidence would be to develop a full probabilistic model or Bayesian Net, but the reviewers' stakeholders made clear at the outset that they should not rely on a method that would not be accessible for criticism to most readers.

Accordingly, the reviewers have structured their narrative to reflect the considerations that would go into a Bayesian net and elicited their posterior degrees of confidence directly after systematically considering the narrative. The reviewers used numbers, as well as the agreed-upon everyday language phrases, to characterize their professional judgments. They also applied the IARC criteria to derive a categorization of the evidence according to traditional guidelines.

8.0 EPIDEMIOLOGY OF THE LEUKEMIAS

STATEMENT TO THE PUBLIC

The reviewers expressed their judgments using two distinct sets of guidelines to evaluate the evidence:

- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for childhood leukemia, their classifications for EMFs ranged from "human carcinogen" to "probable human carcinogen" to "possible human carcinogen" (IARC's Groups 1, 2A, 2B). Panels convened by IARC and the National Institutes for Environmental Health Sciences classified EMFs as a "possible human carcinogen" for childhood leukemia.***
- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for adult leukemia, their classifications for EMFs ranged from "human carcinogen" to "possible human carcinogen" (IARC's Group 1 and 2B). The IARC Working Group classified the EMF evidence on adult leukemia as "inadequate." The National Institutes for Environmental Health Sciences classified it as "possible."***
- ***Using the Guidelines developed especially for the California EMF program, one of the reviewers "strongly believes" that high residential EMFs cause some degree of increased risk of childhood leukemia, another was "prone to believe" that they do, and another was "close to the dividing line between believing or not believing."***
- ***Using the Guidelines developed especially for the California EMF program, one of the reviewers was " prone to believe" that high residential or occupational EMFs cause some degree of increased risk of adult leukemia, while the other two were "close to the dividing line between believing or not believing."***

There are several reasons for the differences between the DHS reviewers and those of IARC. The three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them. Adult leukemia has an incidence of around 1/10,000 per year. If one doubled this rate to 2/10,000 per year and accumulated it over a lifetime of continuous high exposure one would accumulate a lifetime risk of 1%. Thus the vast majority (99%) of highly exposed people would still not contract this disease. Furthermore, calculations suggest that the fraction of all cases of childhood leukemia that one could attribute to EMFs would be no more than a few percent of the total cases (if any). Similar considerations apply to adult leukemia. Nevertheless, if EMFs do contribute to the cause of this condition, even the low fractions of attributable cases and the size of accumulated lifetime risk of highly exposed individuals could be of concern to regulators. Indeed, when deemed a real cause, estimated lifetime risks smaller than this (1/100,000) have triggered regulatory evaluation and, sometimes, actual regulation of chemical agents such as airborne benzene. The uncommon, accumulated high-EMF exposures implicated by the evidence about these conditions come from unusual configurations of wiring in walls, grounded plumbing, nearby power lines, and exposure from some jobs in electrical occupations. There are ways to avoid these uncommon accumulated exposures by maintaining a distance from some appliances, changes in home wiring and plumbing, and power lines. However, to put things in perspective, individual decisions about things like buying a house or choosing a jogging route should involve the consideration of well-recognized certain risks, such as those from traffic, fire, flood, and crime, as well as the uncertain comparable risks from EMFs. The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the added personal risk suggested by the epidemiological studies was "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. The three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	RL*	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASE DISEASE RISK TO SOME DEGREE
Childhood Leukemia					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Strongly believe	140	
	2	2B	Close to dividing line	22	
	3	2A	Prone to believe	17	
Adult Leukemia					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Prone to believe	29	
	2	2B	Close to dividing Line	21	
	3	2B	Close to dividing Line	6	

8.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

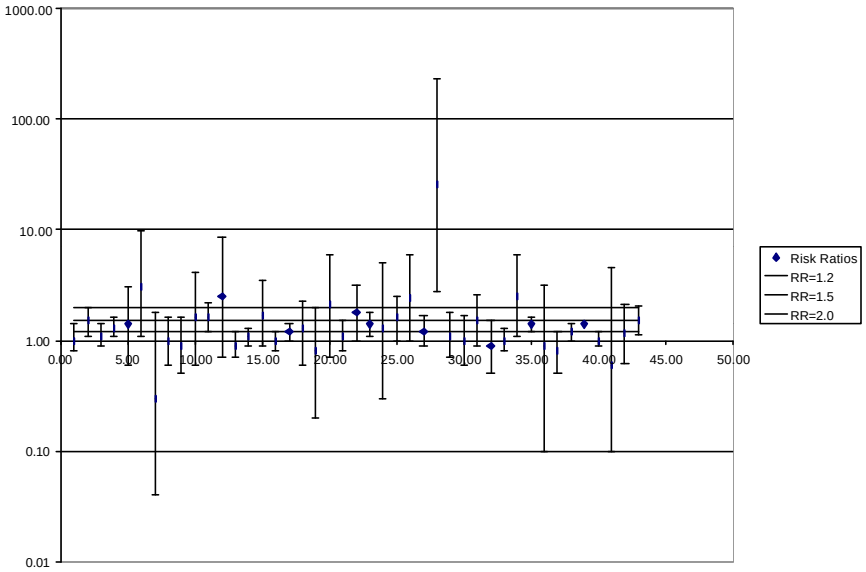


Figure 8.1.1 Studies of Adult Leukemia and EMFs Primarily Based on Kheifets (1997)

NOTE ON THE RISK ESTIMATES IN FIGURE 8.1.1 AND TABLE 8.1.1: Several studies report multiple comparisons (e.g., wire code classification or measured fields; dichotomous or polytomous classification; high vs. low or very high vs. very low). These different classifications lead to different risk estimates, and in a few cases the same data may show a positive association, no association or even a negative association depending on the method of analysis. For the sign test, widely employed in this evaluation, it is important that one and only one result be included from each study. In all cases, the DHS reviewers refrained from making the selection themselves to avoid introducing a subjective bias. Whenever the studies hade been included in a meta-analysis or pooled analysis, they accepted the selection made by the analysts. If a study had not been included in a meta-analysis or pooled analysis, but such an analysis had been performed on other studies for the same endpoint, the reviewers used the same guidelines used in those analyses. For example, the UK study (2000) shows a positive association for a 4 mG cutpoint, but the reviewers report it as negative because most of the other childhood leukemia studies were included in a pooled analysis (Greenland et al., 2000) in which the comparison was made for exposure above 3 mG vs. an exposure < 1 mG and using these cutpoints on the UK data yields a negative association. When no meta-analyses exist, the reviewers used the RR chosen by the authors to summarize their findings, usually in the abstract. These considerations apply to all similar tables/figures in the following chapters.

Figure 8.1.1 and Table 8.1.1 summarize the epidemiological evidence for adult leukemia derived primarily from (Kheifets et al., 1997a) of 43 studies, 29 had odds ratios (ORs) above 1.00 ($p=\leq 0.01$), 20 had ORs above 1.2. The meta-analytic summary was 1.2.

Figure 8.1.2 and Table 8.1.2 summarize the childhood leukemia epidemiological literature. Sixteen of nineteen had ORs > 1.00 ($p = 0.0004$), fifteen of nineteen were above 1.2, nineteen had ORs > 1.5. A meta-analysis by (Wartenberg, 2001) suggests a meta-analytic summary OR of 1.3 (1.0-1.7). Greenland et al. (Greenland et al., 2000) presents the information in Table 8.1.3 with a pooled analysis OR conveyed by being above 3 mG of 1.69 (1.25, 2.29).

TABLE 8.1.1 SUMMARY OF ADULT LEUKEMIA STUDIES

Study	Study No.	Year	Individual Odds Ratio Mean	Lower CL	Upper CL	Source
Savitz & Loomis	1.00	1995	1.00	0.80	1.40	Kheifets 1997
Floderus et al.	2.00	1992	1.50	1.10	2.00	Kheifets 1997
Floderus et al.	3.00	1994	1.10	0.90	1.40	Kheifets 1997
London et al.	4.00	1994	1.30	1.10	1.60	Kheifets 1997
Thierault et al.	5.00	1994	1.40	0.60	3.10	Kheifets 1997
Thierault et al.	6.00	1994	3.10	1.10	9.70	Kheifets 1997
Thierault et al.	7.00	1994	0.30	0.04	1.80	Kheifets 1997
Tynes et al.	8.00	1994	1.00	0.60	1.60	Kheifets 1997
Tynes et al.	9.00	1994	0.90	0.50	1.60	Kheifets 1997
Ciccone et al.	10.00	1993	1.60	0.60	4.10	Kheifets 1997
Guenel et al.	11.00	1993	1.60	1.20	2.20	Kheifets 1997
Matanowski et al.	12.00	1993	2.50	0.70	8.60	Kheifets 1997
Sahl et al.	13.00	1993	0.90	0.70	1.20	Kheifets 1997
Tynes et al.	14.00	1992	1.10	0.90	1.30	Kheifets 1997
Richardson et al.	15.00	1992	1.70	0.90	3.50	Kheifets 1997
Loomis et al.	16.00	1991	1.00	0.80	1.20	Kheifets 1997
Robinson et al.	17.00	1991	1.20	1.00	1.40	Kheifets 1997
Simonato	18.00	1991	1.30	0.60	2.30	Kheifets 1997
Spinelli et al.	19.00	1991	0.80	0.20	2.00	Kheifets 1997
Flodin et al.	20.00	1990	2.10	0.70	5.90	Kheifets 1997
Gallagher et al.	21.00	1990	1.10	0.80	1.50	Kheifets 1997
Garland et al .	22.00	1990	1.80	1.00	3.20	Kheifets 1997
Juutilainen et al.	23.00	1990	1.40	1.10	1.80	Kheifets 1997
Guberan et al.	24.00	1989	1.30	0.30	5.00	Kheifets 1997
Pearce et al.	25.00	1989	1.60	1.00	2.50	Kheifets 1997
Cartwright et al.	26.00	1988	2.40	1.00	6.00	Kheifets 1997
Milham et al.	27.00	1988	1.20	0.90	1.70	Kheifets 1997
Preston-Martin et al.	28.00	1988	25.40	2.80	232.50	Kheifets 1997
Tola et al.	29.00	1988	1.10	0.70	1.80	Kheifets 1997
Olsen et al.	30.00	1987	1.00	0.60	1.70	Kheifets 1997
Stern et al.	31.00	1986	1.50	0.90	2.60	Kheifets 1997
Blair et al.	32.00	1985	0.90	0.50	1.50	Kheifets 1997
Calle et al.	33.00	1985	1.00	0.80	1.30	Kheifets 1997
Gillman et al.	34.00	1985	2.50	1.10	5.90	Kheifets 1997
Milham et al.	35.00	1985	1.40	1.20	1.60	Kheifets 1997
Olin et al.	36.00	1985	0.90	0.10	3.20	Kheifets 1997
Morton et al.	37.00	1984	0.80	0.50	1.20	Kheifets 1997
Coleman et al.	38.00	1983	1.20	1.00	1.40	Kheifets 1997
Howe et al.	39.00	1983	1.40			Kheifets 1997
McDowall et al.	40.00	1983	1.00	0.90	1.20	Kheifets 1997
Polednak	41.00	1981	0.60	0.10	4.50	Kheifets 1997
Severson	42.00	1988	1.15	0.62	2.15	Severson 1988
Wertheimer & Leeper	43.00	1982	1.51	1.11	2.05	Wertheimer & L. 1982

Note: CL = confidence Limit

Fig 8.1.2 Summary Graphic Representation of the Results of Childhood Leukemia Studies

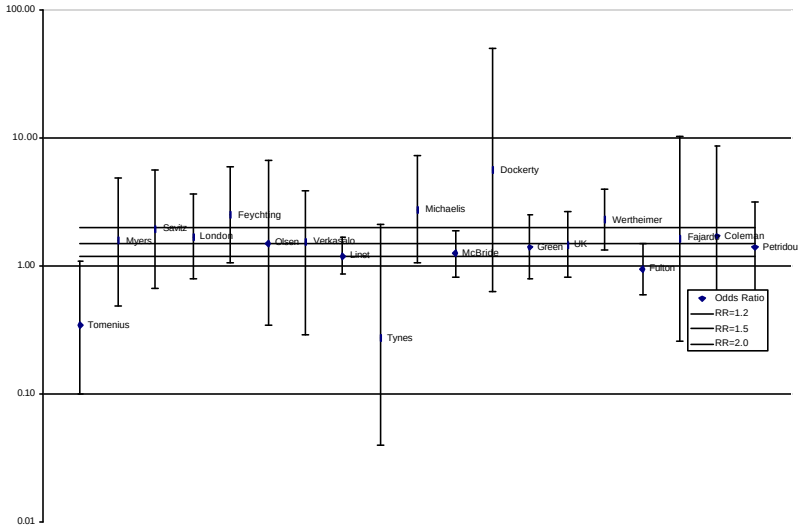


TABLE 8.1.2

From Wartenberg, Childhood Leukemia

Author	Exposure Definition	Study No.	Individual Odds Ratio, Mean	Lower CL	Upper CL
Tomenius	0.3 μT spot	1	0.34	0.10	1.09
Myers	0.03 μT peak	2	1.56	0.49	4.91
Savitz	0.2 μT spot	3	1.93	0.67	5.56
London	0.27 μT 24-hour	4	1.68	0.78	3.64
Feychting	0.2 μT calculated	5	2.49	1.04	5.98
Olsen	0.25 μT calculated	6	1.50	0.34	6.73
Verkasalo+	0.20 μT calculated	7	1.55	0.29	3.81
Linet	0.2 μT 24-hour	8	1.19	0.85	1.68
Tynes	0.14 μT calculated TWA	9	0.27	0.04	2.10
Michaelis	0.2 μT 24-hour	10	2.74	1.04	7.21
McBride	0.2 μT spot	11	1.25	0.82	1.89
Dockerty	0.2 μT spot bedroom	12	5.57	0.62	50.03
Green	0.15 μT interior average	13	1.39	0.78	2.48
UK	0.2 μT calculated	14	1.46	0.81	2.64
Wertheimer	wire code	15	2.28	1.34	3.91
Fulton	wire code	16	0.95	0.60	1.50
Fajardo	wire code	17	1.64	0.26	10.29
Coleman	wire code	18	1.70	0.34	8.64
Petridou	wire code	19	1.39	0.61	3.18

Note: CL = confidence Limit

TABLE 8.1.3 SUMMARY DESCRIPTION OF ADULT LEUKEMIA STUDIES

INVESTIGATOR AND DATE (REFERENCE NUMBER)	STUDY POPULATION AND LOCATION	METHOD USED FOR EXPOSURE ESTIMATE	STUDY TYPE	NUMBER OF CASES OR STUDY SUBJECTS	RISK MEASURE	ALL LEUK.	AML	ALL	CLL	CML
(Savitz & Loomis, 1995)	US: deaths among 138,905 men employed full-time at least 6 months, 1950-1986, at 5 utility companies (all members of the EPRI)	Work history and measurements	cohort	164 cases of leukemia	RR	1.0 (0.8-1.4)	0.9 (0.5-1.6)			1.0 (0.5-2.0)
(Floderus, 1993) (Floderus, 1992)	Sweden: cases among males in 1980 employed and living in mid-Sweden, 1983-1987	Usual job and measurements	CC	250 cases of leukemia; age 20-64	OR	1.5 (1.1-2.0)	0.9 (0.6-1.4)		2.5 (1.6-3.9)	
(Floderus et al., 1994) (Tornqvist et al., 1991) Linet et al. 1988 (7) (Tornqvist, Norell & Knave, 1986)	Sweden: 1,906,660 men employed in 1960, followed from 1961-1979 (133,687 in selected electrical occupations)	Occupation code from census (with estimation of EMF exposure)	cohort	334 cases of leukemia (in selected electrical occupations); age 20-74	SMR	1.1 (0.9-1.4)	1.1 (0.8-1.6)	1.3 (0.4-4.2)	1.2 (0.8-1.8)	1.1 (0.6-1.6)
(London et al., 1994) (Wright, Peters & Mack, 1982)	US: cases among males with known occupation, in Los Angeles County Cancer Registry & measurements, 1972-1990	Occupation code from Registry	MOR	2,355 cases of leukemia; age 20-64	OR	1.3 (1.1-1.6)			1.3 (1.0-1.8)	1.3 (0.8-2.1)
(Theriault et al., 1994)	France: cases among 170,000 active male utility workers at Electricité de France-Gas de France from 1978-1989	Work history and measurements	CC	71 cases of leukemia	OR	1.4 (0.6-3.1)	1.7 (0.5-5.5)		4.8 (0.5-70.6)	
(Theriault et al., 1994)	Canada: cases among 31,543 men employed at Ontario Hydro on Jan. 1, 1973 and new employees, 1973-1988	Work history and measurements	CC	45 cases of leukemia	OR	3.1 (1.1-9.7)	37.8 (3.5->100)		2.1 (0.4-11.6)	

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Theriault et al., 1994)	Canada: cases among 21,749 men employed at Hydro-Quebec on Jan. 1, 1970 and new employees, 1970-1988	Work history and measurements	CC	24 cases of leukemia	OR	0.3 (0.04-1.8)			0.3 (0.02-2.6)	
(Tynes et al., 1994a)	Norway: cases among 13,030 male Norwegian railway workers, 1958-1990	Work history and measurements	CC	52 cases of leukemia	OR	1.0 (0.6-1.6)				
(Tynes et al., 1994b)	Norway: cases of cancer among cohort of 5,088 male workers in 8 large Norwegian hydroelectric power companies, employed at least 1 yr, 1953-1991	Work history and measurements	cohort	11 cases of leukemia	SIR	0.9 (0.5-1.6)				
(Ciccone et al., 1993)	Italy: cases of acute or chronic myeloid leukemia or MDS in main hospital, Torino, Italy, Oct. 1989-1990	Work history (assessed probability of exposure to EMF)	CC	50 cases of AML 17 cases of CML 19 cases of MDS; age 15-74	OR	AML+ CML+ MDS: Males: 1.6 (0.6-4.1)				
(Guenel et al., 1993)	Denmark: cases among 2.8 million Danes, 1970-1987	Occupation code from Central Population Register and measurements	cohort	39 male cases of leukemia; age 20-64	SIR	1.6 (1.2-2.2)	1.4 (0.9-2.4) All acute			
(Matanoski et al., 1993) (19)	US: cases among white males employed at least 2 years, identified from mortality records of ATT, 1975-1980	Work history and measurements	CC	124 cases of leukemia	OR	2.5 (0.7-8.6)				

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Sahl et al., 1993)	US: deaths among 36,221 employees at Southern California Edison Company, 1960-1988	Work history and measurements	CC and cohort	44 cases of leukemia	OR	0.9 (0.7-1.2)				
(Tynes, Andersen & Langmark, 1992)	Norway: cases among cohort of 37,945 male Norwegian electrical workers, 1961-1985	Job titles from census (categorized into 5 levels of exposure)	cohort	107 cases of leukemia	SIR	1.1 (0-9-1.3)	1.3 (0.9-1.2)	1.4 (0.4-3.7)	1.0 (0.6-1.4)	1.5 (0.9-2.3)
(Richardson, 1992) (Bastuji-Garin, 1990)	France: cases in 2 hospitals, 1984-1988	Work history and measurements	CC	185 cases of leukemia (50.2% cases male); age 30	OR	1.7 (0.9-3.5)	4.8 (1.5-15.8) All acute			
(Loomis, 1991) (Loomis & Savitz, 1990)	US: cases among 410,651 male deaths in 16 US states, 1985-1986	Occupation code from death certificates	MOR	3,400 cases of leukemia; age 20	OR	1.0 (0.8-1.2)	1.1 (0.7-1.7)	1.5 (0.7-3.4)	0.6 (0.3-1.1)	
(Robinson et al., 1991)	US: deaths identified from industrial mortality data, 14 states, 1979-1985	Occupation code from mortality data	PMR	183 cases of leukemia	PMR	1.2 (1.0-1.4)	1.1 (0.9-1.5)			
(Simonato et al., 1991)	Europe: cases of cancer among a cohort of 11,902 male welders from 135 companies located in 9 European countries	Work history and type of welding, if known	cohort	11 cases of leukemia	SIR	1.3 (0.6-2.3)				
(Spinelli, 1991)	British Colombia: cases of cancer, 1970-1985; deaths from cancer, 1950-1985; among male workers with 5 or more yrs of experience in an aluminum induction plant	Industrial hygienist identified EMF exposure for each job in company records	cohort	7 cases of leukemia total (mortality data) 3 incident cases of leukemia	SIR	0.8 (0.2-2.0)				
(Flodin, 1990) (Flodin, Fredriksson & Axelson, 1986)	Sweden: cases of AML from hospitals in 4 countries, 1977-1985	Occupation from postal questionnaire	CC	86 cases of AML; age 20-70	OR		2.1 (0.7-5.9)			

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Gallagher et al., 1990)	Canada: deaths among males in British Colombia, 1950-1984	Occupation code	PMR	35 cases of leukemia; age 20-65	PMR	1.1 (0.8-1.5)				
(Garland, 1990)	US: cases of cancer among white, male active-duty, enlisted naval personnel, 1974-1984	Work history	cohort	102 cases of leukemia; age 17-64	SIR	1.8 (1.0-3.2)				
(Juutilainen, Laara & Pukkala, 1990) (Juutilainen, 1988)	Finland: cases among all male industrial workers, 1971-1980	Occupation code from census (categorized as probable, possible, or no exposure to ELF)	cohort	221 cases of leukemia	RR	1.4	1.4			
(Guberan, 1989)	Switzerland: cases among 1,916 male painters and 1,948 male electricians in Geneva, 1970-1984	Occupation code from census	cohort	2 cases of leukemia	SIR	1.3 (0.3-5.0)				
(Pearce, Reif & Fraser, 1989) (Pearce et al., 1986) (22) (Pearce et al., 1985)	New Zealand: cases among males from New Zealand Cancer Registry, 1979-1983	Occupation code from Registry	MOR	546 cases of leukemia; age ≥ 20	OR	1.6 (1.0-2.5)	1.2 (0.4-3.9)		3.4 (1.38-8.9)	0.9 (0.1-6.4)
(Cartwright, 1988)	Yorkshire, UK: cases of AML in hospitals throughout Yorkshire, excluding South Humberside, 1979-1986	Work history from interview	CC	161 cases of leukemia; age ≥ 15	RR		2.4 (1.0-6.0)			
(Milham, 1988) (Milham, 1985)	US: deaths among 67,829 male licensed amateur radio operators in Washington State and California, 1979-1984	Amateur radio operator license, according to FCC files	cohort	36 cases of leukemia	SMR	1.2 (0.9-1.7)	1.8 (1.0-2.9)	1.2 (0.3-3.8)	1.1 (0.4-2.4)	0.9 (0.2-2.5)

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Preston-Martin & Peters, 1988)	US: cases of CML from the Los Angeles County Cancer Registry, April 1, 1979-June 30, 1985	Ever employed in one of 11 specific job titles from questionnaire data	CC	137 CML cases; age 20-69	OR					25.4 (2.8-232.5)
(Tola et al., 1988)	Finland: cases of cancer in Finnish Cancer Registry among cohort of 12,693 male shipyard and machine shop workers, 1945-1960	Work history	cohort	19 cases of leukemia	SIR	All workers: 1.1 (0.7-1.8) welders: 0.9 (0.1-3.3)				
(Olsen, 1987)	Denmark: 93,810 cases (male and female) from Danish Cancer Registry, 1970-1979	Work history	PIR	1,402 cases of acute leukemia	SPIR	1.0 (0.6-1.7)				
(Stern et al., 1986)	US: deaths among 24,545 onshore workers at Portsmouth Naval Shipyard, 1952-Aug 1977	Work history	CC	53 cases of leukemia	OR	1.5 (0.9-2.6)				
(Blair, 1985)	US: 107,563 deaths analyzed among cohort of 293,958 veterans, 1954-1970	Usual occupation from questionnaires	cohort	cases of leukemia; age 31-84	SMR	0.9 (0.5-1.5)				
(Calle & Savitz, 1985)	US: deaths among white men in Wisconsin for 10 electrical occupations, 1963-1978	Occupation code from mortality data (used occupational groups based on Milham data)	PMR	81 cases of leukemia 41 cases of acute leukemia; age ≥ 20	PMR	1.0 (0.8-1.3)	1.1 (41 cases) All acute			

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(Gilman, 1985)	US: 19,000 male coal miners entered into 4 NIOSH cohorts; 6,066 death certificates reviewed, prior to 1985	No. of years of underground mining, employment at time of cohort creation	MOR	40 cases of leukemia	OR	2.5 (1.1-5.9)	3.8	0.6	6.3 ($P < 0.05$)	
(Milham, 1985b) (Milham, 1982)	US: deaths among 486,000 total deaths in white males in Washington state, 1950-1982	Occupation code from mortality data	PMR	146 cases of leukemia 67 cases of acute leukemia; age ≥ 20	PMR	1.4 (1.2-1.6)	1.6 (67 cases) All acute			
(Olin, Vagero & Ahlbom, 1985)	Sweden: deaths among 1,245 male electrical engineers from Royal Institute of Technology in Stockholm, 1930-1979	MS in electrical engineering from Royal Institute of Technology, 1930-1959	cohort	2 cases of leukemia	SMR	0.9 (0.1-3.2)				
(Morton, 1984)	US: cases among total resident population of 4 counties of Portland/ Vancouver, 1963-1977	Usual occupation for cases, occupation code only for non-cases	cohort	1,678 cases of leukemia; age ≥ 16	SMR	0.8 (0.5-1.2)				
(Coleman, Bell & Skeet, 1983)	England: cases among 6.5 million identified through South Thames Cancer Registry, 1961-1979	Occupation code from Registry	PIR	113 cases of leukemia; age 15-74	PIR	1.2 (1.0-1.4)	1.2 (33 cases)	1.5 (12 cases)	1.3 (33 cases)	0.9 (6 cases)
(Howe, 1983)	Canada: deaths among 415,201 males In Canadian labor force, 1965-1971	Occupation code from census and work history	cohort	154 deaths from leukemia and leukemia; 31 cases among transportation communication, and other utility workers	SMR	1.4 (31 cases)				
(McDowall, 1983)	England and Wales: deaths among males, 1970-1972	Occupation code from mortality data	PMR	85 cases of leukemia 11 cases of ALL 31 cases of AML; age 15-74	PMR	1.0 (0-9-1.2)	1.0 (31 cases)	1.0 (1 case)		

Investigator and Date (Reference Number)	Study Population and Location	Method Used for Exposure Estimate	Study Type	Number of Cases or Study Subjects	Risk Measure	All Leuk.	AML	ALL	CLL	CML
(McDowall, 1983)	England & Wales: deaths among males, 1970-1972	Occupation code from mortality data	MOR	537 AML cases; age ≥ 15	RR		2.1	(1.3-3.6)		
(Polednak, 1981)	US: deaths among 1,059 while male welders at 3 plants in Oak Ridge, Tennessee, employed 1943-1973	Work history	cohort	1 case of leukemia	SMR	0.6 (0.1-4.5)				
(Severson et al., 1988)	Residents of Seattle, Washington	Wire coding	Case control	114	OR		1.15 (0.62-2.15)			
(Wertheimer & Leeper, 1982)	Residents of Denver, Colorado, and neighboring towns	Wire coding	Case control	1179	OR	1.51 (1.11-2.05)				

TABLE 8.1.4 SUMMARY DESCRIPTION OF CHILDHOOD LEUKEMIA STUDIES

STUDIES WIRE CODES	EXPOSURE CLASSIFICATI ON	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
(Wertheimer & Leeper, 1979)	Birth address: LCC HCC Death address: LCC HCC	 84 52 92 63	 Reference 2.28 (1.34-3.91) Reference 2.98 (1.78-4.98)		
(Savitz et al., 1988)	HCC/LCC VHCC/Buried	27/70 7/28	1.54 (0.90-2.63) 2.75 (0.94-8.04)	<19/59 6/24	1.28 (0.70-2.34) 2.75 (0.90-8.44)
(London et al., 1991)	UG+VL OLCC OHCC VHCC	31 58 80 42	References 0.95 (0.53-1.69) 1.44 (0.81-2.56) 2.15 (1.08-4.26)		
(Linet et al., 1997)	UG+VLCC OLCC OHCC VHCC			175 116 87 24	Rreferences 1.07 (0.74-1.54) 0.99 (0.67-1.48) 0.88 (0.48-1.63)
(McBride et al., 1999)	VHCC+OHCC	351	0.97 (0.72-1.32)		
CALCULATED FIELDS					
(Feychting & Ahlbom, 1993)	Unmatched analyses (FμT) <0.10.1-0.19 ≥0.2 ≥0.3 Matched analyses: (FμT) 0.1-0.19 ≥0.2	 274 7 7	 References 2.1 (0.6-6.1) 2.7 (1.0-6.3) 3.8 (1.4-9.3) 4.3 (1.0-8.9) 3.5 (0.9-13.6)		

STUDIES WIRE CODES	EXPOSURE CLASSIFICATION	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
(Olsen, Nielsen & Schulgen, 1993)	(μT) < 0.1 0.1-0.24 ≥0.25 ≥0.40	 829 1 3 3	 References 0.5 (0.1-4.3) 1.5 (0.3-6.7) 6.0 (0.8-44)		
(Verkasalo et al., 1993), (Verkasalo et al., 1994)	Cumulative exposure (μT-years) 0.01-0.39 ≥0.40 ≥1.0 Average exposure (μT) 0.01-0.19 ≥0.2	 32 3 3 32 3	 0.90 (0.62-1.3) 1.2 (0.26-3.6) 3.5 (0.7-10) 0.89 (0.61-1.3) 1.6 (0.32-4.5)		
(Tynes & Haldorsen, 1997)	Average exposure (μT) < 0.05 0.05-0.13 ≥0.14 Closest to diagnosis (μT) <0.05 0.05-0.13 ≥0.14 ≥0.2	 139 8 1 134 10 4 2	 References 1.8 (0.7-4.2) 0.3 (0.0-2.1) References 1.5 (0.7-3.3) 0.8 (0.3-2.4) 0.5 (0.1-2.2)		
PROXIMITY TO SOURCES					
(Coleman et al., 1989)	< 25 m substation ≥ 25 m substation	81 3	Reference 1.7(0.31-8.64)		
(Myers et al., 1990)	< 25 m ≥25 m	173 7	Reference 1.56 (0.54-4.53)		
Fajardo 1992	< 20 m distribution ≥ 20 m distribution	43 3	Reference 1.64(0.26-10.29)		
(Petridou et al., 1993)	Categories 1-3 Categories 4,5	106 11	Reference 1.39 (0.61-3.18)		

STUDIES WIRE CODES	EXPOSURE CLASSIFICATION	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
HOME OR PERSONAL MEASUREMENTS					
(Tomenius, 1986)	<0.3μT ≥0.3μT	239 4	Reference 0.34 (0.10-1.09)		
(Myers et al., 1990)	<0.03μT peak ≥ 0.03μT peak	174 6	Reference 1.56 (0.49-4.91)		
(Savitz et al., 1988)	Low power conditions (μT) < 0.2 ≥0.2 High power conditions (μT) < 0.2 ≥0.2 Electric fields (μT) < 12 V/m ≥12 V/m	 31 5 30 7 31 6	 Reference 1.93 (0.67-5.56) Reference 1.41 (0.57-3.50) Reference 0.75 (0.29-1.91)	 23 3 23 4 23 4	 Reference 1.56 (0.42-5.75) Reference 1.05 (0.34-3.26) Reference 0.67 (0.22-2.04)
(London, 1991)	Low power conditions (μT) < 0.032 0.032-0.067 0.068-0.124 ≥0.125	 67 34 23 16	 Reference 1.01 (0.61-1.69) 1.37 (0.65-2.91) 1.22 (0.52-2.82)		
(Michaelis et al., 1997a)	Short-term measurement (μT) < 0.2 ≥0.2	 170 6	 Reference 0.7 (0.3-1.8)		
(London, 1991)	24 hour measurements (μT) 0-0.067 0.068-0.118 0.119-0.267 ≥0 .268	 85 35 24 20	 Reference 0.68 (0.39-1.17) 0.89 (0.46-1.71) 1.48 (0.66-3.29)		

STUDIES WIRE CODES	EXPOSURE CLASSIFICATI ON	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
(Michaelis et al., 1997a)	Median of measurements (μT)				
	< 0.2	125	Reference		
	≥0.2	4	3.2 (0.7-14.9)		
	Mean of measurements (μT)				
	< 0.2	125	Reference		
	≥0.2	4	1.5 (0.4-5.5)		
	Median during the night (μT)				
	< 0.2	1245	reference		
	≥0.2		3.9 (0.9-16.9)		
(Michaelis et al., 1997b)	Median of measurements				
	(FμT)	167	Reference		
	< 0.2	9	2.3 (0.8-6.7)		
	≥0.2				
	Median during the night (μT)	167	Reference		
	< 0.2	9	3.8 (1.2-11.9)		
	≥0.2				
(Linet et al., 1997)	Unmatch analysis (μT)				
	< 0.065			267	Reference
	0.065-0.099			123	1.1 (0.81-1.50)
	0.1-0.199			151	1.1 (0.83-1.48)
	0.2-0.299			38	0.92 (0.57-1.48)
	0.3-0.399			22	1.39 (0.72-2.72)
	0.4-0.499			14	3.28 (1.15-9.39)
	≥0.5			9	1.41 (0.49-4.09)
	≥0.2			83	1.24 (0.86-1.79)
	≥0.3			45	1.7 (1.0-2.9)
	Matched analysis (μT)				
	<0.065			206	Reference
	0.065-0.099			92	0.96 (0.65-1.40)
	0.1-0.199			107	1.15 (0.79-1.65)
	0.2-0.299			29	1.31 (0.68-2.51)
	0.3-0.399			14	1.46 (0.61-3.50)
	0.4-0.499			10	6.41 (1.30-31.73)
	≥0.5			5	1.01 (0.26-3.99)
	≥0.2			58	1.53 (0.91-2.56)

STUDIES WIRE CODES	EXPOSURE CLASSIFICATI ON	LEUKEMIA NO. CASES	RR (95% CI)	ACUTE LYMPHOBLASTIC NO. OF CASES	RR (95% CI)
(UKCSS, 1999)	> 2 mG	1073	0.9 (0.49-1.63)	906	0.92 (0.47-1.79)
(Green et al., 1999a)	>1.5 mG (average indoor)	201	1.74 (0.63-4.82)	75	2.86 (0.88-9.29)
(Green et al., 1999b)	> 1.4 (personal exposure)	88	4.5 (1.3-1.9)	76	3.5 (0.9-13.9)
(McBride et al., 1999)	> 2 mG	297	1.35 (0.86-2.11)		

TABLE 8.1.5. STUDY-SPECIFIC ODDS-RATIO ESTIMATES AND STUDY-ADJUSTED SUMMARY ESTIMATES, MAGNETIC-FIELD DATA. REFERENCE CATEGORY: 0.1, µT.

(From "A POOLED ANALYSIS OF MAGNETIC FIELDS, WIRE CODES, AND CHILDHOOD LEUKEMIA," S. Greenland1, A. R. Sheppard2, W. T. Kaune3, C. Poole4, M.A. Kelsh5, for the Childhood Leukemia-EMF Study Group*)

First Author	Magnetic-field category (µT) >0.1, 0.2	>0.2, 0.3	>0.3
Coghill	0.54 (0.17, 1.74)	no controls	no controls
Dockerty	0.65 (0.26, 1.63)	2.83 (0.29, 27.9)	no controls
Feychting	0.63 (0.08, 4.77)	0.90 (0.12, 7.00)	4.44 (1.67,11.7)
Linet	1.07 (0.82, 1.39)	1.01 (0.64, 1.59)	1.51 (0.92, 2.49)
London	0.96 (0.54, 1.73)	0.75 (0.22, 2.53)	1.53 (0.67, 3.50)
McBride	0.89 (0.62, 1.29)	1.27 (0.74, 2.20)	1.42 (0.63, 3.21)
Michaelis	1.45 (0.78, 2.72)	1.06 (0.27, 4.16)	2.48 (0.79, 7.81)
Olsen	0.67 (0.07, 6.42)	no cases	2.00 (0.40, 9.93)
Savitz	1.61 (0.64, 4.11)	1.29 (0.27, 6.26)	3.87 (0.87,17.3)
Tomenius	0.57 (0.33, 0.99)	0.88 (0.33, 2.36)	1.41 (0.38, 5.29)
Tynes	1.06 (0.25, 4.53)	no cases	no cases
Verkasalo	1.11 (0.14, 9.07)	no cases	2.00 (0.23,17.7)
Study-adjusted summaries:*			
Woolf	0.96 (0.81, 1.14)	1.08 (0.80, 1.45)	1.83 (1.34, 2.49)
MH	0.95 (0.80, 1.12)	1.06 (0.79, 1.42)	1.69 (1.25, 2.29)
Study + age + sex adjusted:†			
MH	1.01 (0.84, 1.21)	1.06 (0.78, 1.44)	1.68 (1.23, 2.31)
Spline‡	1.00 (0.81, 1.22)	1.13 (0.92, 1.39)	1.65 (1.15, 2.36)

*MH = Mantel-Haenszel; maximum-likelihood summaries differed by less than 1% from these summaries. Based on 2,656 cases and 7,084 controls. Summary tests: 3 df MH categorical P = 0.01; 1 df Mantel trend P = 0.06 (from continuous data).

†Excludes Tomenius (no covariate data). Based on 2,484 cases and 6,335 controls with age and sex data. 3 df MH categorical P = 0.01; 1 df Mantel trend P = 0.04 (from continuous data).

‡Estimates comparing odds at category means (0.14, 0.25, 0.58 versus 0.02 µT) from a quadratic logistic spline with one knot at 0.2 µT, plus age and sex terms.

8.2 PRO AND CON ARGUMENTS FOR CHILDHOOD AND ADULT LEUKEMIA

TABLE 8.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Results are due to chance and multiple comparisons.	(F1) Meta-analyses show that overall the association is statistically significant (e.g., unlikely to be due to chance).	(C1) The test of statistical significance on the pooled or meta-analyzed data show that chance is a very unikely explanation ($p<0.02$, one-sided).

TABLE 8.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Bias in some or all studies has been identified. Given the small size of the association and the inconsistencies between and within studies, bias is a plausible explanation for the positive results.	(F1) No bias candidate common to all studies. No evidence or argument for consistent, upward bias. On the contrary, there is evidence that bias has inconsistent direction.	(C1) Pooled analysis shows that most studies are very consistent. While consistency may be due to a common bias, the different environments, methods of subjects recruitments, and exposure assessment and study design make it unlikely that most studies were affected by the same bias.
(A2) In particular, the meta-analytical risk estimate for adult leukemia is VERY close to 1, very susceptible to bias.	(F2) Savitz control and specular control matrix (Zaffanella et al., 1998) exhibits asymmetry of opposite direction to asymmetry in London's control and specular control matrix, suggesting that control selection bias in the two cases were in opposite direction and that therefore they could not both have resulted in a upward bias of the risk estimate.	(C2) The only bias certainly common to all these studies is that deriving from non-differential exposure misclassification, which, in dichotomous analyses, tends to understimate effects in these studies and distorts dose response assessments.
(A3) Exposure assessment in Wertheimer and Leeper studies not blind.	(F3) Convincing evidence against publication bias for children in Wartenberg's meta-analysis (Wartenberg, 2001).	(C3) There is no evidence that bias resulting in an inflation of the risk estimates is common to all studies. The argument that so many positive risk estimates greater than unity are due to bias, although studies are different in design and population base is not convincing and does not diminish the credibility of the hypothesis much.
(A4) Some evidence of non-publication bias in adult studies (Kheifets, 2001).	(F4) Publication bias in adults, insufficient to explain association (Kheifets, 2001).	
(A5) Occupational studies of mixed quality.	(F5) Strong pressures to publish good negative studies.	
(A6) Different control series in Li and Theriault residential study yield different risk estimates.	(F6) In the comparative analyses (Kheifets et al., 1999) the pooled OR = 1.48 (0.96-2.30) for adult leukemia in the highest exposure category. This is is less likely to be due to bias than RR = 1.2 from the meta-analysis.	
(A7) Canadian studies of childhood leukemia are heterogeneous from other studies (possible indication of bias effect).	(F7) The studies in the comparative analysis all use state-of-the-art methods for occupational cancer cohort studies. The cohort method greatly reduces selection and information bias. The significant association from these high-quality studies is not likely to be due to bias, making	

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
	them evidence for causality.	
(A8) The low response rates of the measurement studies increases the possibility of non-response bias.	(F8) As shown by both meta-analyses from Greenland and Ahlbom, the McBride study is homogenous with the other studies; the reason why the Green study is different from all other studies may be due to bias.	
(A9) Hatch et al. (Hatch et al., 2000) show that the results of the Linet (Linet et al., 1997) study could in part be due to selection/non-participation bias.	(F9) Non participation bias: - Savitz (Savitz et al., 1988) estimated that if participation in his study had been greater, the risk estimate would have been increased. - No argument in favor of consistent upward bias (SES is usually associated with participation rate, but according to California data is only weakly correlated to personnally measured exposure (Lee et al., 2002). Plausible argument for downward bias due to non-response of controls away from power lines, who are less interested in EMF debate. - Because of their design, Scandinavian studies are not subject to selection or non-participation bias, yet their result is consistent with that of the US studies. Selection bias: - Preston-Martin's (Preston-Martin et al., 1996b) L.A. child brain cancer study is negative, therefore its case series can be used as a control series for another L.A. study. When used as such with London's (1996) case series, one sees an association similar to that obtained with the original controls. This suggests that London's control series is not subject to selection bias.	(C4) Even if one or more or all of the positive associations were due to bias, it would not change the results of the sign test, which shows that such a skewed pattern of positive results is extremely unlikely to be due to random effects.
(A10) Hatch (Hatch et al., 2000) demonstrated selection bias with regard to the association between front door measurement and ALL. This casts doubt	(F10) The association between front door measurements greater than 3mG and ALL fell from 1.9 (1.1-3.27) to 1.6 (0.98-2.61) when partial participants were included. This difference is not big and not statistically	(C5) Hatch (Hatch et al., 2000) provides some evidence of selection bias but does not conclude that it totally explains the findings in case-control studies. Her findings do not

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
on all case control studies of childhood leukemia.	significant.	apply to the Scandinavian studies

TABLE 8.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Since most causes of leukemia are unknown, it is impossible to rule out confounding, particularly when associations are not very large.	(F1) All known, suspected, and even speculated confounders were controlled for in most study since W&L.	(C1) The existence of a strong, yet unidentified and not even hypothesized confounder present in every population studied is less plausible than accepting EMF as the causal factor.
(A2) Traffic density has been found to be associated with both wire coding and childhood leukemia.	(F2) Savitz (Savitz et al., 1988) found that the association with traffic was not strong enough to explain association with wire coding. Long, in-depth research project aimed to prove traffic fumes as the causal agent concluded that traffic was probably an effect modifier (Pearson et al., 2000). Controlling for traffic density had no effect in the meta-analyses.	(C2) Confounders, like biases, may act both to increase or decrease an association. It is not plausible to believe that in all the diverse populations studied (both occupational and residential, children and adults, different continents, different methods of exposure assessment) all unspecified confounders acted consistently to create an artifactual association.
(A3) Mobility has been associated with wire codes and with leukemia.	(F3) Hatch et al. (2000) determined that known confounders were an unlikely explanation of the leukemia association in their study and that mobility was not associated with leukemia risk and was thus not a confounder.	
	(F4) An unknown, unspecified confounder must be strong risk, fast acting (e.g., probably not an initiator), and/or strongly correlated to MF surrogates. Yet it has escaped detection so far. There are no plausible candidates meeting this requirements.	
	(F5) There are convincing quantitative argument against the plausibility of confounding by an unknown factor (Langholz, 2001).	
	(F6) Most studies reporting an association do not rely on wire coding. Moreover, not all wire code studies show an association with mobility (Preston-Martin et al., 1996).	

TABLE 8.2.4

STRENGTH OF ASSOCIATION (HOW EASILY CAN THIS ASSOCIATION BE INFLUENCED BY FACTORS OTHER THAN CAUSALITY?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Association is not strong, which make the reviewers less confident that it is not due to artifacts.	(F1) An observed RR of 1.3-1.5 is probably equivalent to a true RR of about 2 because of random misclassification of exposure in residential environments.	(C1) Some agents at high ambient or occupational doses have effects that are truly close to the resolution power of epidemiology. In an individual study an effect of that size is viewed with suspicion. When it recurs in many studies without a plausible candidate confounder, the lack of an association easily distinguishable from epidemiological limitations does not lower the confidence of these reviewers much if at all.
	(F2) The inevitably poor exposure assessment in occupational studies probably results in even stronger bias toward the null.	
	(F3) Most hazardous agents at ambient doses do not produce strong risks.	
	(F4) The hypothesis under consideration argues that EMF is one of many risk factors for leukemia, not the only and not even the main cause. herefore a small increase in risk is all that can be expected.	

TABLE 8.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the studies failed to show a statistically significant risk. If there is any consistency, the pattern shows consistently inconclusive results.	(F1) In the absence of an effect, one would expect studies to yield relative risk estimates greater or smaller than one with equal frequency. Instead, when we inspect Figure 8.1.1 summarizing the adult leukemia studies reviewed by Kheifets (1997) or Figure 8.2.1, representing the 44 studies in Table 8.1.3, one finds that the vast majority of relative risks are above 1. When examining the childhood leukemia studies in Table 8.2.5A and Figure 8.2.2, one finds that out of 18 studies conducted in different locales, with different study designs by different investigators using different possibilities of bias and confounding, 14 yielded a risk estimate greater than 1, and 2 additional studies had infinite relative risks because no controls had "high" exposures. Thus, the meta-analytic and pooled estimates of effect do not arise from a few large studies. Rather they reflect a general pattern. One must look for a causal explanation or consistent bias or consistent confounding. (Note: The Myers [1990] data was not available to Greenland and is not included in Table 8.2.5 or Figure 8.2.2.)	(C1) Lack of statistical significance is not related to the likelihood of causality, but to the study power.
(A2) The Tomenius(Tomenius, 1986) study reports a protective effect for childhood leukemia, not the positive association displayed in Table 8.1.5.	(F2) As explained above, the DHS reviewers adopted the same cutpoints used in the pooled analysis (Greenland et al., 2000). In that peer-reviewed and published paper, based on the original raw data of Tomenius (1986), the comparison between subjects exposed to fields > 3 mG vs. those exposed to less than 1 mG shows a risk for the high-exposure subjects.	(C2) If EMF is a promoter, co-promoter, or growth modifier, the endpoint also depends on the presence in the environment of an initiator and possibly a promoter. Hence, complete consistency between studies cannot always be expected.
		(C3) The pattern of results is undeniably skewed toward a positive association. Given the very small probability of this happening by chance, the pattern increases the confidence in a causal effect.

Figure 8.2.1 Pattern of Relative Risks of Adult Leukemia from Table 8.1.3 Including Electric Railroad Engineers

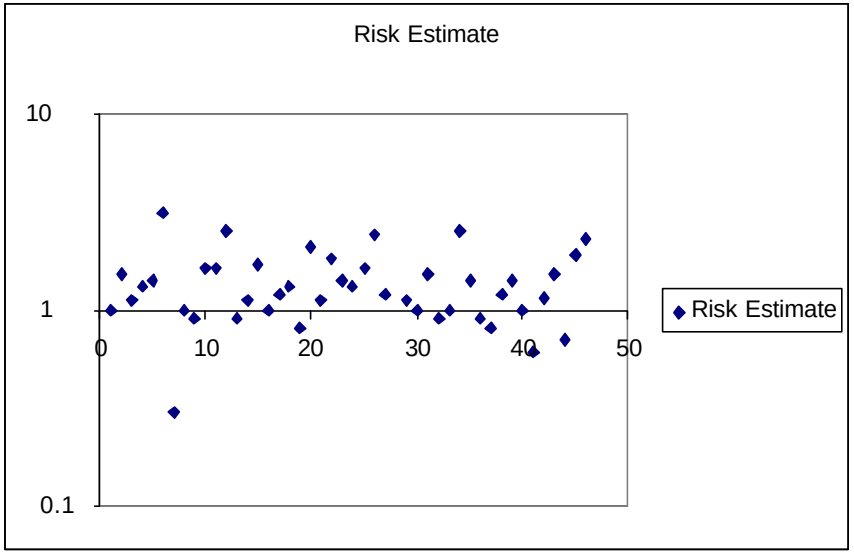
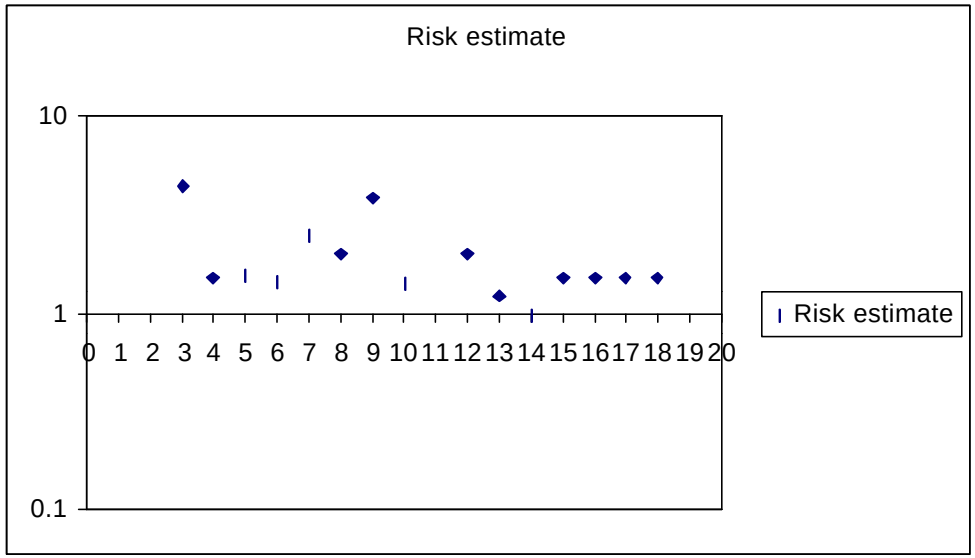


TABLE 8.2.5A SUMMARY OF THE CHILDHOOD LEUKEMIA STUDIES (COMPARING EXPOSURE > 3 MG VS EXPOSURE < 1 MG)

STUDY #	AUTHOR	COUNTRY	RISK ESTIMATE	BINARY OUTCOME FOR >0.3 µT
1	Coghill	UK	no controls	?
2	Dockerty	New Zealand	no controls	?
3	Feychting	Sweden	4.44	+
4	Linet	USA	1.51	+
5	London	USA	1.53	+
6	McBride	Canada	1.42	+
7	Michaelis	Germany	2.48	+
8	Olsen	Denmark	2.00	+
9	Savitz	USA	3.87	+
10	Tomenius	Sweden	1.41	+
11	Tynes	Norway	no cases	?
12	Verkasalo	Finland	2.00	+
13	Green	Canada	1.23	+
14	UK	UK	0.97	–
NON-MEASUREMENT STUDIES			**RISK FOR THE HIGH EXPOSURE GROUP**	
15	Wertheimer	USA	2.28	+
16	Fajardo	Mexico	1.64	+
17	Coleman	UK	1.70	+
18	Petridou	Greece	1.39	+

FIGURE 8.2.2 BASED ON TABLE 8.2.5A



Note: the last four studies, based only on wire code classification, have all reported a risk estimate > 1.0 However, the numerical value of the risk estimate is not comparable to that of studies using a quantitative exposure assessment. In this graph they have been assigned an arbitrary value of 1.5, simply to indicate that the point estimate is > 1.

TABLE 8.2.6

HOMOGENEITY (ARE THE POSITIVE STUDIES CONSISTENT WITH EACH OTHER OR ARE THER LARGE DIFFERENCES BETWEEN THEIR FINDINGS?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Of the wire code studies, one (Linet, 1998) shows no risk whatsoever, one (Fulton et al., 1980) is so flawed that the leading author, after publishing a negative result, used the same data to co-author a second paper with positive findings.	(F1) The pooled analysis by Greenland et al. (Greenland et al., 2000) concluded that all studies relying on calculations or measurements of exposure were homogeneous. Similarly, Kheifets (Kheifets, 1997) found that adult occupational studies (composing most of the data base) were not heterogeneous.	(C1) Most of the studies are consistent with the pooled analyses risk estimates.
(A2) The other wire code studies, showing no threshold of risk, are homogenous between themselves and with the Green study, but not with the results of the studies using a continuous exposure assessment metric.	(F2) Wiring practices differ from one locale to another. The original Denver wire code is unlikely to be a reliable universal exposure assessment protocol.	(C2) Some discrepancy may be expected due to methodological limitation.

TABLE 8.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all childhood studies show a clear dose response. While the recent pooled analysis and the Linet and the UK studies show evidence of a threshold, no such threshold was suggested by earlier studies.	(F1) All studies use surrogate exposure measures. The true exposure metric or optimum dosing schedule is not identified, therefore the surrogate-response curve is only loosely related to the true dose-response curve. Nevertheless, children studies suggest increasing risk with increasing exposure. The question of threshold depends on which surrogate is used and may reflect the fact that different surrogates measure different EMF properties. Spot measurements measure the mode of the exposure distribution (e.g., the most common value), while wire codes are more related to the maximum capacity of the electrical installations.	(C1) There is no biological or logical reason to believe that the dose response should be linear with no threshold or ceiling. The suggestion that certain biological processes may only be perturbed up to a point and no more is perfectly plausible. Greenland's (Greenland et al., 2000) systematic presentation of data shows no evidence of a historical shift in what the dose-response data.
(A2) Adult leukemia studies of electric train operators, in which the exposed group is often exposed to fields (100mG) many times higher than the that of the reference group (1mG), and even electrical workers (10 mG), show no evidence of a proportionally high risk.	(F2) The adult studies are consistent with a sigmoid risk function. -Clearer associations found with highest exposure group. -Evidence of stronger risk if exposed at work AND home (Feychting et al., 1997). -Some evidence of stronger risk with longer duration of employment (Savitz, Checkoway & Loomis, 1998a). -Theoretical data show that misclassification of exposure may increase risk estimate in intermediate exposure category (Dosemeci, Wacholder & Lubin, 1990), (DelPizzo, 1992). -Saturation of effect is consistent with proposed mechansims (e.g., disrupted hormone production, depression of immune system, ODC production).	(C2) The fact that extremely high exposures do not convey a proportionally higher risk deserves further investigation, but does not cancel the fact that, overall, there is evidence that within the range of common residential exposure more is worse, adding to the confidence of causality.

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A3) Symmetry arguments from physics suggest that any dose response should be by the square of the magnetic field intensity. It is not. Therefore, one's confidence in causality should fall sharply.	(F3) See biophysics arguments in Table 4.1.	(C3) The "square of field" argument is overly simplistic and unconvincing.
		(C4) Most studies could not investigate this issue appropriately because of limits in their size.

TABLE 8.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The hypothesis is not consistent with empirical observations. There is no evidence of an increase in leukemia rates with increase of power consumption.	(F1) If high end (3 mG) exposure produced risk, then even a doubling of the population exposure will not necessarily produce an increase in leukemia rate observable above normal historical fluctuations.	(C1) Ecological studies are insensitive and non-specific. An estimated attributable risk of 3-4% can be hardly demonstrated by incidence data.
(A2) The Swedish study is either internally inconsistent (if all subjects are included), or inconsistent with other studies (if limited to single-family homes).	(F2) Swedish study results limited to single-family homes are not inconsistent with pooled analysis.	(C2) The different sensitivity of field calculation when applied to single-family homes and apartments is a convincing explanation for the internal inconsistency of the Swedish results.
(A3) The Green (Green et al., 1999b) study shows a dose-response pattern different from that of the other studies.	(F3) Exposure estimates by calculation could not reliably predict the field in apartment homes and single family homes. (Feychting & Ahlbom, 1993). Therefore, the resulting misclassification bias may well account for the internal inconsistency between risk in single family and apartment homes.	(C3) On the face of it, the Green (Green et al., 1999b) study is puzzling, but its sample is too small to rule out a dose response similar to that suggested by the pooled analyses.
(A4) Jaffa (Jaffa, Kim & Aldrich, 2000) has shown that the Feychting study (Feychting & Ahlbom, 1993) relied on historical current flow data whose accuracy was too crude to have been able to make an accurate historical reconstruction of fields within the homes. The better prediction of risk by these estimates than concurrent measurements suggests that something is wrong with this study and by	(F4) Jaffa (Jaffa et al., 2000) is invoking non-differential exposure misclassification to explain away four well-conducted cohort studies. On average, non-differential misclassification should not be producing false-positive associations.	(C4) The reviewers acknowledge that the data available for reconstructing historical exposure was subject to non-differential misclassification but doubt that this produced false-positive results in this and the other Scandinavian studies.

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
extension, all the Scandinavian studies. They should all be ignored.		
(A5) The Milham (Milham & Ossiander, 2001) observation that death registrations from toddler childhood leukemia increased between 1920 and 1950 in just those states that had widespread electricification is not due to electrificiation. The opinion of Court Brown and Doll (Court Brown & Doll, 1961) notwithstanding, the apparent increase in leukemia death registrations could indeed be an artifact of diagnosis. The diagnosis and understanding of leukemia in the early part of the 20th century was quite different from today. The 1908 edition Diseases of Children by Pfaundler and Schlossman (Pfaundler & Schlossmann, 1908) speculates on an infectious origin, describes the blood as milky in color, and the course often brief. The importance of microscopic blood examination is already recognized. In the 1930s (Pfaundler & Schlossmann, 1935), the same textbook points out that the color of the blood depends on the degree of leukocytosis (that is, less obvious cases were now being recognized). The time from diagnosis to death of this febrile illness is described as being 1-3 months. It seems quite possible that the increased access to electricity was correlated with the increased access to physicians who in turn had access to microscopic blood tests during the brief course of this terrible childhood illness.	(F5) Court Brown and Doll (Court Brown & Doll, 1961) are not alone in taking this increase in death registration in England and the United States seriously. Cooke (Cooke, 1942),Gilliam (Gilliam & Walter, 1958), and Fraumeni (Fraumeni & Miller, 1967) hoped to find some explanation for it. There were many rural areas where government sponsored electrification may not have been well correlated with access to medical care.	(C5) Despite the interest in this pattern, which was first noticed 40 to 60 years ago, the possibiltiy of trends in diagnosis and death registration have to be taken seriously.
(A6) If as Milham avers (Milham & Ossiander, 2001), the threefold increase of toddler leukemia deaths in electrified areas is CAUSED by exposure to magnetic fields, the reviewers have a problem in reconciling this population increase with the results of the well-conducted epidemiology studies. The reviewers know from the studies in Table 8.1.4 that only a small proportion of the children in an	(F6) No one is completely free of magnetic field exposure, so the recent studies are analogous to comparing 2-pack-a-day smokers to 1-pack-a-day smokers instead of non-smokers. It is quite possible that there are effects at lower levels of magnetic fields that exposure misclassification has obscured. The increased risk was occurring to some degree at all non- zero levels of magnetic field and was not	(C6) It IS possible to distinguish 2-pack-a-day smokers from 1-pack-a-day smokers epidemiologically. The vast majority of leukemic and healthy children have exposures below 2 mG and there is plenty of data to see if there is evidence of risks conveyed by low exposures as compared to very low exposures. Greenland's analysis reproduced in Table 8.1.5 does not provide much support for that. Hence,

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
electrified community accumulate a 2-4 mG exposure. For the apparent rate in the entire community to seem to triple, the rate in this small exposed group would need to increase several hundredfold. Even with random misclassification, it seems highly implausible that the recent studies should be missing such an effect.	restricted to the small group with the highest exposure.	Milham's (Milham & Ossiander, 2001) observation has not increased the reviewers' degree of certainty much if at all.

TABLE 8.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.13

SPECIFICTY AND OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "General Issues" chapter.		

TABLE 8.2.14

SUMMARY TABLE FOR DISEASE			
	HOW LIKELY IS THIS PATTERN OF EVIDENCE UNDER:		
	THE "NO EFFECT" HYPOTHESIS	THE HYPOTHESIS OF CAUSALITY	EFFECT ON CERTAINTY
Chance is not a likely explanation.	Very unlikely	Very likely	Increases certainty
Bias not proven.	Possible	Possible	Pulls down certainty only slightly, if at all
Confounding not identified.	Possible	Possible	No impact
Combined chance, bias, confounding. Strength of association.	Possible Possible	Possible Possible	Pulls down certainty only slightly, if at all No impact
Consistency: most studies show increase in risk.	Unlikely	Very likely	Increases certainty quite a lot
Homogeneity: meta-analytical results or other summary risk estimates are not driven by a few studies with large risk estimates, but most studies paint a similar picture.	Possible	Likely	Increases certainty a bit
Dose response.	Unlikely	Likely	Increases certainty somewhat
Coherence/visibility.	Possible	Possible	No impact
Experimental evidence.	Possible	Possible or likely	No impact or slight decrease in certainty
Plausibility.	Possible	Possible	No impact or increases certainty somewhat
Analogy.	Possible	Possible	No impact
Temporality.	Possible	Possible	No impact
Specificity and association with other diseases.	Possible	Possible	No impact

8.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

8.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

Reviewer 1 (DelPizzo)

Childhood Leukemia

Many of the attributes of the epidemiological evidence considered in this evaluation share similar characteristics, irrespective of the endpoints to which they refer. Therefore, some of the considerations described below apply to other endpoints also, and this reviewer will refer to them repeatedly when other endpoints are evaluated.

Bias: Reviewer 1 sees no evidence of a clear bias common to all or most studies that can explain away the association. While this reviewer believes that all studies are affected by some small degree of bias, the net effect of these unidentified biases should be null. Even considering a worst-case scenario, in which the results of all studies using random digit dialing to recruit subjects could be ***totally*** explained by bias, the p-value of the sign test would not increase to the point where the reviewer's judgment would be affected.

Confounding: See bias.

Strength of association: It was never suggested, even by the hypothesis generating studies by Wertheimer and Leeper, that exposure to EMF was a strong risk factor for childhood leukemia or any other endpoint. If it were, it would have manifested itself in clearly visible clusters and historical trends. There is no reason to believe that the association needs to be strong to be credible. An intrinsically weak association is much more consistent with the fact that these fields are non-ionizing and transfer a minimal amount of energy to the living organism. This attribute does not affect Reviewer 1's degree of certainty in the causal nature of the association.

Consistency: This is the strongest factor arguing for causality. Not one of the studies reviewed is inconsistent with a weak positive association, while many are inconsistent with a null effect. Considering that these studies were conducted over a period of almost a quarter of a century, in different nations in four different continents, using different study designs and analysis methodologies, the possibility that these results are due to a common bias or confounder which has escaped identification, or to a host of diverse biases or confounders which, by chance, almost always biased the risk estimate upward and never downward (which should be equally probable) is virtually ruled out.

Homogeneity: According to Greenland et al. (Greenland et al., 2000), studies using measurements or calculations to estimate exposure are homogenous (consistent with each other), while those using wire coding or proximity to power lines are not. The former conclusion increases this reviewers degree of certainty considerably because these studies were often different in design and execution. The latter does not decrease it because the effectiveness of wire codes are very much dependent on local wiring practice, therefore heterogeneity of results is to be expected.

Experimental Evidence

There is clearly no supportive experimental evidence that exposure to EMF increases the leukemia risk in laboratory animals. However, the literature is full of experimental results that contradict theoretical predictions that environmental EMFs are incapable of inducing biological effects. The theorists response to these results is far from convincing. In some cases they have speculated that these are artifactual results due to microchanges in temperature, in some cases they have been dismissed without explanation. It is Reviewer 1's opinion that the strongest argument for a low prior confidence level is one of dose, that is, that environmental EMFs levels are too low to have observable effects. Thus, the credibility of these experimental results are crucial, even if they do not directly pertain to the endpoint under evaluation. The question for Reviewer 1 is: are false-positive results in absence of a true causal effect more or less likely than false negatives in the presence of a true effect? False positives are possible, but false negatives are more then possible. Considering the absence of a clear theoretical model to guide the experimentalist in designing and conducting the experiment, the intrinsic experimental difficulties of studying a complex system (whether *in vivo* or *in vitro*), the complex nature of the EMF mixture of components and attributes and the engineering challenges in designing exposure systems and measuring the many parameters involved, false negatives are a virtual certainty.

Other associations: Since this is the first association to be evaluated, its credibility should not be influenced by other associations that have not been evaluated yet.

Dose response: Several studies detected a statistically significant dose-response trend. The Greenland (Greenland et al., 2000) pooled analysis shows clearly that higher fields correspond to stronger associations.

Visibility: No additional comment to those presented in the discussion.

Plausibility: No additional comment to those presented in the discussion.

Analogy: No additional comment to those presented in the discussion.

Temporality: The Swedish study is the only one where this attribute can be explored. The fact that the association exists with exposure calculated using historical current load data, but not with that calculated using contemporary loads argues in favor of causality.

Conclusion for Childhood Leukemia

None of the evidence speaks convincingly against the hypothesis of no risk, while the consistency of the association speaks strongly in favor of the hypothesis of causality and some of the controversial evidence is harder to explain under the hypothesis of no risk than under that of causality. This reviewer's opinion is that the consistency of the pattern of results by itself is sufficient to increase his level of confidence above 50%. The presence of some experimental results unexplained under conventional biophysical mechanisms, some evidence of dose response, and the homogeneity of the studies, all compound to add credibility to the risk hypothesis. Therefore, Reviewer 1's posterior level of certainty in a causal association is high, around 95, or in the category, "strongly believe" that EMFs increase the risk of childhood leukemia to some degree. On a certainty scale from 0 to 100 his confidence bounds range from 70 to 100.

Conclusion for Adult Leukemia

Most of the arguments for causality in the evaluation of childhood leukemia apply to adult leukemia as well. The pattern of results is slightly less consistent, the dose-response relationship much less clear, but having determined that EMFs are virtually certain to be a risk factor for childhood leukemia, the confidence in the causality of the adult leukemia association is also boosted. This reviewer's posterior level of confidence is about 85 with a range from 60-95. Thus, he is "prone to believe" that EMFs increase the risk of adult leukemia to some degree.

IARC Classification: In the EMF case, the animal and mechanistic evidence is less consistent and of lower quality than the human evidence. Therefore, since the IARC criteria rank animal and mechanistic evidence below human evidence, the Group 1 classification (the agent or mixture is carcinogenic to humans) can only be assigned if the human evidence can be regarded as "sufficient evidence of carcinogenicity." For this to happen, chance, bias, and confounding must be ruled out with reasonable evidence. The difficulty is to assign a precise meaning to the term "reasonable." Reviewer 1 believes the safest method is to use a comparative approach and question which of all the possible alternative explanations is more reasonable than the others.

This reviewer believes that for childhood leukemia this is the case, for the reasons given below:

Chance: By chance effect Reviewer 1 considers not only the sampling variations, but also the effects of biases and confounding that escape identification or even reasonable suspicion. For example, misclassification bias can be reasonably suspected in all EMF studies. Recall bias can be suspected in some occupational studies. Confounding from SES or subject mobility have been suspected, even if not confirmed. In all these cases, the direction of the point estimate bias can be anticipated, even if not confirmed or quantified. These are not "random biases or confounders." However, to suggest that since the etiology of childhood leukemia is unknown it is possible that unidentified confounders exist, cannot be controlled, but may affect the risk estimates, implies the possibility that this bias may be toward or away from the null. There is no reason to believe that biases in one direction are more likely than biases in the other direction. These are random events that are accounted for by an appropriate statistic test, such as determining the p-value using a sign test.

In the case of childhood leukemia, performing such a test on the results listed in the most recent meta-analysis (Wartenberg, 2001), combining the results of the few studies relying on proximity to exposure sources alone with those using measurements or calculations, yields a p-value of less than 0.001 for the hypothesis that residential EMF exposure conveys a risk greater than one. Therefore, Reviewer 1 concludes that chance is not a reasonable explanation for the observed positive association.

As for bias and confounding acting to create an artifactual association, all the obvious candidates and many very speculative ones have been considered. In some cases, these have managed to reduce the strength of the association, or at least to suggest a downward movement of the point estimate, but not to fully explain the positive association.

One possibility is that the positive associations reported over two decades of investigations, in several diverse locales, using a variety of study designs and of exposure assessment surrogates, are mostly due to a host of subtle biases or confounding agents that exist, some acting in one locale, some in another, some affecting one study design, some another, and all affecting the study results in the same direction. This is not a reasonable explanation.

The remaining question is whether it is reasonable to believe that one or two unsuspected biases and/or unidentified confounders exist that explain enough positive studies so that the remaining ones can be attributed to chance. What appears to be unreasonable here is the fact that such sources of error, which would have to be powerful and consistent, would remain unidentified over twenty years of efforts, notwithstanding the powerful social and economic motivations and resources to do so.

In summary, keeping in mind that accurate and consistent exposure assessment and ascertainment of the true dose response relationship is complicated by the fact that EMF is a mixture of agents, rather than a single factor, and this fact alone introduces inconsistencies between studies, it seems more reasonable to believe that the positive association reported by so many and diverse studies is indeed causal rather than due to such undefined and implausible alternative explanations.

While the lack of strong animal and mechanistic evidence is frustrating, in Reviewer 1's opinion the human evidence meets the criteria to justify a Group 1 classification.

Adult Leukemia

Most of the considerations of the childhood leukemia assessment apply here. Chance is even less likely as an explanation, given the larger number of studies (p = 0.000). However, since most of the studies are occupational, they are slightly more homogeneous than those of childhood leukemia, sharing a somewhat more similar environment and a slight possibility that recall bias may have played a greater part. Nevertheless, it still borders on unreasonable to believe that bias or confounding may be responsible for over 30 independent reports of positive associations and yet have eluded a positive identification.

Reviewer 1 cannot bring himself to accept chance, bias, or confounding as a more reasonable explanation for the association than causality. Therefore, his assessment is again for a Group 1 classification.

Reviewer 2 (Neutra)

Childhood Leukemia

Degree of Certainty: With regard to childhood leukemia, Reviewer 2 noted that the pattern of associations in the 19 studies reviewed was unlikely to occur by chance and that the pooled analysis by Greenland et al. (Greenland et al., 2000) and meta-analysis by Wartenberg (Wartenberg, 2001) also suggested chance as an unlikely explanation. The different study designs and locations of the studies made a common bias, other than non-differential measurement error, unlikely. It also seemed that the combination of chance, bias, and confounding in all these studies was less likely than a true effect not much above the resolution power of epidemiology. Early in the 1990s, when the early studies seemed to point more to proximity to power lines than to measured fields, there was suspicion that some other environmental factor such as traffic density or social factor associated with neighborhoods where power lines were above ground, might confound the association and explain it. Greenland et al. (Greenland et al., 2000) point out that when the newer studies are analyzed together the association between leukemia and measured or calculated fields is more consistent than is the wire code association. Magnetic fields come partly from easily observed power lines which may correlate with neighborhood characteristics and partly from less visible internal sources, such as stray ground currents and wiring net currents which are more random and probably less correlated with social factors. Specific studies of traffic density and neighborhood characteristics have not explained away the association. Langholz (Langholz, 2001) suggests that putative confounders need to be very strong risk factors indeed to explain away the childhood leukemia/magnetic field associations. Kavet and Zaffanella (Kavet et al., 2000) have suggested contact with ground currents as a possible explanation. In favor of this hypothesis are the calculations which suggest that the current entering the bone marrow would be larger than physiological background noise. Thus there is a plausible physical induction mechanism. But there is no hypothesis, much less experimental evidence, suggesting a biological mechanism leading to physiological or pathophysiological change. There are no animal pathology studies. There are no studies to document if such exposures are correlated with home magnetic fields or how common are such exposures, which involve grounded children touching plumbing long enough to be effective. Common sense suggests that such events would occur a few times a week to a few times a day. Reviewer 2 looks at this alternative hypothesis as unlikely but worthy of investigation because if true, simple inexpensive measures could be taken to avoid them. Another hypothetical confounder is the presence of charged pollutant particles around power lines (Fews, Henshaw & Wilding, 1999a). These relate to high electric fields, particularly near transmission lines. There is little or no evidence, experimental or epidemiological to support this hypothesis; but if true it would have implications for mitigation and should thus be pursued. In short, Reviewer 2 sees little or no evidence of credible confounders for the EMF/childhood leukemia association and the possiblity of as yet unknown confounders reduces his certainty only slightly.

The analyses presented by Greenland et al. (Greenland et al., 2000) and Wartenberg (Wartenberg, 2001) increase this reviewer's confidence substantially, and his confidence would not be pulled down much for bias and confounding even though the size of the association is not much above the resolution power of the studies and the dose-response relationships at the scanty top of the exposure distribution are not very consistent.

The the lack of a clear mechanistic explanation of the physical induction step or the chain of events leading to pathology provides little or no support, but does not pull confidence down much because these streams of evidence based on selected aspects of the "EMF mixture" are prone to false negatives about the mixture itself. Also, the biophysical arguments that recognized effects seen experimentally above 1,000 mG are not relevant to the epidemiology about associations with a few mG means that experiments must be done at ambient levels to be convincing. This is a requirement that many agents would not be able to meet. Reviewer 2 notes the suggestive results from the chicken embryo studies and the MCF-7 cell lines and thinks they warrant further work before they would increase his degree of certainty much.

Reviewer 2 is convinced that high intensity pure sinusoidal 60 Hz or 50 Hz magnetic fields do not produce enough of an effect to be observed reliably in conventionally sized studies with the species tested. Since the epidemiology that triggered the animal pathology studies to begin with did not suggest that the EMF mixture conveyed monotonically increasing risk at very high doses, the way that often happens with pure chemicals, he was on record before these studies began that they ran a high risk of

providing null results. For this reason the largely null results have not lowered his degree of certainty much.

The types of associations seen in the studies, related as they are to the rare highest associations, could have been easily missed in national leukemia trends as electrification gradually extended through the world in the 20th century. Court Brown and Doll (Court Brown & Doll, 1961) noticed that toddler leukemia death registrations began to climb in the 1920s and Milham (Milham & Ossiander, 2001) has shown that this mortality pattern appeared geographically at the same time that these areas received electrification. The increased mortality is around threefold, but this is a much larger increase than would be predicted by the recent epidemiological studies. For reasons given under "Coherence/Visibility," Reviewer 2 is inclined to view the changes in reported mortality as an artifact of diagnosis and was not much influenced by this evidence.

Thus, despite the fact that ALL streams of evidence are not supportive, the pattern of evidence in the many epidemiology studies is strong enough that this reviewer has moved upward substantially from the prior degree of certainty.

Given the prior probabilities for different ranges of relative risks which this reviewer held, and considering the pattern of all streams of evidence, the degree of certainty that the observed epidemiological associations are substantially causal in nature (for purposes of the policy analysis) would be best expressed as "close to the dividing line between believing and not believing" that EMFs increase the risk of childhood leukemia to some degree. The degree of certainty on a scale from 0 to 100 would be 54 with a range of confidence from 25 to 80.

IARC Classification: The IARC classification usually requires larger associations and clearer dose-response relationships than seen here to consider the epidemiology definitive, and with the lack of supportive animal pathology studies or mechanistic explanations, this body of evidence would receive a "possibly carcinogenic 2B" IARC classification, "limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals"

Adult Leukemia

Degree of Certainty: Reviewer 2 considered that the pattern of associations among the 41 studies reviewed by Kheifetz et al. (Kheifets et al., 1997b) in her meta-analysis was quite unlikely to have occurred by chance and the meta-analysis itself did not suggest chance as a likely explanation.

Many of these studies were state of the art, of different designs, and in different locations and unlikely to share a single bias which would have inflated the apparent association. No plausible confounders have been advanced.

There is a wide range of exposures in different occupations, with the highest being in electric train operators, yet these studies do not demonstrate larger associations than studies of workers with more moderate exposures. This pulls down confidence somewhat, but could reflect low power or a dose response which truly does not increase monotonically over the full range of real world occupational exposures.

As indicated for childhood leukemia and in the pro and con discussion even without the support of animal pathology or mechanistic explanations, Reviewer 2's degree of certainty moved substantially upward from the prior position on the basis of the pattern of epidemiological evidence.

Considering all the evidence, and the prior starting point, the degree of certainty for purposes of the policy analysis would be best expressed as "close to the dividing line between believing and not believing" that EMFs increases risk of adult leukemia to some degree with a range of confidence from 15 to 70 and a best judgment of 52 on a certainty scale of 0 to 100.

IARC Classification: Since IARC usually requires larger associations and clearer dose response than is present in these studies to consider the epidemiology definitive, and since the animal pathology experiments and mechanistic explanations do not provide much support, adult leukemia could be viewed as on the border between have inadequate and "possible 2B carcinogen." Reviewer 2 judges the pattern of epidemiological evidence for adult leukemia regardless of type to warrant a "possible 2B" classification", "limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals"

Reviewer 3 (LEE)

Childhood Leukemia

Degree of Certainty: Of the Hills criteria to evaluate the human evidence, the consistency of the positive relative risks across studies is the strongest and hence increases Reviewer 3's posterior considerably. The posterior is also increased slightly by evidence of this positive effect even after adjustment for confounders by the careful assessment of bias, by evidence of a dose response even with surrogate exposure measures, and by evidence of an association of EMF with other disease. The posterior is slightly decreased due to inadequate biological and animal evidence. Hence, the posterior degree of certainty for purposes of the policy analysis could be expressed as "prone to believe" that EMFs increase the risk of childhood leukemia to some degree. On a certainty scale from 0-100, the best judgment certainty would be 65 with a confidence range from 25 to 80.

IARC Classification: The human evidence is sound and credible and based on the strong consistency of positive results across studies. The probability of chance contributing to the positive effect is low. Known cofounders have been considered and the positive effect remains. Bias has been evaluated and is not a likely explanation of the observed positive effects. An effect has been observed even though surrogate measures have been used. The evidence is sufficient for a Group 2A classification, "probably carcinogenic to humans," since the animal studies are weak. However, a clear biological model has not been adequately demonstrated.

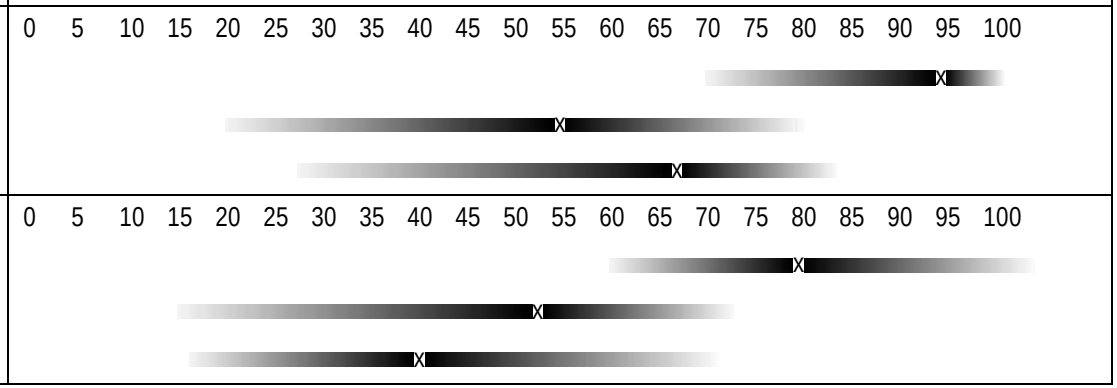
Adult Leukemia

Degree of Certainty: The human evidence of the adult leukemia studies is not as strong or as consistent as the childhood studies. Nonetheless, the posterior is increased by a relative likelihood of a consistent weak effect across these occupational studies. Also, the posterior is slightly increased by evidence of an EMF association with other diseases, in particular childhood leukemia. The posterior is slightly decreased by the fact that most of the studies with positive effects are occupational studies and are vulnerable to confounding and bias, by the lack of a dose response, and by the lack of supporting animal evidence. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "close to the dividing line between believing and not believing" that EMFs increase the risk of adult leukemia to some degree category. On a certainty scale from 0 to 100, this reviewer would give a 40 with a confidence range from 15 to 70.

IARC Classification: The human evidence is weak but consistent where chance explaining the pattern of the weak positive associations is low. However, bias and confounding cannot be completely ruled out. Also, the animal evidence is inadequate. The evidence as a whole is sufficient for a Group 2B classification, "possibly carcinogenic to humans."

SUMMARY OF REVIEWERS' CONCLUSIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Childhood Leukemia				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Strongly believe	
	2	2B	Close to dividing line	
	3	2A	Prone to believe	
Adult Leukemia				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	1	Prone to believe	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	



8.4 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 8.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
See discussion in Chapter 3.	

TABLE 8.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No empirical evidence of plateau, however: (C2) Studies on subjects exposed to very strong fields do not show proportionally high risks. (C3) Many of the hypotheses suggested to explain the association (depression of the immune system, disruption of endocrine system, co-promotion) can only potentially explain a finite effect. (C4) Spline regression (Greenland et al., 2000) is compatible with many risk functions including no-threshold . In summary: - No conclusions can be drawn at this time on plateau. - Suggestive evidence of a 2-3 mG threshold.	(I1) Insufficient evidence to determine existence of plateau, but some suggestion that lowering extremely high fields to high fields may not convey any benefit. (I2) Reasonably reliable evidence that mitigation of TWA < 2 mG exposure may not be required.

TABLE 8.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	

TABLE 8.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	

TABLE 8.4.5

EMF COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Little is known about risk factors for these diseases, but the few known factors are not strong and do not account for most of the incidence.	

TABLE 8.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
AGAINST RELEVANCE	**IMPACT ON POLICY**
(C1) This association, if true, would generate theoretical lifetime risk greater than those regarded as *de minimis*.	(I1) Could be considered for regulation if real.

TABLE 8.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	

TABLE 8.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Exposure assessment can be improved by measuring more field parameters (e.g., maximum personal exposure, time coherence, contact currents, etc.).	(I1) Identifying contact currents or shocks as explaining the epidemiology would affect mitigation strategies.

TABLE 8.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Childhood Leukemia: Italy: Principal Investigator: Magnani, due in about 5 years, marginal statistical power Japan: Principal Investigator: Kabuto, 2,000 cases, unknown prevalence of exposure Germany: Principal Investigator: Michaelis, 200 cases and 200 controls California: a) Principal Investigator: Buffler, 580 cases b) Principal Investigator: Folliart, Study of EMFs and Case Fatality (C2) Adult Leukemia: Britain: Principal Investigator: Harrington, Occupational Mortality in Utility Industry	(I1) Unlikely for the foreseeable future.

TABLE 8.4.10

CAPABILITY OF CHANGING ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There is only one study in progress for adult leukemia. (C2) The database for childhood leukemia is too large to be substantially modified by the few studies in progress. (C3) Some better insight on the dose-response relationship is possible, but unlikely.	(I1) Not likely in foreseeable future.

TABLE 8.4.11

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Further epidemiological studies of these rare conditions are unlikely to resolve controversy. Epidemiological studies of other more common endpoints that can be studied prospectively could help guide mechanistic and animal pathology studies.	(I1) Not known

8.5 CONCLUSIONS ON SCIENTIFIC RELEVANT ISSUES

1 Dose-response Issues

2 At least for childhood leukemia, the evidence suggests that little or no risk is incurrent for
3 exposure lower than 2-3 mG and there is not much evidence to suggest that lowering
4 very high fields (like those experienced by electric train operators) to high fields (like the
5 fields near transmission lines) would modify risk much.

6 Research Policy

7 Future epidemiological studies should explore the relationship between more common
8 endpoints that can be studied prospectively and various aspects of the EMF mixture,
9 other than TWA.

9.0 EPIDEMIOLOGY OF ADULT BRAIN CANCER

STATEMENT TO THE PUBLIC

The reviewers expressed their judgments using two distinct sets of guidelines to evaluate the evidence:

- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for adult brain cancer, their classifications for EMFs was "possible human carcinogen" (IARC's Group 2B). Panels convened by IARC and the National Institutes for Environmental Health Sciences on the other hand thought the evidence was "inadequate" to make a classification (IARC's Group 3).***

- ***Using the Guidelines developed especially for the California EMF program, one of the reviewers was "prone to believe" that high residential EMFs cause some degree of increased risk of adult brain cancer, and the other two were "close to the dividing line between believing or not believing."***

There are several reasons for the differences between the DHS reviewers and those of IARC. The three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them. Adult brain cancer has an incidence of around 1/10,000 per year. If one doubled this rate to 2/10,000 per year and accumulated it over a lifetime of continuous high exposure one would accumulate a lifetime risk of 1%. Thus the vast majority (99%) of highly exposed people would still not contract this disease. Furthermore, calculations suggest that the fraction of all cases of adult brain cancer that one could attribute to EMFs would be no more than a few percent of the total cases (if any). Nevertheless, if EMFs do contribute to the cause of this condition, even the low fractions of attributable cases and the size of accumulated lifetime risk of highly exposed individuals could be of concern to regulators. Indeed, when deemed a real cause, estimated lifetime risks smaller than this (1/100,000) have triggered regulatory evaluation and, sometimes, actual regulation of chemical agents such as airborne benzene. The uncommon, accumulated high-EMF exposures implicated by the evidence about these conditions come from unusual configurations of wiring in walls, grounded plumbing, nearby power lines, and exposure from some jobs in electrical occupations. There are ways to avoid these uncommon accumulated exposures by maintaining a distance from some appliances, changes in home wiring and plumbing, and power lines. However, to put things in perspective, individual decisions about things like buying a house or choosing a jogging route should involve the consideration of well-recognized certain risks, such as those from traffic, fire, flood, and crime, as well as the uncertain comparable risks from EMFs. The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the added personal risk suggested by the epidemiological studies was "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. The three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Adult Brain Cancer				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Prone to believe	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

9.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

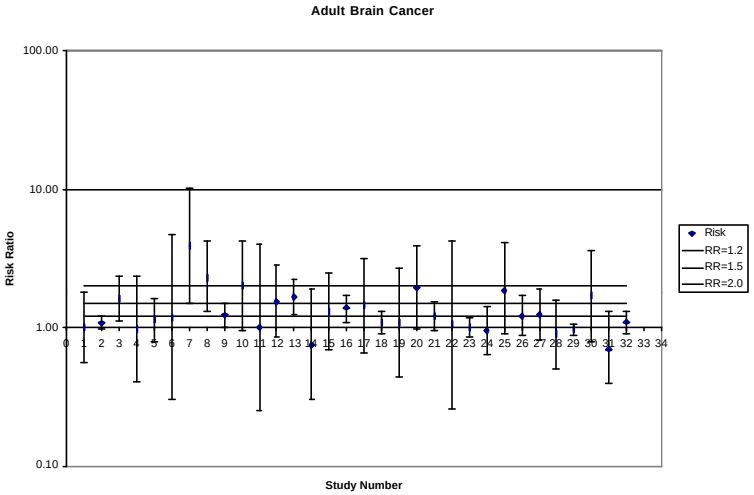


Figure 9.1.1 Studies of Adult Brain Cancer Derived Primarily from Kheifets et al. (1995)

Figure 9.1.1 and Table 9.1.1 summarize the epidemiological evidence for adult brain cancer which is primarily occupational in nature. Of the 29 studies reviewed by Kheifets (Kheifets et al., 1995) in her meta-analysis, 23 had ORs above 1.00 (p = 0.0004), and 15 were above 1.2 (p = 0.14). The meta-analytic summary of (Kheifets et al., 1995) for the occupational studies was 1.2 (1.1-1.3). If one adds the residential exposure studies of Wrensch, Li, and Feychting (Wrensch et al., 1999), (Li, Theriault & Lin, 1997), (Feychting & Ahlbom, 1994), (Feychting et al., 1997) one sees a similar pattern. The three other studies that focused on Scandinavian electrical railway workers with exposures in the 10 to 100 μT range (Tynes et al., 1994a), (Floderus et al., 1994), and (Alfredsson et al., 1996) did not show high relative risks (see table 9.1.2). On the contrary, RR were close to 1.0 with confidence limits which included a RR of 1.2.

TABLE 9.1.1 KEY FOR FIGURE 9.1.1

Study	No.	Individual Odds Ratio, Mean	Lower CL	Upper CL
(Pearce et al., 1989)	1	1.01	0.56	1.82
(McLaughlin et al., 1987)	2	1.08	0.98	1.20
(Lin et al., 1985)	3	1.62	1.12	2.34
(Vagero et al., 1985)	4	0.98	0.41	2.35
(Tornqvist et al., 1986)	5	1.15	0.80	1.64
(Guberan, 1989)	6	1.18	0.30	4.72
(Speers MA, 1988)	7	3.94	1.52	10.20
(Thomas et al., 1987)	8	2.30	1.30	4.20
(Milham, 1985b)	9	1.23	1.01	1.49
(Coggon et al., 1986)	10	2.00	0.95	4.20
(McMillan, 1983)	11	1.00	0.25	4.00
(Thierault, 1994)	12	1.54	0.85	2.81
(Savitz & Loomis, 1995)	13	1.68	1.26	2.23
(Ryan et al., 1992)	14	0.75	0.30	1.89
(Magnani et al., 1987)	15	1.30	0.70	2.50
(Loomis & Savitz, 1990)	16	1.40	1.10	1.70
(Preston-Martin et al, 1987)	17	1.45	0.66	3.18
(Tynes et al., 1992)	18	1.09	0.91	1.30
(Sahl et al., 1993)	19	1.09	0.44	2.69
(Spinelli, 1991)	20	1.94	0.97	3.88
(Gallagher et al., 1991)	21	1.21	0.95	1.54
(Olin et al., 1985)	22	1.05	0.26	4.20
(Tornqvist et al., 1991)	23	1.00	0.85	1.17
(Juutilainen et al., 1990)	24	0.95	0.63	1.43
(Schlehofer et al., 1990)	25	1.87	0.90	4.10
(Floderus, 1993)	26	1.22	0.88	1.71
(Preston-Martin, 1989)	27	1.25	0.82	1.90
(Demers et al., 1991)	28	0.90	0.50	1.60
(Guenel et al., 1993)	29	0.97	0.89	1.05
(Wrensch et al., 1999)	30	1.70	0.80	3.60
(Feychting & Ahlbom, 1994)	31	0.70	0.40	1.30
(Li et al., 1997)	32	1.10	0.90	1.30

TABLE 9.1.2 MORE DETAILS OF THE STUDIES REVIEWED

INVESTIGATOR, DATE	STUDY POPULATION	METHOD FOR EXPOSURE ESTIMATE	STUDY TYPE	RISK MEASURE	RISK ESTIMATE
(Pearce et al., 1989)	New Zealand: All male cancer patients in Cancer Registry, 1980-1984. 431 cases; 19,904 controls.	Job title	CC	OR	1.01 (0.56-1.82)
(McLaughlin et al., 1987)	Sweden: Cancer Environment Registry, 1961-1979. 3,394 cases.	Occupation and industry codes	Cohort	SIR	1.08 (0.98-1.20)
(Lin et al., 1985)	USa: 951 deaths, 1969-1982.	Usual occupation & industry on death certificate	Mortality	OR	1.62 (1.12-2.34)
(Vagero et al., 1985)	Sweden: Incidence among 2,918 workers at 3 work sites, 1958-1979. 5 CNS cases.	Employment at telecommunication work sites	Cohort	SMR	0.98 (0.41-2.35)
(Tornqvist et al., 1986)	Sweden: Incidence among 10,061 utility workers, 1961-1979. 30 cases CNS cancer.	Job titles	Cohort	SMR	1.15 (0.80-1.64)
(Guberan, 1989)	Switzerland: Incidence among 3,864 workers, 1971-1984. 3 cases.	Job titles	Cohort	SMR	1.18 (0.30-4.72)
(Speers MA, 1988)	US: Male residents, east Texas, 1969-1978. 202 cases; 238 controls.	Usual occupation and industry on death certificate	Mortality	OR	3.94 (1.52-10.2)
(Thomas et al., 1987)	US: White males in Northeast, 1978-1981. 435 cases; 386 controls.	Occupation & industry codes	Mortality	OR	2.30 (1.30-4.20)
(Milham, 1985b)	US: Males working in electrical occupations, 1950-1982. 2,649 Brain cancer deaths, 12,714 controls.	Death certificate occupation	PMR	PMR	1.23 (1.01-1.49)
(Coggon et al., 1986)	England: 2,942 males diagnosed with cancer, 97 CNS cancers as cases, other cancers as controls.	Occupation and industry from postal questionnaire	PMR	PMR	2.00 (0.95-4.20)
(Theriault et al., 1994)	Canada & France: 223,292 electrical utility workers, employed from 1970-1989, 108 brain cancer cases.	Job titles and measurements	CC	OR	1.54 (0.85-2.81)
(Savitz & Loomis, 1995)	US: 138,905 electrical utility workers, employed between 1950-1988. 151 Brain cancer cases.	Job titles and measurements	Cohort	RR	1.68 (1.26-2.23)
(Ryan et al., 1992)	Australia: All incidents of primary brain tumors in adults. 190 brain tumor cases.	Job titles	CC	OR	0.75 (0.30-1.89)
(Magnani et al., 1987)	England: 1,265 males, 1959-1963 and 1965-1979. 423 brain cancer deaths.	Occupation and industrial codes plus job exposure matrix	Mortality	OR	1.30 (0.70-2.50)
(Loomis & Savitz, 1990)	US: All brain cancer deaths in 16 states, 1985-1986.	Job titles	Mortality	OR	1.40 (1.10-1.70)
(Preston-Martin, 1989)	US: Males in L.A. county, 1980-1984. 272 cases.	Job titles with high likelihood of EMF exposure	CC	OR	1.45 (0.66-3.18)

INVESTIGATOR, DATE	STUDY POPULATION	METHOD FOR EXPOSURE ESTIMATE	STUDY TYPE	RISK MEASURE	RISK ESTIMATE
(Tynes et al., 1992)	Norway: 37,945 male workers, 1961-1985. 119 cases brain cancer.	Job title SIR Engine Drivers	Cohort		1.09 (0.91-1.30) 0.67 (0.2-1.6)
(Sahl et al., 1993)	US: 36,221 electrical utility workers, 1960-1988. 32 brain cancer deaths.	Job titles and measurements	Cohort	RR	1.09 (0.44-2.69)
(Spinelli, 1991)	Canada: 4,213 aluminum reduction plant workers, 1954-1985. 8 incidences of brain cancer.	Job activity	Cohort	SIR	1.94 (0.97-3.88)
(Gallagher et al., 1991)	Canada: 320,423 male deaths, 1950-1984. 55 brain cancer deaths.	Job titles	PMR	PMR	1.21 (.95-1.54)
(Olin et al., 1985)	Sweden: 1,254 electrical engineering graduates. 2 brain cancer deaths, 1930-1979.	MS degree in electrical engineering, RIT	Cohort	SMR	1.05 (0.26-4.20)
(Tornqvist et al., 1991)	Sweden: All men working in electrical occupations, 1961-1979. 250 cases of brain tumors.	Job titles	Cohort	SMR	1.00 (0.85-1.17)
(Juutilainen et al., 1990)	Finland: Male industrial workers, 1971-1980. 366 incident brain tumors.	Broad job category	Cohort	RR	0.95 (0.63-1.43)
(Schlehofer et al., 1990)	Germany (Heidelberg region): 1987-1988. 226 incident brain tumors, 418 controls.	Job activities	CC	OR	1.87 (0.90-4.10)
(Floderus, 1993)	Sweden: 1983-1987. 261 brain tumor cases, 1,121 controls.	Job activities and measurements	CC	OR	1.22 (0.88-1.71)
(Preston-Martin, 1989)	US: L.A. county, 1972-1985. 8612 incident brain tumors.	Broad job category	PMR	PIR	1.25 (0.8-1.9)
(Demers et al., 1991)	US: Washington State, 1969-1978. 904 brain cancer deaths	Job titles	Mortality	OR	0.90 (0.5-1.6)
(Guenel et al., 1993)	Denmark: 2.8 persons, 537 brain cancers.	Job titles	Cohort	RR	0.97 (0.9-1.1)
(McMillan, 1983)	2,568 men employed at HM Dockyard Devonport 1955-1975 (UK).	Job activity (Welders)	PMR	PMR	1.00 (0.3-4.0)
(Wrensch et al., 1999)	492 incident gliomas. 462 RDD controls.	Front door spot measures 73 mG	CC	OR	1.7 (0.8-3.6)
(Feychting & Ahlbom, 1994)	223 incident CNS cancer cases. 446 pop. controls.	Historically-estimated residential fields at diagnosis > 2 mG	Nested CC	OR	0.7 (0.4-1.3)
(Feychting et al., 1997)	223 incident CNS cancer cases. 446 pop. controls.	Historical fields > 2 mG occupational JEM > 2 mG	Nested CC	OR Exp both vs. Exp neither	1.3 (0.0-4.8)
(Li et al., 1997)	577 incident brain cancer cases. 552 "other cancer" controls.	Calculated historical magnetic field with field validation > 2mG	CC	OR	1.1 (0.9-1.3)

INVESTIGATOR, DATE	STUDY POPULATION	METHOD FOR EXPOSURE ESTIMATE	STUDY TYPE	RISK MEASURE	RISK ESTIMATE
(Wertheimer & Leeper, 1987)	Death addresses of 1,179 cancer deaths matched with addresses of non-cancer deaths or random sample from city directory of Denver.	Wire code	CC	Ratio of discordant to concordant matched pairs = "Cratio"	C ratio = 227 for "Nerv. System"
(Miller et al., 1996)	24 Malignant (MT) 11 Benign Brain (BT) 2,179 Controls	JEM magnetic and electric fields to job history	Nested CC	OR for > 345 V/m-yrs OR for > 7.1 μT-yrs vs ref.	BT 0.53 MT 0.99 BT0.03-105 MT 2.4 0.5-10.8
(Tynes et al., 1994a)	39 Brain ca, 194 controls from 13,300 electric and non-Norwegian electric train workers.	JEM linked to job history of magnetic and electric fields, control for smoking, creosote, pesticides	Nested CC	OR Reference: 0.1-310 311-3600 μT-yrs	1.0 0.81 (0.3-2.0) 0.94 (0.4-2.3)
(Floderus et al., 1994)	Incident brain cancer (8 engine drivers and 16 conductors) rates compared to general Swedish population, 1961-1969	Job title	Cohort	SIR Engineers Conductors	1.1 (0.6-2.2) 1.3 (0.8-2.1)
(Alfredsson et al., 1996)	Incident astrocytoma (10 engineers, 2 conductors) rates compared to general Swedish population, 1976-1990.	Job title	Cohort	SIR Engineers Conductors	1.0 (0.5-1.8) 0.8 (0.1-3.6)
(Guenel et al., 1996)	69 Incident brain tumors. 276 Controls.	JEM electric fields to job history	Nested CC	OR for > 387 V/m arithmetic mean	3.1 (1.1-8.7)

9.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 9.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the studies are not statistically significant.	(F1) Meta-analysis can help understand the pattern of evidence in epidemiological studies as well as experiments.	(C1) The reviewers think chance alone is an unlikely explanation so that a non-chance explanation including a causal one is relatively more likely.
(A2) Meta-analysis is not appropriate for anything but randomized trials.	(F2) Attending only to statistically significant results avoids false positives, while meta-analysis may avoid false negatives.	
(A3) Chance probably contributes a lot in the apparent pattern of evidence.	(F3) Both the meta-analysis and the sign test on ORs above and below 1.00 suggest that chance alone is not a likely explanation.	
(A4) Many of these studies have multiple comparisons so "p-values" are over-interpreted.	(F4) The later occupational studies had brain cancer and cutpoints pre-specified.	

TABLE 9.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
Residential Studies (A1) Wertheimer's (Wertheimer & Leeper, 1987) study was not blind as to wire code.	(F1) These objections were raised with regard to Wertheimer's childhood studies too, yet the Savitz, London et al., and Feychting studies showed associations with proximity to power lines, even though these studies evaluated incident cases blindly.	(C1) The generic possibility of bias when there is weak experimental and mechanistic support is not a strong argument against causality because bias can affect the risk estimate in either direction.
(A2) Wertheimer's use of deaths might have made the bad survival of poor people and the prevalence of poor people near power lines introduce a bias.	(F2) One should require some evidence for specific bias before pulling down confidence because of bias.	(C2) The universal problem of non-differential exposure misclassification tending to underestimate an effect would lead us to worry about underestimating the effect.
Occupational Studies (A3) Studies with better measurement protocols did not show larger effects, which shows that the exposure misclassification had not been a problem. Our inability to rule out bias should pull down confidence a lot.	(F3) It is not clear how much better these later studies were at reconstructing historic TWAs, much less the reconstruction of other exposure metrics.	(C3) In sum, the issue of bias does not change the reviewers' confidence much; it pulls confidence down a little or not at all.
(A4) Perhaps researchers didn't publish null study associations or results.	(F4) Kheifets (Kheifets et al., 1995) concluded that publication bias was unlikely.	
(A5) There is little or no experimental animal pathology or mechanistic support for a causal interpretation of associations seen, so they must be due to bias or confounding.	(F5) If one has a rule of thumb that all controversial bodies of evidence are by default due to some unspecified bias, one will avoid false positives but also introduce false negatives.	
	(F6) If there is any bias in <u>all</u> these studies, it is downward from non-differential exposure misclassification.	

TABLE 9.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There are not many known risk factors for brain cancer, so one cannot control for them in the analysis.	(F1) By assuming without good experimental and mechanistic support, hidden unknown confounders as a default explanation for results, one avoids false positives but produce false negatives.	(C1) One can never rule out confounding.
(A2) There is little or no experimental animal pathology or mechanistic support for a causal interpretation of associations seen, so they must be due to bias or confounding.	(F2) One should require positive evidence of a confounder to have it pull down confidence.	(C2) However, confounding can affect the risk estimates either way.
	(F3) So far known risk factors such as ionizing radiation have not been associated with EMF exposure or confounded the EMF brain cancer association.	
	(F4) The possibility of unspecified confounding without any supporting evidence should not decrease confidence.	

TABLE 9.2.4

STRENGTH OF ASSOCIATION (*LARGE ENOUGH TO BE CAUSE AND NOT BIAS*?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The association between adult brain cancer and highly exposed jobs and estimated exposures has been estimated meta-analytically as an odds ratio of only 1.2. Many of the individual studies did not reach statistical significance and should have been ignored.	(F1) Occupational and environmental agents may convey a risk which truly is not large enough to be easily detected by epidemiological studies, particularly when they can only estimate historical exposure with surrogate measures. An association, albeit small relative to the resolution power of the body of studies, increases confidence somewhat.	(C1) The effect may be intrinsically weak, so low ORs should not be construed as an argument against causality. An OR slightly above the resolution power of the body studies pulls up confidence in a modest effect of causality somewhat but not as much as a strong association would whose strength would make unidentified bias and confounding less likely.
(A2) This is barely above the resolution power of the combined studies. The absence of a strong association should pull down confidence in a causal explanation for this association a lot because a small association is much more vulnerable to any confounding and bias.	(F2) One needs to invoke one upward bias in all 28 studies of different design and different location or a series of different biases that are only upward. Unknown biases can be downward also.	(C2) The size of the association provides an additional penalty for bias and confounding but not a large one.
(A3) Some of the early, less well-designed studies had higher risk ratios and may have skewed the meta-analysis upward.	(F3) Because of exposure misclassification, the true association may be larger, and therefore less vulnerable to bias than one would think.	

TABLE 9.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One should only consider studies with statistically significant associations.	(F1) Only heeding statistically significant results instead of the overall pattern of evidence, it is true, avoids false-positive results but is a strategy that produces too many false negatives.	(C1) The body of epidemiological evidence on occupational exposures (and to some extent on residential exposures) for adult brain cancer is consistent with an effect just above the resolution power of the various studies.
(A2) The majority of the occupational and residential studies do not show statistically significant results. This is a random pattern of evidence and should pull down the reviewers' degree of certainty a lot.	(F2) Of 29 studies, 23 showed ORs above 1.00 when, by chance, 14 would have been expected. The p-value for 23/29 = 0.0004. The associations are pretty consistently above the null.	(C2) If the effect were statistically significant in all studies (which is tantamount to saying an association that is large relative to the resolution power of the studies), it would have increased confidence a lot.
		(C3) The few residential studies do not alter the confidence. They are consistent with the occupational evidence but do not stand on their own.

TABLE 9.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of these associations are not statistically significant and thus not consistent or homogeneous.	(F1) If EMFs were promoters requiring the presence of initiators whose prevalence varies from place to place, one would expect some inconsistency above and beyond that created by statistical imprecision.	(C1) The various results, occupational and residential, are consistent with an association a little above the resolution power of the studies.
(A2) Kheifets (Kheifets et al., 1995) shows less of an association in Scandinavia and in studies with good designs.	(F2) Perhaps Scandinavia lacks some co-factor. The Scandinavian studies tended to have less exact exposure assessment.	
(A3) Later studies show less of an effect.	(F3) In Kheifets, the average RR of studies fell from 1.29 in 1985 to 1.12 in 1994, only a 13% decrease.	
(A4) The 16/29 better quality studies in Kheifetz show a smaller association. RR =1.06 (1.0-1.12).	(F4) In her meta-analysis of occupational brain cancer studies, Kheifets (Kheifets et al., 1995) found the summary results not sensitive to adding or subtracting individual studies and consistent with a RR of 1.2 (1.1-1.33).	
	(F5) The three "best studies" in Kheifets's meta analysis (Floderus, Theriault, and Savitz) averaged to RR above 1.2 from exposures above the 50th percentile (but showed no monotonic increasing dose response).	

TABLE 9.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Even in occupational studies where cases tended to have higher estimated exposures than did controls, there was not an orderly monotonic increase in relative risk.	(F1) It is true that the presence of an orderly monotonic dose response within and between studies is extremely unlikely by chance or bias and when present would pull up confidence a lot.	(C1) The evidence does not suggest an effect that is large compared to the resolution power of the studies at any dose. Nor does it suggest an effect that becomes ever larger at extremely high occupational exposures. A similar pattern is observed for adult leukemia, where electric train engineers have RRs not much different from utility workers with lower exposures.
(A2) There was no consistent increase in risk estimated by studies investigating occupational groups exposed to levels of 2-5 mG (residence near power lines), 10-20 mG (most heavily exposed electrical occupations), and 70-150 mG (electrical train operators) (see (Floderus et al., 1994), (Tynes et al., 1994a), (Alfredsson et al., 1996), (Tynes et al., 1992)). This lack of dose response should pull confidence down a lot.	(F2) But it is not guaranteed that a suspected promoter acting indirectly on carcinogenisis would always convey linearly increasing risk as dose increased, as is the case with some initiators.	(C2) A promoter or co-promoter truly may not have a monotonically increasing dose response.
	(F3) The effect, if real, is not very large relative to the resolution power of the body of evidence so it would be difficult to discern the shape of a dose response curve in any case.	(C3) Exposure misclassification can mask dose-response relationships (Dosemeci et al., 1990), (DelPizzo, 1992).
	(F4) The approximate methods for reconstructing historical exposures makes this even more difficult.	
	(F5) Using TWA, which may not be the right metric, makes it more difficult still.	
	(F6) The absence of dose response should not pull down confidence much.	
	(F7) Exposure misclassification can mask dose response trends.	

TABLE 9.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Everyone is exposed to electricity, so an epidemic of brain cancer should have been seen as the use of electricity increased.	(F1) There has been an increase in the incidence of brain cancer over the last twenty years.	(C1) To the extent that it suggests anything, the epidemiology suggests that the associations appear in the top percentiles of exposure. An OR of 1.2 applied to the risk of the top 5% of the population would increase the overall rate by a factor of 1.01, not something which would be visible as an epidemic.
		(C2) The increase in brain cancer incidence may be partly due to better diagnosis. Since it is hard to assess how personal EMF exposure has changed in the last 20 years, the reviewers do not think scrutiny of temporal trends in brain cancer is reliable enough to contribute to the confidence of EMF causality.

TABLE 9.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Animal bioassays have shown no increased risk of nervous system tumors.	(F1) Animal bioassays of one aspect of a complex mixture which, if it has any effect, is not linear in risk at high dose, are not highly sensitive. Null results do not pull down confidence as much as positive results should pull them up.	(C1) The animal evidence does not increase confidence but does not pull it down greatly.
	(F2) Experimental studies showing bioeffects at high doses, and isolated studies showing co-promotional effects on other types of cancer should increase confidence somewhat.	

TABLE 9.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no coherent mechanistic chain of events that suggests EMFs as a contributory cause of CNS cancer.	(F1) Many agents do not have mechanistic explanations	(C1) The absence of a mechanistic explanation does not pull down confidence as much as the presence of one would pull it up.

TABLE 9.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See generic discussion.		

TABLE 9.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See generic discussion.		

TABLE 9.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no greater association that is statistically significant with particular cell types.	(F1) Kheifets (Kheifets et al., 1995) mentions a slight tendency for gliomas to show a stronger association.	See "Generic Issues" chapter.

TABLE 9.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 9.2.15

SUMMARY TABLE FOR ADULT BRAIN CANCER			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CONFIDENCE?**
Chance highly unlikely in meta-analysis.	Unlikely		Need non-chance explanation
Upward bias not supported.	Possible	Possible	No impact to slight decrease
Confounding possible but not supported.	More possible	Possible	No impact to slight decrease
Combined effect of chance, bias, confounding.	More possible	Possible	No impact to slight decrease
Strength of association doesn't exceed possible bias or confounding.	More possible	Possible	No impact to slight decrease
Consistency: 23/29 studies have RR = 1.0.	Unlikely	Likely	Increase
Homogeneity: less association in Scandinavian studies but compatible with effect near resolution power of studies.	Possible	Possible	No impact to slight decrease
Coherent with national and temporal trends.	Possible	Possible	No impact
Experimental evidence shows no effect on CNS cancer, but other experimental data suggest bioactivity.	Possible	Possible	No impact to slight decrease
Plausibility: lack of strong mechanistic explanation (chicks, MCF-7).	Possible	Possible	No impact to slight increase
Analogy.	Possible	Possible	No impact
Temporality.	NA	NA	No impact
No specificity of cell type, leukemia association.	Possible	More possible	No impact to slight increase

9.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

9.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

Reviewer 1 (DelPizzo)

Degree of Certainty: The evidence regarding this endpoint has attributes very similar to those of childhood leukemia, with the dose-response relationship being less clear, but the consistency of results being even stronger and the plausibility being increased by having already established a high degree of certainty for the childhood leukemia risk. This reviewer is "prone to believe" that EMFs increase the risk of adult brain cancer to some degree. For the purpose of policy analysis, this reviewer would use values between 60 and 100, with a median of 80 in a certainty scale from 0-100.

IARC classification: "Possible Human Carcinogen, 2B."

Reviewer 2 (Neutra)

Degree of Certainty: The overall pattern of epidemiological associations is compatible with an effect a little above the resolution power of the body of studies, and the best occupational studies are compatible with a slightly greater effect. The fact that the association is so near the resolution power of the epidemiology leaves it more vulnerable to unspecified bias and confounding, but not so much, with so many studies of different design and location, that one's confidence is decreased substantially. The lack of obvious animal pathology or mechanistic support pulls confidence down somewhat, but the epidemiological evidence remains and moves one's degree of certainty substantially upward from wherever it started. For the purposes of the policy projects, reviewers need to quantify their degree of certainty and uncertainty. This reviewer is "close to the dividing line between believing and not believing" that EMFs increase the risk of adult brain cancer to some degree. In a certainty scale from 0 to100, he would select 51 and a range form 30 to 70.

IARC Classification: The animal and mechanistic streams of evidence provide little if any support. The epidemiological evidence as usually assessed by IARC would not eliminate all doubts of possible confounding or bias yet it is highly unlikely to be due to chance. In fact, it looks similar to the evidence for adult lymphocytic leukemia except that there is no cell type specificity for adult brain cancer. This warrants a Possible (2B) carcinogen IARC classification, "limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals."

Reviewer 3 (Lee)

Degree of Certainty: The meta-analysis for the occupational brain cancer studies indicates a slightly higher risk for electrical workers. As a result, this reviewer's posterior for a relative risk around 1.2 is considerably increased from the initial prior by a consistent association slightly above the resolution power of the many occupational studies and by the positive association of EMF with childhood and adult leukemia. The childhood brain cancer results do not increase the confidence in adult brain cancer. This reviewer's posterior is only slightly decreased by the fact that for most of the studies, confounding and bias cannot be completely ruled out and by the lack of a dose response. Given the rudimentary way exposure is classified, weak associations such as these are to be expected; a stronger effect may be observed if exposure classification was not as crude. Also, dose-response effects are difficult to detect using such surrogate measures for exposure. The classified groups may not even indicate a gradient of high to low exposure. Hence, this reviewer is "close to the dividing line between believing and not believing' that EMFs increase the risk of adult brain cancer to some degree. For purposes of the policy analysis, she would select 60 with a range of 30 to 75 on a certainty scale ranging from 0 to 100.

IARC Classification: The human evidence is credible but bias and confounding cannot be completely ruled out. The associations observed are weak, however; the strong consistency of slightly positive effects has a very low probability of being explained by chance alone. The animal studies are less than sufficient. There is support from positive findings associated with leukemia. The evidence as a whole is sufficient for a Group 2B classification, "possibly carcinogenic to humans."

9.3.2 Summary of the Three Reviewers' Classifications

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Adult Brain Cancer				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Prone to believe	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

9.4.1 Questions Relevant to Dose Response and Policy

Table 9.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Guenel (Guenel et al., 1996) found an OR 3.08 (1.08-8.74) for electric field above 387 volt/meter with 12 cases. Miller (Miller et al., 1996) reported an OR of 0.53 (0.03-8.10) for the possibility of an electric field effect. But Guenel and Miller explored the associations between many diseases and many metrics of exposure. Some were bound to come out "significant." (C2) Sahl systematically explored associations with various metrics and found none. (C3) The evidence for or against electric-field effects and brain cancer are not extensive or clear enough to affect confidence. (C4) Floderus (Floderus, 1993) shows slight tendency for "time above 2 mG" to show stronger association than "TWA." The reverse was the case for the leukemias. There is not strong support for one or the other summary exposure metric.	(I1) No consistent guidance possible. Evidence for magnetic field is stronger.

TABLE 9.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The cross-study comparison does not suggest a steady increase in risk over the wide range of human exposure, but the data is insufficient to locate a plateau or threshold, if any. (C2) The evidence is not extensive enough or of such quality to alter one's confidence in the presence or location of thresholds or plateaus.	(I1) No ability to set refined exposure standards.

TABLE 9.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The fact there is an association with (primarily) daytime workshift exposures and perhaps a hint of (primarily) nighttime residential associations would not much support the idea of diurnal differences in vulnerability.	(I1) There is no reason to suspect vulnerable periods.

TABLE 9.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The scant evidence is contradictory. Thieriault et al. (Thierault, 1994) suggest a long latency. (C2) Sahl (Sahl et al., 1993) found no pattern. (C3) Savitz (Savitz & Loomis, 1995) and Guenel (Guenel et al., 1996) suggest shorter incubation periods. (C4) There is weak support for the effect of exposures from the last 5-10 years. This fact makes EMFs more compatible with a promoter than an initiator. One cannot tease out the independent effects, if any, of duration of exposure and interval between first exposure and disease.	(I1) If causal, concern would not be restricted to populations with decades of exposure.

TABLE 9.4.5

EMF COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Except for genetic predisposition, the few suspected risk factors for brain cancer have ORs and attributable fractions which also are not large. Exposure to ionizing radiation, nitrosamines, head trauma, etc. are all rare and have modest associations. They do not account for much of the burden of brain cancer. (C2) The comparison of the size of the EMF "effect" relative to the effect of other agents has no bearing on the confidence in causality or on policy. Cost benefit policy is driven by relative cost per case avoided, not on comparison with other risk factors.	(I1) No impact.

TABLE 9.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A relative risk of 1.2 applied to the low baseline rate of brain cancer over a 40-year occupational period would not exceed 1/1000 lifetime risk but would exceed 1/100,000.	(I1) Might be considered *de minimis* for regulatory purposes for occupational exposure but not for residential exposure.

TABLE 9.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	(I1) No evidentiary base.

TABLE 9.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The later residential studies, which have been viewed as "null," although they are they are compatible with the occupational results, and the later occupational brain cancer studies, are very sophisticated and large, but not large enough. They are some of the best occupational studies done to date. Studies of highly exposed electric train engineers could have been bigger and more detailed. (C2) Any epidemiological study of brain cancer would have the potential problem of confounding by as yet unknown risk factors.	(I1) Larger studies and studies of electric train engineers could be helpful in understanding dose response issues.

TABLE 9.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO MODIFY ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Reanalysis of the Harrington study not likely to cancel evidence to date.	(I1) None

TABLE 9.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Job exposure matrix studies of magnetic and electric fields, contact currents, and shocks using a variety of exposure summary metrics could be used to reanalyze existing data sets related to a variety of diseases and could guide future experimental studies.	(I1) Because brain cancer is a rare and poorly understood disease it may not provide the most relevant policy information.

9.5 CONCLUSIONS ON SCIENTIFICALLY RELEVANT ISSUES

9.5.1 DOSE-RESPONSE ISSUES

The associations reported for neighbors of power lines, exposed vs. unexposed electrical workers, and exposed vs. unexposed electric train workers all are close to the resolution power of the studies. If there is any effect, it does not seem to increase monotonically with dose, although the evidentiary base is insufficient for identifying either thresholds or plateaus of effect. If true, this makes it difficult to assess EMFs in the usual small cancer bioassay which is designed with the assumption that high doses will produce an obvious effect even in a few hundred animals. The evidence on electric fields is limited and contradictory. The possibility that contact currents or repeated shocks might confound magnetic field exposure has been raised for amyotrophic lateral sclerosis (see Chapter 15). There is no evidentiary base to link these other aspects of the EMF mixture to magnetic field exposure. If this were confirmed for ALS it would become a hypothesis for other EMF-associated diseases as well. The evidence for something associated with the TWA magnetic field is compatible with a 1.2-fold relative risk which if true would be of regulatory concern for long-term environmental exposures but might fall below the *de minimis* bench mark of 1/1,000 for occupational exposures.

9.5.2 RESEARCH POLICY

The reviewers are not aware of animal or epidemiological studies in the pipeline that are likely to change the overall assessment. Brain cancer has a number of characteristics that make it difficult to study epidemiologically. It is rare, the causes are poorly understood, and they are not always reliably diagnosed as to histological type. Nonetheless, one or more job exposure matrix studies exploring contact currents, shocks, electric fields, and magnetic fields using various summary exposure metrics would allow one to reanalyze the large occupational cohort and nested case control studies to determine if these other aspects of the EMF mixture might better explain the associations seen with brain cancer and other diseases. From a policy and logistic point of view, brain cancer studies are not the highest priority.

10.0 CHILDHOOD BRAIN CANCER

STATEMENT TO THE PUBLIC

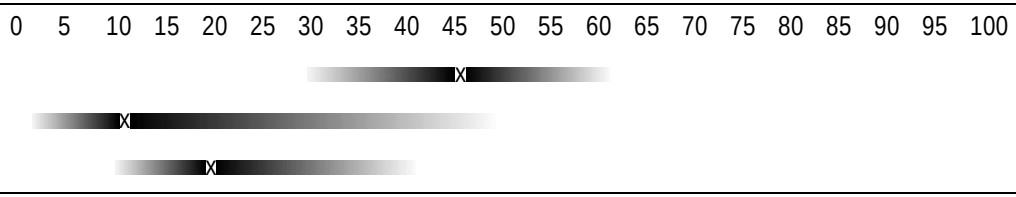
The reviewers expressed their judgments using two distinct sets of guidelines to evaluate the evidence:

- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC) for childhood brain cancer, their classifications for EMFs was "inadequate" (IARC's Group 3). Panels convened by IARC and the National Institutes for Environmental Health Sciences also thought the evidence was "inadequate" to make a classification.***

- ***Using the Guidelines developed especially for the California EMF program, two of the reviewers were "prone to believe" that high residential EMFs do NOT cause any degree of increased risk of childhood brain cancer, one "close to the dividing line between believing or not believing" in any effect.***

The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the added personal risk suggested by the epidemiological studies was "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. The three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIEWER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY IN CAUSALITY FOR POLICY ANALYSIS
Childhood Brain Cancer				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	Inad. 3	Close to Dividing Line	
	2	Inad. 3	Prone Not to Believe	
	3	Inad. 3	Prone Not to Believe	



10.1 EPIDEMIOLOGICAL EVIDENCE REGARDING CHILDHOOD BRAIN CANCER

Figure 10.1.1 Studies Relating Childhood Brain Cancer to Proximity to Power Lines and Prenatal Exposure to Electric Blankets

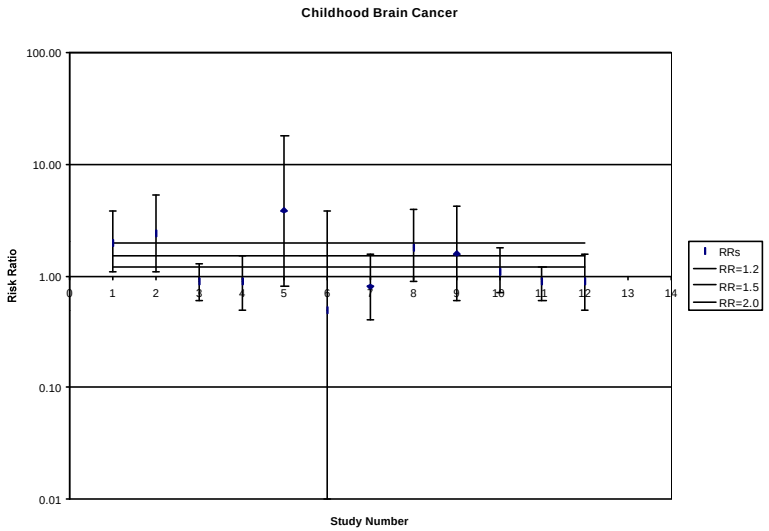


TABLE 10.1.1 KEY TO FIGURE 10.1.1

STUDY	NO.	INDIVIDUAL ODDS RATIO	LOWER CL	UPPER CL	
(Savitz et al., 1988)	1	2.00	1.10	3.80	OHCC
(Wertheimer & Leeper, 1979)	2	2.40	1.08	5.36	OHCC
(Preston-Martin et al., 1996b)	3	0.90	0.60	1.30	OHCC
(Gurney et al., 1996)	4	0.90	0.50	1.50	OHCC
(Tomenius, 1986)	5	3.90	0.80	18.00	<150 m from line
(Feychting & Ahlbom, 1993)	6	0.50	0.01	3.80	<50 m from lines
(Tynes & Haldorsen, 1997)	7	0.80	0.40	1.60	<50 m
(Savitz, John & Kleckner, 1990)	8	1.80	0.90	4.00	Electric Blanket
(Kuijten, Bunin & Nass, 1990)	9	1.60	0.60	4.20	Electric Blanket
(McCredie, 1994)	10	1.10	0.70	1.80	Electric Blanket
(Preston-Martin et al., 1996)	11	0.90	0.60	1.20	Electric Blanket
(Gurney et al., 1996)	12	0.90	0.50	1.60	Electric Blanket

Figure 10.1.2 Studies of Childhood Brain Cancer and Measured Magnetic Residential Fields

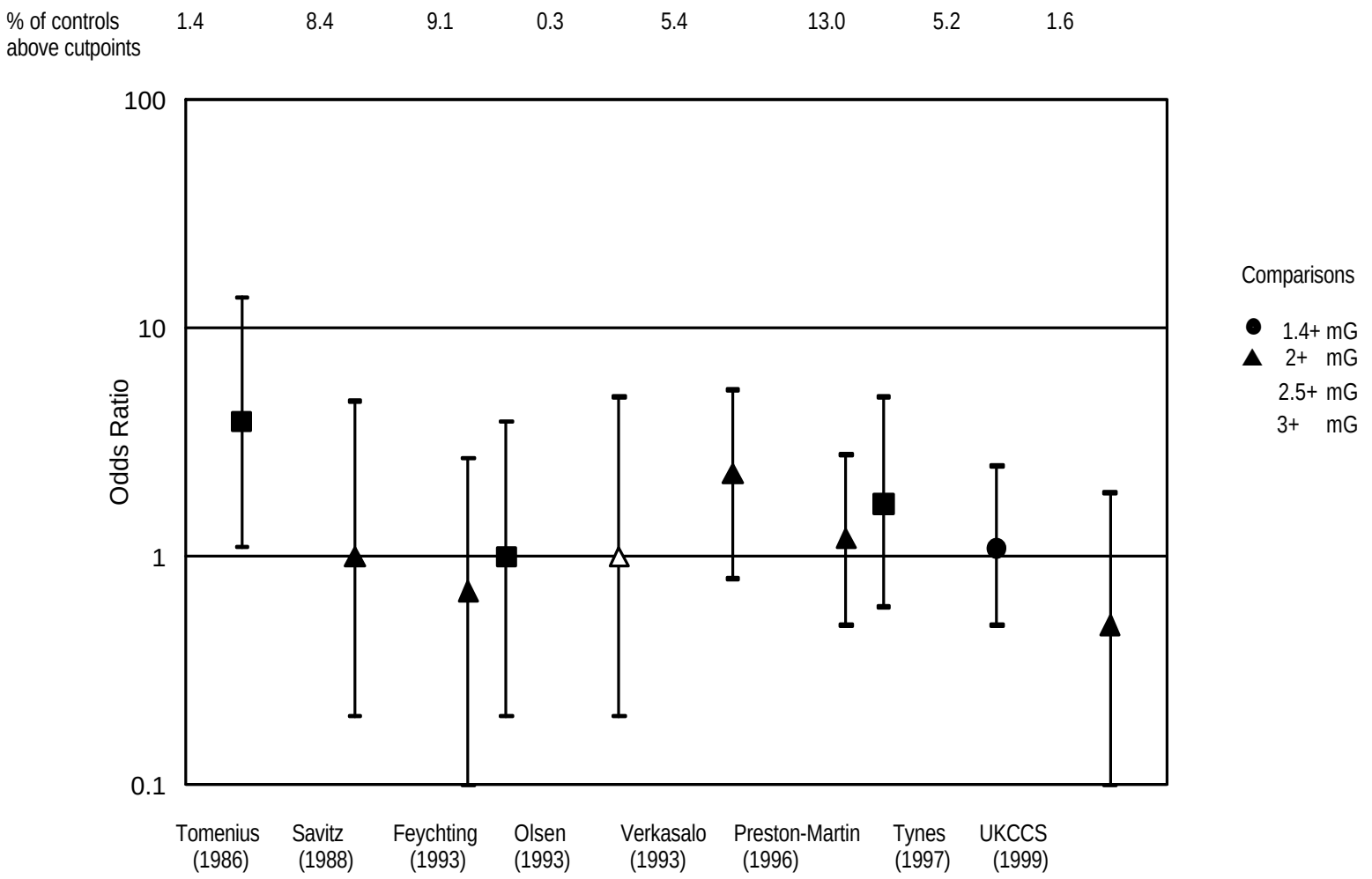


TABLE 10.1.2

Investigator, Date	Design	Definition of Case Series[1]	Age Group	Number of Cases/ Control or Cohort	Control Selection Procedure	EMF Exposure Surrogate[2]				
						1	2	3	4	5
(Wertheimer & Leeper, 1979)	Case-control	CNS	0-18	66/66	Birth Records	X[3]				
(Savitz et al., 1988)	Case-control	brain	0-14	59/259	RDD	X		X[4]		X
(Tomenius, 1986)	Case-control	CNS	0-18	294/253	Birth Records		X	X		
(Feychting & Ahlbom, 1993)	Nested Case-control	CNS	0-15	33/141	Cohort		X	X	X	
(Olsen et al., 1993)	Case-control	CNS	0-14	624/1872	Population Register		X		X	
(Verkasalo et al., 1993)	Cohort	CNS	0-19	39/134, 800	-----				X	
(UKCSS, 1999)	Case-control	CNS	0-14	359/371	Population Register		X	X	X	
(McCredie, 1994)	Case-control	CNS	0-14	82/162	Electoral Role					X
(Gurney et al., 1996)	Case-control	brain	0-19	133/270	RDD	X				X
(Preston-Martin et al., 1996b)	Case-control	brain	0-19	298/298	RDD	X		X		X
(Kuijten et al., 1990)	Case-control	astrocytoma	0-15	163/163 matched pairs	RDD					X
(Tynes & Haldorsen, 1997)	Nested Case-control	CNS	0-14	156/639	Cohort		X		X	

From Kheifets et al., 1999

[1] All studies (except for Wertheimer-Leeper) are based on incident cases.
[2] Exposure surrogate: (1) wire code, (2) distance, (3) measured fields, (4) calculated fields, (5) appliance use.
[3] HCC/LCC comparison only.
[4] Spot measurements only.

Figure 10.1 and its key show associations between exposure ("wire code," distance from lines, and appliance use), and childhood brain cancer. With regard to the first seven studies in the graph, which examined distance from power lines and wire code, 3 showed ORs >1.00 (exact binomial probability = 0.27). Of 5 studies reporting associations with prenatal electric blanket exposure, 3 had ORs > 1.0 (p = 0.31). For the most part, the studies had wide confidence intervals.

Figure 10.2 shows eight studies reporting associations with measured magnetic fields four reported RR > 1 (p = 0.27). Once again the confidence limits around the odds ratios are wide.

10.2 Arguments For and Against Causality

Table 10.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The larger and better designed studies show no statistically significant results.	(F1) The power of these studies may be insufficient to detect an effect of the rare higher exposures.	(C1) A meta-analysis by Wartenberg (Wartenberg, 1998) and an inspection of the associations above and below 1.00 for wire codes, measurements, and the history of appliance use all reveal a pattern which could be due to chance.
(A2) This pattern of results could be due to chance.		(C2) Several of the case control studies had several hundred incident cases accumulated over a number of years. Because childhood brain cancer is a rare condition, it will be difficult to conduct larger studies.

TABLE 10.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Wertheimer (Wertheimer & Leeper, 1979) exposure assessment not done blindly could bias upward.	(F1) Wire codes were associated with leukemia in Los Angeles and Sweden. Wertheimer (Wertheimer & Leeper, 1979) blindly validated a sample of wire codes. There was no evidence for bias from lack of blinding.	(C1) The associations with childhood brain cancer are less consistent than is the case with leukemia and there is nothing about the study decisions which suggest biases operating in these studies that are not operating in leukemia studies.
(A2) Savitz (Savitz et al., 1988) had mobility criteria which produced selection bias and inflated the OR.	(F2) Poole (Poole, 1996) suggests mobility bias is not an explanation of the Savitz findings.	(C2) If the greater than 1.00 ORs from well-designed brain cancer studies are discarded as biased then their leukemia results should be discarded too. Yet those leukemia results are not inconsistent with results from later better designed leukemia results. The reviewers rely on chance, not bias, to explain the pattern of evidence.
(A3) High case fatality in the cases associated with high wire codes would falsely inflate wire code/brain cancer association in Wertheimer's (Wertheimer & Leeper, 1979) mortality study.	(F3) The Preston-Martin (Preston-Martin, 1989) study gathered controls concurrently after 1989. The control series matching cases before that time has a falsely low prevalence of underground lines, which biased the OR for underground lines upward. Preston-Martin cases also were lost to follow up. This may have biased the wire code association downward.	(C3) Imprecise exposure information may be pulling the associations toward the null.
(A4) The Preston-Martin (Preston-Martin et al., 1996b) cases and controls lost equal numbers of subjects to follow up. The null result is not a biased result as alleged in F3.	(F4) Wire codes for distribution lines do not work well outside of Denver hence the null results of wire code studies elsewhere.	
(A5) The Gurney (Gurney et al., 1996) study is good quality and its null result should pull down confidence.	(F5) Non-differential exposure misclassification biases associations toward the null for measurements, estimated historical fields, and wire codes.	

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A6) Wire code for distribution lines can work elsewhere than Denver, contrary to the allegation in F4. While wire codes were developed for the Denver utility system, wire code associations with leukemia were seen in Los Angeles (London et al., 1991). The Preston-Martin study also was done in Los Angeles, and its null result cannot be discounted on the basis of poor wire codes.	(F6) The numbers available to study appliances are small, which leads to inconsistencies.	
(A7) Null results from wire code studies need to attract the same consideration as results with ORs greater than 1.00.	(F7) Not all appliances that patients might suspect and over-report are associated with disease, so there is little direct evidence of recall bias.	
(A8) Appliance studies are inconsistent and subject to recall bias.		

TABLE 10.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The associations are inconsistent.	(F1) Controlling for known causes of childhood brain cancer made no difference in results.	(C1) The reviewers see no evidence that confounding explains the pattern of epidemiological evidence.
(A2) The only two statistically significant studies are from Denver. There may be confounding in that particular location.	(F2) Special confounding was invoked for the leukemia studies, too, and despite case-specular studies for neighborhood factors (Zaffanella & Hooper, 2000) and traffic (Pearson et al., 2000), no such confounder was found.	
(A3) The causes of childhood brain cancer are not understood, so one cannot control for these unknown confounders.	(F3) Why would confounding only occur in the studies with ORs greater than 1.00?	
	(F4) To invoke confounding, one needs specific evidence that it is present, not generic invocation. to dismiss association with which one disagrees.	

TABLE 10.2.4

STRENGTH OF ASSOCIATION (*LARGE ENOUGH TO BE CAUSE NOT BIAS?*)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The overall association is so close to 1.0 as to be vulnerable to bias and confounding and thus should be ignored. It is so close to 1.0 that it should be considered null in any case.	(F1) Not all the associations in all the studies are so small.	(C1) Taken as a whole, the evidence is not compatible with an effect that is much different than 1.0. Unspecified bias and confounding could easily occur, but chance is a more salient concern here.

TABLE 10.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One should only consider statistically significant results.	(F1) One should look at all the evidence.	(C1) The pattern of associations is not consistent and there are no really strong associations.
(A2) Most of the studies show no statistically significant results.	(F2) It is not all null.	
(A3) About half the wire code and the minority of the measurement studies have ORs below 1.	(F3) Overall, it is compatible with an OR of 1.2 with wide confidence intervals.	
(A4) The appliance ORs are inconsistent and modest.		
(A5) This should pull down confidence a lot.		

TABLE 10.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Only the early, poor-quality Tomenius (Tomenius, 1986) paper showed a statistically significant association with measurements. Judging by Figure 10.2, the subsequent six studies did not achieve statistical significance for measurements or wire codes.	(F1) The associations are not all null. Something may be going on.	(C1) Even among the studies reporting RRs greater than 1.0, the pattern of odds ratios is heterogeneous. The later studies are less supportive.
(A2) Most of the wire code and appliance studies did not reach statistical significance.		
(A3) The studies are consistent in their lack of support.		
(A4) The later, better studies are less supportive.		

TABLE 10.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Within individual studies and between studies there is no orderly increase in risk as dose increases.	(F1) The number of children at the higher exposures is small enough that one's ability to discern dose-response relationships is not good.	(C1) The lack of power to detect dose-response relationships at the high end of residential exposures means that the lack of a dose-response relationship does not pull down confidence as much as the presence of a clear relationship would pull it up.
(A2) This should pull down confidence a lot.	(F2) Perhaps childhood brain cancer requires even higher exposures than childhood leukemia.	
	(F3) Imperfect exposure assessment can obscure dose response relationships.	

TABLE 10.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Everyone is exposed to electricity so an epidemic should have been seen by now.	(F1) There has been an increase in childhood brain cancer (NCI, 1991).	(C1) If there is any observable effect, it would be from the rare high exposures and with a modest effect not easily detected in national rates.
		(C2) Brain cancer trends are affected by trends in diagnostic procedures.

TABLE 10.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Animal bioassays for brain tumors have been null.	(F1) One cannot always predict cancer type in humans from animal bioassays.	(C1) Null results in a non-sensitive test do not have as much weight as a positive result would have.
	(F2) Testing a few aspects of a complex mixture on the assumption that the risk increases monotonically into high doses with a non-human species is not a sensitive test for a complex mixture like EMFs.	
	(F3) Experiments at high doses on general bioeffects should increase confidence.	

TABLE 10.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no coherent mechanistic explanation based on agreed-upon experimental results on how exposure to residential EMFs could lead to physiological effects and then brain cancer.	(F1) Agents that cause harm often have no mechanistic explanation for a long time.	(C1) The lack of a mechanistic basis does not pull down confidence as much as the presence would pull it up.

TABLE 10.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See generic discussion.		

TABLE 10.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 10.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 10.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Without mechanistic justification, other disease associations should have no bearing.	(F1) Associations with adult leukemia and brain cancer and childhood leukemia should boost confidence in the credibility of childhood brain cancer as caused by EMFs.	(C1) The other associations should have some weight.

TABLE 10.2.15

SUMMARY TABLE FOR CHILDHOOD BRAIN CANCER			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENC	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance is credible explanation.	Likely		Chance has not been ruled out .
Upward bias not suggested for body of evidence.	Possible	Possible	None
Confounding unlikely.	Possible	Possible	None
Combined, chance, bias, confounding	Likely	Possible	Chance has not been ruled out
Strength of association doesn't exceed possible confounding or bias.	Possible	Less possible	No impact or slight decrease
Not consistently above the null.	Possible	Less possible	No impact or slight decrease
Homogeneity lacking between size of effects in few positive studies.	Possible	Less possible	No impact or slight decrease
Dose response not clear in studies.	Possible	Less possible	No impact or slight decrease
Coherence/Visibility: temporal trends would not reflect these near-null effects.	Possible	Possible	None
Experimental evidence for brain tumors is null.	Possible	Less possible	No impact or slight decrease
Plausibility: lack of strong mechanistic explanation.	Possible	Possible	None
Analogy.	Possible	Possible	None
Temporality.	NA	NA	None
Specificity: no specific subtype of tumor. Adult brain cancer shows some association.	Possible	More possible	None to slight increase

10.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

10.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

Reviewer 1 (DelPizzo)

Degree of Certainty: The results are less consistent than those for childhood leukemia. Therefore, chance becomes a plausible explanation. However, the other arguments against causality are unconvincing, so that in this reviewer's opinion, the combined pattern of evidence is many more times likely to occur if the association is causal than if EMFs were really harmless. The posterior level of certainty on a scale from 0 to 100 is about 45 ("Close to the dividing line between believing and not believing"). For the purpose of decision analysis, a range between 30 and 60 should be used.

IARC classification: 3 (inadequate evidence).

Reviewer 2 (Neutra)

Degree of Certainty: The pattern of epidemiological evidence is quite likely under the no-effect hypothesis, particularly with the later better designed studies. The speculations about bias and confounding have not changed the assessment much and the lack of support from animal and mechanistic streams of evidence pulled the confidence down a little further. The adult brain cancer and leukemia associations pull confidence up, but only somewhat. The overall evidence leaves this reviewer's confidence of a causal effect of EMFs on childhood brain cancer about what it was to begin with but with a range that extends somewhat higher. This leaves a median posterior degree of certainty of about 11, falling into the "prone not to believe" category. For the purposes of the decision analysis, values ranging from 2 to 45 would be scientifically defensible.

*IARC Classification***:** The inconsistent epidemiology and the unsupportive animal and mechanistic information would classify the EMF/childhood brain cancer evidence as insufficient or "inadequate" to implicate EMF as a carcinogen and falls into Group 3.

Reviewer 3 (Lee)

Degree of Certainty: The evidence of the human studies lack power, even those well-designed studies, making them difficult to evaluate and do not rule out chance as a possibility. In both the wire code and measurement studies there are about an equal number of reported relative risks above 1.0 as there are below 1.0. Also, confounding and bias cannot be ruled out and there is a lack of a dose response as well as supporting animal studies. However, this reviewer's posterior is slightly increased over the prior on the basis of evidence of an EMF association found for childhood leukemia, and to a lesser extent adult brain cancer. Hence, this reviewer's posterior degree of certainty for purposes of the policy analysis falls within the "prone not to believe" category with a median posterior certainty of 20 and a range of 10 to 40.

IARC Classification: The human evidence is inconsistent where bias, confounding, and chance cannot be ruled out. The animal studies are less than sufficient or "inadequate" for EMF as a carcinogen even though there is support from positive findings associated with leukemia. The evidence would imply a Group 3 classification.

10.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIEWER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY IN CAUSALITY FOR POLICY ANALYSIS
Childhood Brain Cancer				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	Inad. 3	Close to dividing line	
	2	Inad. 3	Prone not to believe	
	3	Inad. 3	Prone not to believe	

10.4 POLICY RELATED SCIENTIFIC ISSUES

The following tables deal with evidence relevant to potentially bioactive aspects of the EMF mixture, the shape of dose response curves (if any), evidence for unequal vulnerability or exposure (if any), and the state of the science.

10.4.1 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 10.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Kaune (Kaune, 1994a, 2002) found childhood cancer (including brain cancer) more associated with 180 Hz than 60 Hz. There was not a clear support for AC/DC resonance. (C2) Preston-Martin (Preston-Martin et al., 1996b) explored resonance with DC fields, time above 2 mG, and average size of the difference between consecutive measurements and found little or no evidence to support an effect from these metrics. (C3) Magnetic fields over water pipes in the Preston-Martin (Preston-Martin et al., 1996b) study were not associated with childhood brain cancer either. (C4) (Savitz et al., 1988) found no association with electric fields. (C5) Preston-Martin (Preston-Martin et al., 1996b) observed that peaks (the 90th percentile) during 24-hour measurements in the child's bedroom and "other" room studies showed ORs of 2-3 for the highest category of 4-22 mG. Those had wide confidence intervals.	(I1) Not enough evidence to focus on alternative metrics or aspects.

TABLE 10.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Any associations begin to appear at or above 3 mG. It is not clear if this is a threshold.	(I1) None.

TABLE 10.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	(I1) None.

TABLE 10.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Birth and death address wire code were equally associated in Wertheimer's (Wertheimer & Leeper, 1979) study. (C2) Tynes (Tynes & Haldorsen, 1997) found larger (but imprecise) ORs with first year address rather than with diagnosis address. (C3) Swedish/Danish meta-analysis (Feychting et al., 1995) shows a larger imprecise association for year of diagnosis exposure than cumulative lifetime exposure.	(I1) Some suggestion of efficacy of recent exposure but the evidence is very weak.

TABLE 10.4.5

EMF COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Aside from genetic risk factors, there are few established risk factors for childhood brain cancer, and they do not convey high relative risks (Kuijten & Bunin, 1993). (C2) The relative size of the association may be relevant for risk communication but not for cost-benefit oriented policy.	(I1) None.

TABLE 10.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) With an annual incidence of a few cases per 100,000, 20 years of RR of 1.2 would accumulate an added risk above 1/100,000 and if real would be of regulatory concern. The degree of certainty about this association is quite low.	(I1) Could be of regulatory concern if real.

TABLE 10.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base.	(I1) None.

TABLE 10.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The study designs have been state of the art, just not very powerful from a statistical point of view because childhood brain cancer is even more rare than leukemia and high exposures are rare. (C2) The use of surrogate metrics for exposure tends to bias associations toward a null result, but is not an argument against causality.	(I1) It will be difficult to improve on the existing studies.

TABLE 10.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO CHANGE ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A large case-control study by Kabuto et al. is planned for Japan.	(I1) Could be influential regardless of results because of projected size and equivocal nature of existing evidence.

TABLE 10.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Exposure assessments which would examine magnetic fields, electric fields, contact currents, and shocks in the residential environment, and which used various summary exposure metrics, might indicate potential confounding between these EMF aspects and metrics and could guide future epidemiology and laboratory research. (C2) Childhood brain cancer is quite rare and would not drive a cost-benefit oriented policy. It may be more productive to focus on other, more common diseases.	(I1) Not clear that further information on this condition would drive EMF policy.

10.5 CONCLUSIONS ON POLICY-RELEVANT SCIENTIFIC ISSUES

10.5.1 DOSE-RESPONSE ISSUES

The associations with EMFs are not clear for this disease, nor is there a sufficient evidentiary base to speculate about pathogenic aspects of the EMF mixture or summary exposure metrics, which might be more strongly associated. Similarly, there is insufficient evidentiary base to provide insight into induction period or shape of dose-response relationships. There is no evidentiary base to address the issue of unequal vulnerability or exposure.

10.5.2 RESEARCH POLICY

There is one large case-control study in the pipeline from Japan. Even if it implicates EMF as a cause of childhood brain cancer, it likely will leave questions about dose response, pathogenic aspects of EMF mixture, etc. If it is well conducted and is a null study it probably would put the childhood brain cancer issue to rest. The rarity of this disease means that it would not drive a cost-benefit oriented policy and makes it difficult to conduct studies. This may not be a priority area for further research. The results of the Japanese study may conceivably alter this conclusion.

11.0 BREAST CANCER

STATEMENT TO THE PUBLIC

The reviewers used two distinct sets of guidelines to evaluate the evidence:

A) Female Breast Cancer

- *Using the traditional guidelines of the International Agency for Research on Cancer (IARC) the DHS Reviewers considered the evidence "Inadequate" (Group 3) to implicate EMFs. This was also the opinion of review panels at IARC and the National Institutes of Environmental Health Sciences (NIEHS).*
- *Using the guidelines developed by the California EMF program one reviewer was "Close to the Dividing Line between Believing and not Believing" and two were "Prone Not to Believe" that EMFs increase the risk of female breast cancer to any degree.*

B) Male Breast Cancer

- *Using the traditional guidelines of IARC the DHS Reviewers considered the evidence "Inadequate" (Group 3) to reach a conclusion. This was also the opinion of review panels at IARC and NIEHS.*

Using guidelines developed by the California EMF program one reviewer was "Close to the Dividing Line between Believing and not Believing" and two reviewers were "Prone Not to Believe" that EMFs increased the risk of male breast cancer to any degree.

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASE DISEASE RISK TO SOME DEGREE
Breast Cancer, Female				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	
Breast Cancer, Male				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing Line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

11.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 11.1.1 (Female Residential and Electrical Devices)

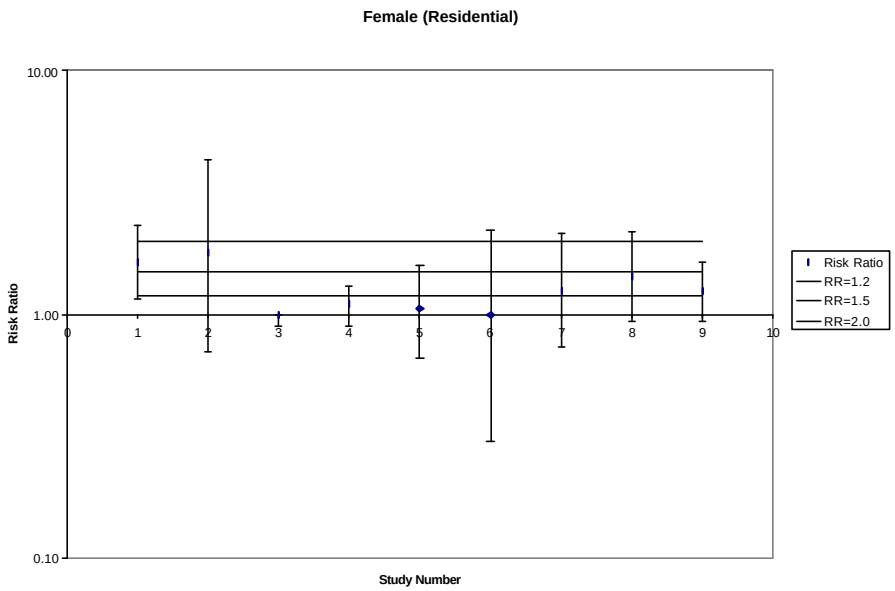


Figure 11.1.2 (Female Occupation)

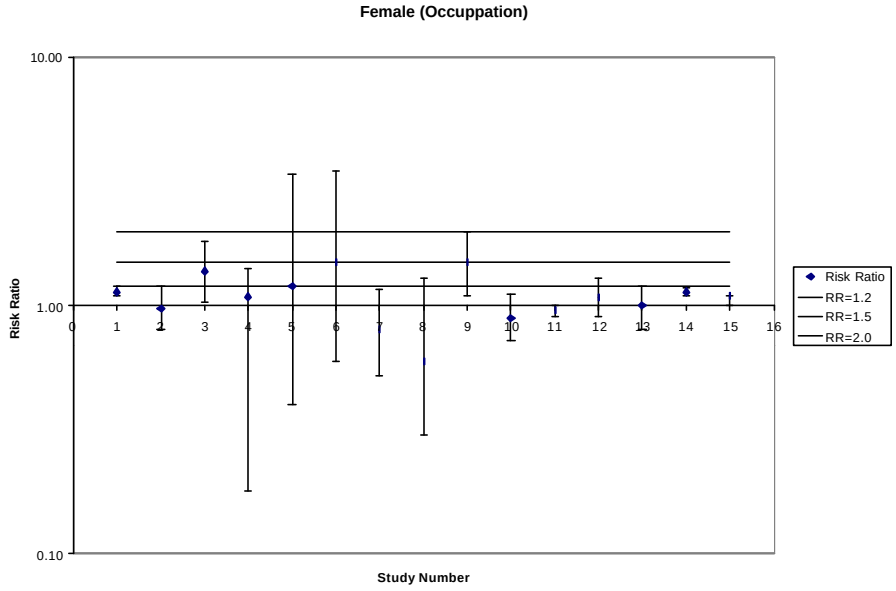


Figure 11.1.3 (Male Occupation and Residential)

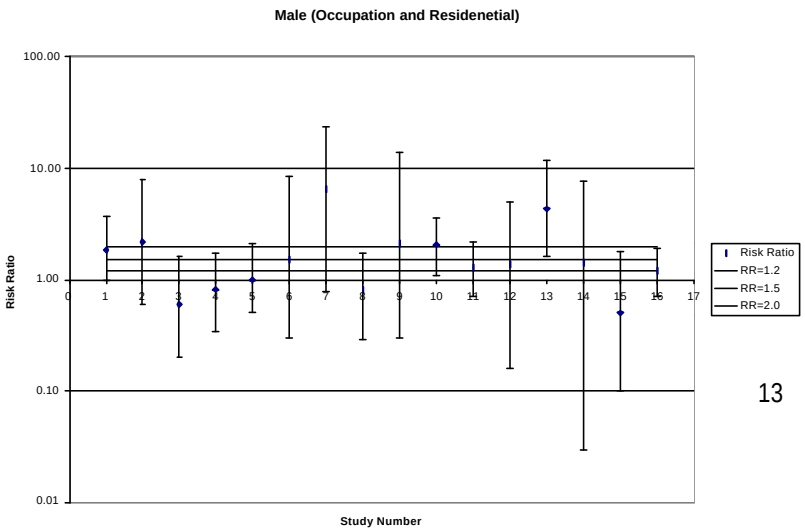


Figure 11.1.1 shows the reported relative risks and odds ratios of female breast cancer for residential power line assessment and electrical devices. These studies are listed in Table 11.1.1. Figure 11.1.2 shows the relative risks and odds ratios of female breast cancer for occupational exposures. Combining both residential and occupational exposures, 16 of the 24 relative risks are above 1.0, with an exact binomial probability of .04; 8 of the relative risks are above 1.2, with an exact binomial probability of .04. Only 2 of the studies had relative risks above 1.5; and none of the studies had relative risks above 2.0. Figure 11.1.3 shows the reported relative risks and odds ratios of male breast cancer for occupational exposures and residential exposure (one study). Eleven of the 16 relative risks are above 1.0, 10 are above 1.2, and 5 are above 1.5, respectively, with an exact binomial probability of .07, .12, and 0.07 respectively.

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TABLE 11.1.1 FEMALE RESIDENTIAL AND ELECTRICAL DEVICES

STUDY NAME	STUDY NUMBER	STUDY LOCATION	STUDY TYPE	POPULATION	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Wertheimer & Leeper, 1987)	1	USA	Mortality Case-control	<55 yrs	Wire codes	1.64	1.16	2.33
(Feychting, Rutqvist & Ahlbom, 1998a)	2	Sweden	Incidence Case-control	<50 yrs	Calc fields	1.80	0.70	4.30
(Verkasalo et al., 1996)	3	Finland	Incidence CHT	All	Calc fields > 0.01 μT	1.00	0.90	1.00
(Li et al., 1997)	4	Taiwan	Case-control		Estimated expos > 0.2 μT	1.10	0.90	1.30
(McDowall, 1986)	5	England	Mortality CHT	All	Distance < 30m	1.06	0.66	1.60
(Schreiber et al., 1993)	6	Netherlands	Mortality	All	Distance < 100m	1.00	0.30	2.20
(Vena et al., 1991)	7	NYC, US	CHT	postmeno.	Elect Blanket use (cont).	1.25	0.73	2.16
(Vena et al., 1994)	8	NYC, US	Case-control	premeno.	Elect Blanket use (cont).	1.43	0.94	2.17
(Gammon, Schoenberg & Britton, 1998)	9	US	Case-control	<10 mos use, <45 years old	Elect Bed Heater kept on	1.24	0.94	1.63

TABLE 11.1.2 FEMALE OCCUPATIONAL

STUDY NAME	STUDY NUMBER	STUDY LOCATION	STUDY TYPE	POPULATION	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Cantor et al., 1995b)	1	US	Case-control Whites			1.14	1.10	1.20
(Cantor et al., 1995a)	2	US	Case-control Whites	Electrical workers	Title/matrix	0.97	0.80	1.20

Study Name	Study Number	Study Location	Study Type	Population	Exposure Metric	Individual Odds Ratio, Mean	Lower CL	Upper CL
(Loomis, Savitz & Ananth, 1994)	3	US	Case-control	Electrical workers	Title	1.38	1.04	1.82
(Coogan et al., 1996)	4	US	Case-control		Job Title	1.09	0.18	1.42
(Coogan & Aschengrau, 1998)	5	US	Case-control		Job Title	1.20	0.40	3.40
(Forssen, Feychting & Rutqvist, 2000)	6	Sweden	Case-control	Age<50	Matrix	1.50	0.60	3.50
(Kelsh, 1997)	7	US	Cohort	Electric utility, usual occ.	Matrix	0.80	0.52	1.17
(Vagero et al., 1985)	8	Sweden	Cohort		Job title	0.60	0.30	1.30
(Tynes et al., 1996)	9	Norway	Cohort		Title (meas)	1.50	1.10	2.00
(Fear et al., 1996)	10	England	PRR		Job title	0.89	0.72	1.12
(Guenel et al., 1993)	11	Sweden	Cohort	Occupations w potential EMF exposure	Title intermed exp	0.96	0.91	1.01
(Johansen & Olsen, 1998)	12	Denmark	Cohort	Electric util workers	Matrix	1.08	0.90	1.30
(Petralia, Chow & McLaughlin, 1998)	13	China	Cohort		Matrix	1.00	0.80	1.20
(Kliukiene, Tynes & Martinsen, 1999)	14	Norway	Cohort	Occup's with potential EMF exposure	Expert panel/ measurement	1.14	1.10	1.19
(Floderus, Stenlund & Persson, 1999)	15	Sweden	Cohort		Matrix	1.10	1.00	1.10

Table 11.1.3 Male Residential and Occupational

Study Name	Study Number.	Study Location	Study Type	Exposure	Exposure Assessment	Individual Odds Ratio, Mean
(Demers et al., 1991)	1	US, I	Case-control	Occupations w/ potent. EMF exp.	Work history, n=33 cases exposed, job title	1.85
(Loomis, 1992)	2	US, DC	Case-control	Electrical workers	Job title, n=4 cases exposed	2.20
(Rosenbaum et al., 1994)	3	US	Case-control	Occup exp. to EMF	Job title, n=6 cases exposed	0.60
(Theriault et al., 1994)	4	Canada/ France	Case-control	Electric util workers	Work history, some measurement	0.82
(Cocco, Figgs & Dosemeci, 1998)	5	US, DC	Case-control		Job matrix	1.00
(Stenlund & Floderus, 1997)	6	Sweden	Case-control	Occ. exp. to EMF	Work history, job exp matrix, some meas.	1.5
(Matanowski, Breysse & Elliott, 1991)	7	US	Cohort	Telephone workers	Current job title, some measurements	6.50
(Savitz & Loomis, 1995)	8	US	Cohort	Electric util workers	Work history, some measurement	0.8
(Feychting et al., 1998a)	9	Sweden	Case-control	Transmission line	<300 m	2.10
(Tynes et al., 1992)	10	Norway	Cohort	Electrical workers	Job title, estimate type of exposure	2.07
(Fear et al., 1996)	11	England	PRR		Job titles	1.29
(Guenel et al., 1993)	12	Denmark	Cohort	Occupations w/ potential EMF Exp, continuous	Job title	1.36
(Floderus et al., 1994)	13	Sweden	Cohort	Railway workers, 1961-69	Job title	4.30
(Tynes et al., 1994b)	14	Norway	Cohort	Hydroelectric co. workers	Work history, expos estimates	1.40
(Johansen & Olsen, 1998)	15	Denmark	Cohort	Util. workers	Job matrix	0.50
(Floderus et al., 1999)	16	Sweden	Cohort		Job matrix	1.20

TABLE 11.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the results are not statistically significant.	(F1) For most of the studies, especially the male cohort studies, the number of cases were very small, resulting in low power, which explains the insignificant positive associations. All of the studies used surrogate measures to assess exposure; these measures misclassify exposure tremendously and hence may not even be predictive of exposure, thereby increasing the probability of a non-significant association.	(C1) The pattern of meta-analytic associations just above the resolution power of the studies with EMF for male and female breast cancer does not support chance as a likely explanation.
(A2) Most of the occupational cohort studies have assessed many different cancers resulting in significant "p-values," which could be due to chance.	(F2) Both meta-analyses suggest that chance is not an easy explanation of the pattern seen. For females a pooled relative risk was 1.12 (1.09-1.15) (Erren, 2001). For the male breast cancer studies, even though the disease is very rare and there was considerable random misclassification of exposure, an overall association of 1.37 (1.11-1.71) was still observed [Erren, 2001 #1534).	

TABLE 11.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The studies that assessed exposure after the occurrence of the disease may result in better recall or ascertainment of exposure for cases resulting in spurious positive results.	(F1) Observation bias is an unlikely explanation because the overall, weak positive associations of the meta-analyses for the cohort studies (where exposure was assessed prior to the occurrence of the disease) were similar to those found for the case-control studies.	(C1) If there is any bias in these studies, it is downward resulting from non-differential exposure misclassification.
(A2) Stronger positive findings were not more pronounced for those studies with more comprehensive exposure measures, suggesting that exposure misclassification is not a major problem.	(F2) Exposure misclassification bias is the major concern for all of the studies. Only crude, rudimentary estimates of exposure were used. No study directly measured a person's exposure during the critical period of time. These exposure surrogates may not even predict a person's exposure. Also, only partial exposure information was obtained—either work related or residential related, but not both. This would considerably decrease an effect. Hence, those studies with positive results would probably show a greater effect if exposure were directly measured.	

TABLE 11.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A weak to moderate confounder would easily "explain" the apparent weak, positive associations found for the majority of these studies.	(F1) For those positive interview studies that collected information to assess confounders, the risks were not changed after adjustment.	(C1) Important known risk factors have not been controlled for in all of these studies. However, there is no particular evidence that this would be biased to produce false-positive results.
(A2) Very few studies were able to control for important confounders such as diet, alcohol consumption, reproductive behavior and history, and other residential and occupations exposures (such as chemical exposures and x-rays) since information about the participants were from death certificates, occupation records, and census records. This could result in a bias away from the null.	(F2) For those studies that focussed on breast cancer and obtained covariate information, the control for confounding was limited because their meta-analysis results were similar to those studies where covariaties were not assessed (Erren, 2001).	(C2) Invoking unspecified confounders to explain away results is inappropriate.

TABLE 11.2.4

STRENGTH OF ASSOCIATION (*LARGE ENOUGH TO BE CAUSE NOT BIAS*?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) For females, no or little association has been found between breast cancer and EMF exposures. For those studies that found a positive association, the magnitude was close to one. The summary relative risk estimate from meta-analysis was 1.12 (Erren, 2001). The slight positive relationships observed for some of the studies are quite likely due to bias or some unsuspected or uncontrolled confounding variable.	(F1) All of the studies used very rudimentary estimates of residential and occupational EMF exposures. Surrogate measures of exposures may convey a risk that, due to random misclassification, is not large enough to be easily detected by epidemiological studies, and hence, are expected to convey weaker relative risks than that of a direct exposure measure.	(C1) Weak effects, if real, are of public health importance, especially those associated with common exposures and relatively common diseases such as female breast cancer. All the studies used rudimentary methods to estimate exposures, and most had a problem with power. Hence, even a modest positive association would be difficult to detect in such studies. The strength of the observed associations supports a non-causal association, but the study design issues tend to neutralize this support.
(A2) For the male breast cancer studies the summary relative risk estimate from meta-analysis was weak (1.37).	(F2) The residential studies mainly estimated high exposure as living in an area at a certain distance from transmission lines, with the cutoff range such a distance away from the transmission line that the line was not even a source of exposure for most of the participants in this group. The calculated fields generally were for buildings in this large area but not directly estimated for the location of the participant's homes. The strengths of the association were stronger from the two studies where the estimates were directly associated with the participants' residences (Wertheimer & Leeper, 1987), (Feychting et al., 1998a).	
	(F3) Those cohort studies where no male breast cancer was found had extremely low power in detecting a disease as rare as male breast cancer, thereby not contributing one way or another to the body of evidence for male breast cancer.	

TABLE 11.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The majority of the studies show a random pattern of non-significant results above and below the null, where the individual relative risk estimates are close to 1.0. This is most pronounced for the female breast cancer studies where the disease is not as rare as male breast cancer.	(F1) For the female studies, 16 out of 24 studies revealed a relative risk of above 1.0.	(C1) The evidence is modestly consistent.
	(F2) Also, for the male breast cancer, across all 16 studies, there were 11 with relative risks above 1.0 ($p = 0.07$).	

TABLE 11.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is a lack of homogeneity for a positive association across studies supporting the possibility of a chance occurrence.	(F1) The extreme heterogeneity in population definition across studies and the crude and widely different methods used to assess exposure for all studies make it difficult to evaluate homogeneity.	(C1) The lack of homogeneity across studies does not necessarily decrease the likelihood of a causal relationship. This may be due to the difference in the definition of study populations and exposure assessment across studies.
(A2) Some studies found a slight positive association for some population subgroups. However, these particular subgroups were not the same from study to study. The lack of homogeneity in various subgroups suggest that the positive associations found are more likely to represent chance fluctuations in the data than true increased risk.	(F2) Homogeneity was observed for those subgroups adequately defined and where an increased risk of breast cancer is expected. Not all studies looked at similar subgroups and most studies were not able to evaluate subgroups due to a small number of cases.	(C2) The pattern for the female breast cancer results is heterogeneous, making it difficult to either support or refute its causal association with EMF.
(A3) For the male breast cancer studies no breast cancers were found for the seven cohort studies (see Erren, 2001) supporting the notion that the weak meta-analysis risk estimate is probably due to chance.		

TABLE 11.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No consistent gradient is found, even in the occupational studies, where higher exposures are expected relative to residential environments and in the electric bed heater studies where these devices are expected to emit strong fields and occur at night, which is the time most likely to influence the natural circadian rhythm of melatonin production (one of the main biological hypotheses for breast cancer). The likelihood of a causal relation is strengthened if a dose-response effect is found.	(F1) A dose-response relationship can frequently be masked by an inability to measure exposure sufficiently to distinguish between risks associated with different levels. A dose response cannot be adequately assessed for the breast cancer studies. Most of the studies only included one level of EMF exposure, and those that had data on two or more levels used surrogate estimates of exposure associated with a high level of misclassification into high to low exposure groups. These studies used different exposure groupings to assess dose response. The electric bed heater studies did not assess a gradient in exposure but rather a gradient in the duration of use, and one study did not differentiate among the types of bed heaters. Also, it may be that electric bed heaters do not emit fields as strong as once thought (Lee et al., 2000).	(C1) The absence of a dose-response gradient does not mean that a cause-effect relationship does not exist. Moreover, it is not unusual for biologic factors to demonstrate a threshold phenomenon, where no effect is present until a certain level of the exposure is reached.
	(F2) Of the 22 studies which present some kind of very crude estimate of an EMF dose, 8 suggest that there might be a dose-response relationship (Vena et al., 1991), (Vena et al., 1994), (Demers et al., 1991), (Tynes et al., 1996), (Coogan et al., 1996), (Li et al., 1997), (Feychting et al., 1998a), (Kliukiene et al., 1999), (Forssen et al., 2000). One of these studies found the strongest relationship for men exposed before age 30 and where > 30 years elapsed before diagnosis (Demers et al., 1991).	(C2) The studies that categorized different levels of exposure used crude estimates (i.e., the categories defined as "high" to "low" groups may not actually reflect low to high exposures). The misclassification of exposure along with the rarity of the disease, especially for males, decreases the ability of the studies to detect a dose response. Hence, a lack of a dose-response gradient does not support a non-causal association.

TABLE 11.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Everyone is exposed to electricity so we should have seen an epidemic of breast cancer as the use of electricity increased. No clear epidemic has been demonstrated.	(F1) There has been a slight increase in the age-adjusted incidence of, at least female, breast cancer over the last twenty years. Also, there is an increased rate in industrialized regions compared to non-industrialized regions. This implies that risk increased with increase of electricity use.	(C1) It is possible that, over time, EMF exposure may be more variable as environmental sources increase via industrialization. However, an increase in industrialization or urbanization also may be associated with an increase in other important breast cancer potential risk factors. Hence, visibility does not influence the likelihood of causation one way or the other.
(A2) A more pronounced risk was not observed for the most heavily exposed groups.	(F2) The assessment of a heavily exposed group was based on very crude measures where this group may not have high exposures. Furthermore, very few studies were able to evaluate the effect for heavily exposed groups compared to those with little or no exposures.	(C2) The consistency of a slightly stronger association with more vulnerable subgroups suggests a slight coherence of the results. However, this does not necessarily support a causal association because these subgroups were crudely defined, and only a small number of studies assessed these subgroups.
	(F3) Of the few studies that assessed more homogenous subgroups, the effect was more pronounced for those groups assumed to be susceptible to breast cancer. Overall, the effect was somewhat higher for younger or pre-menopausal women (Wertheimer & Leeper, 1987), (Forssen et al., 2000), (Coogan et al., 1996), (Coogan & Aschengrau, 1998), (Gammon et al., 1998) especially for those with estrogen positive breast cancer (Feychting et al., 1998a), (Forssen et al., 2000).	
	(F4) The summary, weak positive relative risk estimates from the meta-analyses were similar regardless of study design and country (US vs. other) of the study population.	

TABLE 11.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Overall, the animal bioassays have been inconsistent with most studies not supporting an association of exposure with mammary tumors.	(F1) Several studies support an association with mammary tumors, and two studies showed a dose-response relationship (Loscher et al., 1994), (Mevissen et al., 1996a).	(C1) Some of the promotional animal studies have been positive with two showing a dose response, thereby supporting a causal hypothesis.

TABLE 11.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A specific biologic mechanism involving the suppression of the nighttime hormone, melatonin, has been proposed to increase cancer risk. The animal evidence is not consistent with this hypothesis, especially the large animal studies, which are consistently negative. Unidentified, critical parameters result in the false positives observed for some of the few small animal studies.	(F1) EMF exposures do affect melatonin as observed in some small animal studies; however, the lack of consistency is the result of not yet defined critical parameters that mediate the response. For these studies there is misclassification and bias for most of the existing data. There are fewer studies with large animals than with small animals, and these studies mainly assess circulating melatonin. Also, among the animal studies there are a number of different endpoints assessed as to the synthesis, secretion, and metabolism of melatonin, thereby increasing the likelihood of observing inconsistency across these studies.	(C1) There is a specific biological rationale associated with EMF exposure and breast cancer risk, which has, to some extent, been supported by animal studies.
(A2) Even though a melatonin-cancer association has been observed, an EMF-melatonin link has not been established. For the positive animal studies, only small reductions of melatonin after EMF exposure have been observed. Given the large variation of melatonin in humans, it is unclear how a small reduction in melatonin, as observed in the animal studies, could result in an adverse health effect.	(F2) Other experimental and laboratory studies, such as the *in vivo* rodent experiments (where deprivation of pineal function increases tumor incidences) and the *in vitro* MCF-7 cell line studies (showing the anti-proliferative nature of melatonin) support the small animal findings.	
	(F3) There are well-established risk factors with unknown mechanisms.	

TABLE 11.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.15

SUMMARY TABLE FOR BREAST CANCER			
HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:			
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance is unlikely.	Possible	Less possible	Some increase
Upward bias not supported.	Possible	Possible	No impact
Confounding possible but not supported.	More possible	Possible	No impact or slight decrease
Combined chance, bias, confounding.	More possible	Possible	Slight decrease
Strength of association: (1) does not exceed possible bias or confounding.	More possible	Possible	No impact
Strength of association: (2) a weak positive pattern for female breast cancer but with considerable heterogeneity; a weak positive pattern for male breast cancer slightly supported.	Female: possible Male: possible	Female: possible Male: more possible	No impact or slight increase
Consistency and homogeneity across studies is modest.	More possible	Possible	No impact or slight decrease
Dose response is difficult to evaluate.	Possible	Possible	No impact
Coherent with national and temporal trends.	Possible	Possible	No impact
Experimental evidence slightly supported.	Possible	More possible	No impact or slight increase
Plausible mechanistic melatonin explanation has some support.	Possible	More possible	No impact or slight increase
Lack of analogous agent.	Possible	Possible	No impact
Temporality: exposure precedes disease.	Possible	Possible	No impact
No specificity, other disease associations.	Possible	Possible	No impact

11.3 Posterior (Updated) Degree of Certainty and IARC Classification

11.3.1 Statements of Individual Reviewers

Reviewer 1 (DelPizzo)

Female Breast Cancer

The epidemiological studies are rather consistent in indicating a relative risk of 1.1. Overall, there are 27 risk estimates greater than 1, out of 40 studies. The p-value for such a pattern is < 0.01, arguing that that chance is not a plausible explanation. In addition, there is some directly pertinent animal evidence in support of the hypothesis, and, as in the cases of other endpoints, no convincing alternative explanation for the association. Reviewer 1 is "close to the dividing line between believing and not believing." He would use certainty values between 35 and 80 with a median value of 49.

IARC classification: Because of the limited quality of human studies and the lack of published replication of animal studies, Reviewer 1 believes that the most prudent classification under these guidelines is inadequate evidence.

Male Breast Cancer

There are only a few human studies, with some suggesting a considerably stronger association than others. This is boosted somewhat by the high degree of certainty attributed to other associations, particularly female breast cancer, but overall the evidence falls short of reaching the 51 confidence level. Reviewer 1's evaluation is "close to the dividing line between believing and not believing." For decision analysis purposes, Reviewer 1 would use values between 30 and 75 with a median of 45.

IARC Classification: Inadequate evidence.

Reviewer 2 (Neutra)

Female Breast Cancer

Degree of Certainty: While 16 of the 24 studies reviewed had odds ratios above 1.0 (which is an improbable distribution), Erren's (Erren, 2001) meta-analytic summary OR was 1.1 (1.09-1.15). Nonetheless, there was substantial heterogeneity among the studies, most of which had very crude indices of exposure. The melatonin hypothesis which motivated these studies requires that the effect of EMFs on lowering melatonin in humans be clearly demonstrated and that the in vivo oncostatic effect of modest increases in melatonin be clearly demonstrated. Neither of these conditions has been met definitively. The unreplicated Loscher experiments did not affect this reviewer. For all the reasons given in the discussions above, this pattern of evidence increased Reviewer 2's confidence about female breast cancer only slightly above the prior. With an association close to the resolution power of the studies, this reviewer's degree of certainty would best be expressed as being on the low side of "prone not to believe" with a median of 11 and a range from 2 to 45.

IARC Classification: The lack of clear animal pathology or mechanistic support and the weakness of the epidemiological support to date would make this body of evidence "inadequate" to implicate EMFs as carcinogens and falls into Group 3.

Male Breast Cancer

Degree of Certainty: The pattern of associations for male breast cancer in the studies reviewed by Erren (Erren, 2001) shows 11 of 16 with odds ratios above 1.0 (p = 0.07), while Erren's meta-analytic summary was 1.4 (1.1-1.7). The higher odds ratios reported in the early 1990s have not persisted in the later studies. The other streams of evidence have been discussed above and have similar weights as with female breast cancer. The overall pattern of evidence has increased this reviewer's degree of certainty upward from what it was originally.

With the prior degree of certainty for a just-detectable effect, this reviewer's posterior degree of certainty would best be describes as "prone not to believe" with a median of 39 and a range from 2 to 60.

IARC Classification: The lack of definitive animal pathology and mechanistic explanation and the less than conclusive epidemiology would leave this body of evidence as "inadequate" to implicate EMFs as a carcinogen and falls into Group 3.

Reviewer 3 (Lee)

Female Breast Cancer

Degree of Certainty: The human evidence of female breast cancer is based on occupational and residential studies, both of which used extremely crude methods to estimate exposures and had low power to detect weak associations. The relative likelihood of a consistently weak positive association across studies does not influence Reviewer 3's prior for a relative risk around 1.2. Mainly, this reviewer's posterior prior is slightly increased over her prior by the support of the animal

evidence and by the positive EMF association with childhood leukemia. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "prone not to believe" category with a median of 15 and a range of 5 to 35.

*IARC Classification***:** The human evidence is inadequate where most studies were not primarily designed to test an EMF-related hypothesis, most lack power, and most are susceptible to biases and confounding due to the crude exposure estimates. The overall relative risks are weak where chance cannot be ruled out as an explanation. On the other hand, the animal evidence supports a clear biological model with some inconsistencies. Furthermore, there is evidence that the proposed mechanism operates in humans. Given this, along with support from the childhood leukemia findings, the evidence is in the upper end of the Group 3 classification, "inadequate."

Male Breast Cancer

Degree of Certainty: Like the female breast cancer evidence, the human evidence of male breast cancer is based on both occupational and residential studies that used extremely crude methods to estimate exposures and had low power to detect weak associations. Reviewer 3's posterior is slightly increased above her prior by the consistently weak positive association across studies, by the support of the animal evidence, and by the positive EMF association with childhood leukemia. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "Prone not to Believe" category with a median of 20 and a range of 10 to 45.

IARC Classification: This is similar to that of female breast cancer. The human evidence is inadequate where most studies were not designed to test an EMF-related hypothesis, most lack power, and most are susceptible to biases and confounding due to the crude exposure estimates. The overall relative risks are weak, where chance cannot be ruled out as an explanation. On the other hand, the animal evidence while suggestive (Loscher) has some inconsistencies. There is some evidence that the proposed mechanism operates in humans. Nonetheless the evidence is at the upper end of the Group 3 classification, "inadequate."

11.3.1 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASE DISEASE RISK TO SOME DEGREE
Breast Cancer, Female				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	
Breast Cancer, Male				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

11.4 Questions Relevant to Dose Response and Policy

Table 11.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

Table 11.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

Table 11.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

Table 11.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

TABLE 11.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The few known risk factors for breast cancer show weak to moderate associations, generally larger than those found for the EMF-breast cancer studies. However, the studies evaluating these other risk factors used better exposure-measurement protocols than those assessing the EMF-breast cancer association. (C2) The common prevalence of both the exposure and at least female breast cancer could result in a considerable public health burden even if the true effect is weak. However, due to the poor quality of exposure data, the low power, and for some studies the low participation response rate of the breast cancer, it is difficult to compare the strengths found for the breast cancer studies with the strengths of known risk factors.	No impact.

TABLE 11.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A relative risk of 1.12 for female breast cancer applied to moderate baseline rate of female breast cancer over a 40-year period would exceed a 1/1000 lifetime risk. (C2) A relative risk of 1.37 applied to the very low baseline rate of male breast cancer over a 40-year period would not exceed a lifetime risk of 1/1000 but may exceed a 1/100,000 lifetime risk.	(I1) The risk could be of regulatory concern if real.

TABLE 11.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base	

TABLE 11.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There is room for improvement in all studies in one way or another. All studies had one or more of several major problems in design, making it difficult to assess if the overall weak positive relationship observed could be due to chance or could reflect a causal association.	

TABLE 11.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are 5 female breast cancer studies currently in progress (Davis; London; Fechting; Demers and Weis; and Long Island Breast Cancer study). These studies have better exposure assessment protocols and are collecting important risk factors to adequately assess confounding. There are no male breast cancer studies currently in progress.	(I1) If all 5 studies showed an association this would drive policy; otherwise the question would remain open.

TABLE 11.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Somewhat likely for female breast cancer, depending on the design of future studies. Studies need large number of women in EMF-related jobs defined specifically for women, not men, for occupational studies and residential studies that estimate personal exposures. Also, the new studies should take into account shift work or light at night, include residential and occupational exposures, define exposures that may capture a dose-response, and evaluate timing, assess potential confounders adequately, and assess menopausal status as well as disease estrogen-receptor status.	(I1) Studies are worth pursuing, especially for female breast cancer.

11.5 Conclusions on Scientifically Relevant Issues

11.5.1 Dose-Response Issues

The associations reported for residential power lines, electrical bed heaters, and occupational exposures (utility workers with assumed high EMF levels) are all close to the resolution power of the studies. If there is any effect, it does not seem to increase monotonically with dose, although, due to the crude assessment of exposure, the evidentiary base is insufficient for identifying either thresholds or plateaus of effect. Even though there is a plausible biological model with some support from animal studies, it may be difficult to capture even a dose response in bioassay studies that are designed with the assumption that high doses will produce an obvious effect even in a few hundred animals. The component of the electric magnetic field that may be a biologically active agent has not be adequately explored because all studies only assessed surrogate estimates for exposure.

11.5.2 Research Policy

No studies are currently in the pipeline for male breast cancer. There are five epidemiological female breast cancers in the pipeline. If all five studies result in positive findings, this would change the overall policy assessment because these studies are using better exposure assessment and are better able to address confounding compared to the currently published studies. A few large job-matrix studies designed for female occupations and using various summary exposure metrics would allow one to reanalyze the current large case-control studies to determine what aspects of the EMF mixture might better explain the associations seen with breast cancer and other diseases. From a policy and logistic point of view, female breast cancer studies are a high priority, due to the prevalence of the disease. The evidence for an association with the surrogate estimates of EMF is compatible with a 1.12-fold relative risk for females, which if true, would be of regulatory concern for long-term environmental and occupational exposures, especially for females.

12.0 ALL CANCERS

STATEMENT TO THE PUBLIC

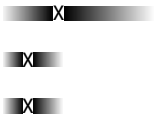
EMFs as a general cancer risk

The reviewers used two distinct sets of guidelines to evaluate the evidence:

Using the traditional guidelines of the International Agency for Research on Cancer, they considered the evidence as "inadequate" to implicate EMFs.

- *Using the Guidelines developed especially for the California EMF Program, they concluded that they "strongly believe that exposure to EMFs at home or work do not add" to an individual lifetime risk of contracting cancers of any kind, other than those specifically in this document.*

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY IN CAUSALITY FOR POLICY ANALYSIS
Do EMFs increase the risk of all cancers?	1	3	Strongly believe not	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	2	3	Strongly believe not	
	3	3	Strongly believe not	



12.1 EVIDENTIARY BASE

Several studies on utility workers (Miller et al., 1996) have reported a number of associations with cancers other than those for which a clear hypothetical risk has been established (leukemia, CNS/brain, breast). However, only one study (Floderus et al., 1999) looked systematically at incidence rates for all cancer sites. The study explored the correlation between cancer incidence and exposure in occupations reported in census forms, assessed using a job exposure matrix.

The strengths of this study include:

- Large numbers (1,596,959 men and 806,278 women)
- Good data bases

The main weaknesses are:

- Registry, census-based study
- Coarse job-matrix exposure assessment (low, medium, high)

Summary of results:

- No dose-response relationship
- About 10% increase in risk in medium- and high-exposure groups
- Clear differences between results for men and women

Notable associations found in men:

- Colon
- Biliary passages and liver
- Larynx and lung
- Testis and kidney
- Urinary organs
- Malignant melanoma
- Non-melanoma skin cancer
- Astrocytoma III-IV

Notable associations found in women:

- Lung
- Breast
- Corpus uteri
- Malignant melanoma
- Chronic lymphocytic leukemia

The authors suggest that their results point to a possible interaction with the endocrine/immune system.

12.1.1 SUMMARY OF THE EVIDENCE

Figure 12.1.1

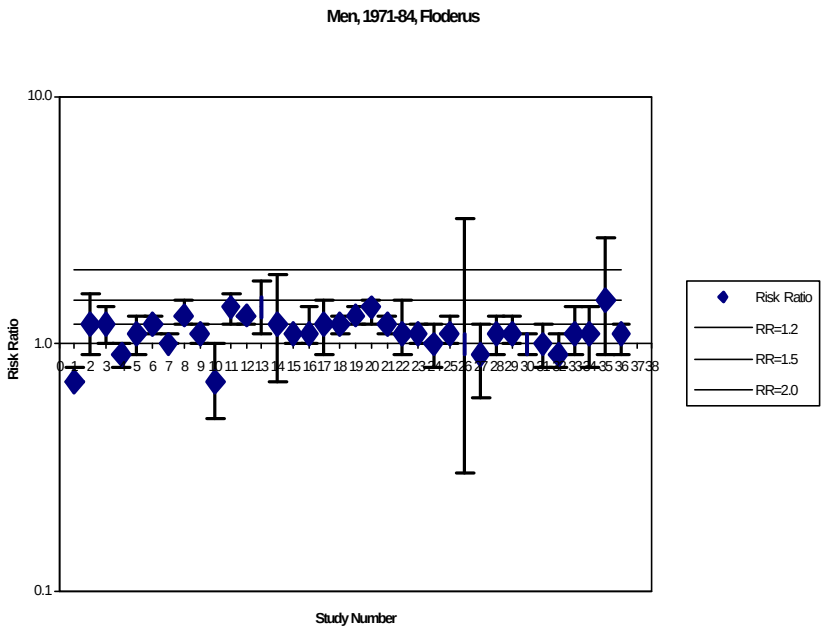


TABLE 12.1.1 MEN 1971-84

CANCER TYPE	STUDY NUMBER	N	INDIV. RISK RATIO, MEAN	LOWER CL	UPPER CL
Buccal cavity	1	253	0.7	0.7	0.8
Pharynx	2	91	1.2	0.9	1.6
Esophagus	3	315	1.2	1.0	1.4
Stomach	4	1,393	0.9	0.8	1.0
Small intestine	5	147	1.1	0.9	1.3
Colon	6	1,774	1.2	1.1	1.3
Rectum	7	1,360	1.0	1.0	1.1
Biliary passage & liver	8	588	1.3	1.2	1.5
Pancreas	9	941	1.1	1.0	1.2
Nose & nasal sinuses	10	71	0.7	0.5	1.0
Larynx	11	421	1.4	1.2	1.6
Lung, primary	12	2,999	1.3	1.2	1.3
Lung, other	13	129	1.4	1.1	1.8
Breast	14	37	1.2	0.7	1.9
Prostate	15	3,409	1.1	1.0	1.1
Testes	16	303	1.1	1.0	1.4
Other male genital organs	17	150	1.2	0.9	1.5
Kidney	18	1,343	1.2	1.1	1.3
Urinary organs excl. kidney	19	1,791	1.3	1.2	1.4
Malignant melanoma, skin	20	1,097	1.4	1.2	1.5
Non-melanoma skin cancer	21	1,240	1.2	1.1	1.3
Eye	22	104	1.1	0.9	1.5
Nervous system	23	1,100	1.1	1.0	1.2
Thyroid gland	24	200	1.0	0.8	1.2
Other endocrine glands	25	437	1.1	1.0	1.3
Phaeochromocytoma	26	5	1.0	0.3	3.2
Bone	27	80	0.9	0.6	1.2
Connective tissue, muscle	28	228	1.1	0.9	1.3
Connective tissue, other/unspec.	29	694	1.1	1.0	1.3
Malignant non-Hodgkin's lymphoma	30	776	1.0	0.9	1.1
Hodgkin's disease	31	257	1.0	0.8	1.2
Multiple myeloma, plasmocytoma	32	391	0.9	0.8	1.1
Acute myeloid leukemia	33	199	1.1	0.9	1.4
Chronic myeloid leukemia	34	116	1.1	0.8	1.4
Acute lymphoblastic leukemia	35	32	1.5	0.9	2.7
Chronic lymphocytic leukemia	36	301	1.1	0.9	1.2

Figure 12.1.2

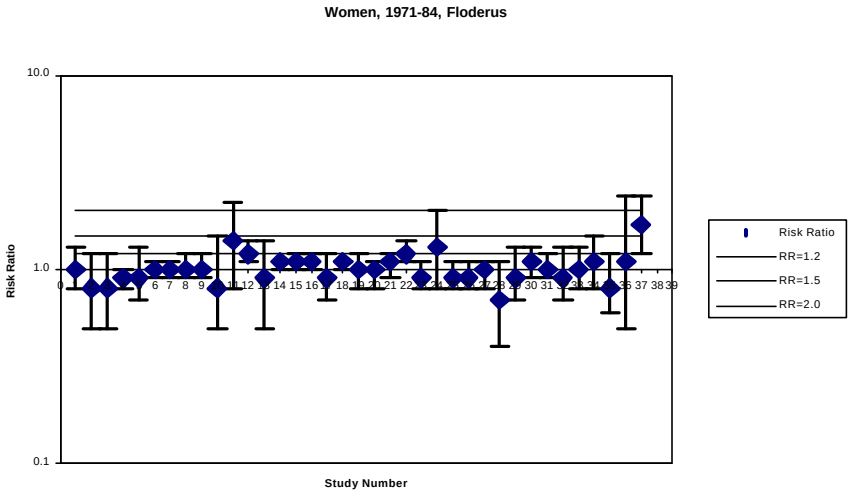


TABLE 12.1.2 WOMEN 1971-84

CANCER TYPE	STUDY NUMBER	N	INDIV. RISK RATIO, MEAN	LOWER CL	UPPER CL
Buccal cavity	1	128	1.0	0.8	1.3
Pharynx	2	36	0.8	0.5	1.2
Esophagus	3	40	0.8	0.5	1.2
Stomach	4	442	0.9	0.8	1.0
Small intestine	5	64	0.9	0.7	1.3
Colon	6	1,018	1.0	0.9	1.1
Rectum	7	603	1.0	0.9	1.1
Biliary passage & liver, primary	8	398	1.0	0.9	1.2
Pancreas	9	394	1.0	0.9	1.2
Nose & nasal sinuses	10	21	0.8	0.5	1.5
Larynx	11	37	1.4	0.8	2.2
Lung, primary	12	646	1.2	1.1	1.4
Lung, other	13	32	0.9	0.5	1.4
Breast	14	4,886	1.1	1.0	1.1
Cervix uteri	15	909	1.1	1.0	1.2
Corpus uteri	16	1,368	1.1	1.0	1.2
Uterus, part unspecified	17	130	0.9	0.7	1.2
Ovary, tube & broad ligament	18	1,479	1.1	1.0	1.1
Other female genital	19	188	1.0	0.8	1.2
Kidney	20	4,161	1.0	0.8	1.1
Urinary organs excl. kidney	21	306	1.1	0.9	1.2
Malignant melanoma, skin	22	657	1.2	1.1	1.4
Non-melanoma skin cancer	23	481	0.9	0.8	1.1
Eye	24	47	1.3	0.8	2.0
Nervous system	25	598	0.9	0.8	1.1
Thyroid	26	275	0.9	0.8	1.1
Other endocrine glands	27	457	1.0	0.8	1.1
Bone	28	28	0.7	0.4	1.1
Connective tissue, muscle	29	98	0.9	0.7	1.3
Connective tissue, other & unspec.	30	412	1.1	0.9	1.3
Malignant non-Hodgkin's lymphoma	31	297	1.0	0.9	1.2

CANCER TYPE	STUDY NUMBER	N	INDIV. RISK RATIO, MEAN	LOWER CL	UPPER CL
Hodgkin's disease	32	72	0.9	0.7	1.3
Multiple myeloma, plasmocytoma	33	187	1.0	0.8	1.3
Acute myeloid leukemia	34	107	1.1	0.8	1.5
Chronic myeloid leukemia	35	57	0.8	0.6	1.2
Acute lymphoblastic leukemia	36	12	1.1	0.5	2.4
Chronic lymphocytic leukemia	37	87	1.7	1.2	2.4

1 For this evaluation the reviewers will exclude from the above data all information
2 relating to the cancers individually evaluated elsewhere in this document

12.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 12.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the results are not statistically significant.	(F1) The commonly chosen 95% level of significance is a safeguard against false positives, but may result in many false negatives if not accompanied by an equally high statistical power. Many elevated ORs argue at least for further investigation	(C1) The database is very limited and chance cannot be excluded as an explanation, but cannot be confidently assumed as THE obvious explanation. Some results are suggestive of an association; some are statistically significant and deserve more attention. On the whole, it may be said that "something seems to be going on here," but the evidence is not statistically stable enough to affect the reviewers prior.

TABLE 12.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) This is a registry-based study, where many biases may have crept in.	(F1) Biases can affect the risk estimates in either direction.	(C1) There is no reason to believe that biases are more likely to be responsible for an association, rather than diminishing or masking one.

TABLE 12.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See argument for bias.	See argument for bias.	See discussion for bias.

TABLE 12.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the positive associations are not strong, which decreases confidence that they are not due to artifacts.	(F1) If the effect is intrinsically weak, the association is correspondingly weak. This cannot be construed against causality.	(C1) If the association is intrinsically weak, low ORs cannot be construed as an argument against causality. While a strong relative risk would increase confidence in the hypothesis, there is no reason why the opposite should decrease it.
	(F2) The inevitably poor exposure assessment in occupational studies is very likely to result in a strong bias toward the null.	
	(F3) Some associations are quite strong.	
	(F4) Most hazardous agents at ambient doses do not produce strong risks.	

TABLE 12.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no consistency in the pattern of results.	(F1) It is true that the pattern of results for women is inconsistent and compatible with the null hypothesis.	(C1) There appears to be a clear difference between the results for the two genders. There really is no evidence to support the hypothesis that EMF exposure is a broadband risk factor for all cancer in women. However, the pattern of results for men is quite different and suggestive of a risk for a number of cancers.
	(F2) The pattern of results for men is quite different. The number of risk estimates above 1 is far greater than what would be expected by chance (p = 0.003)	

TABLE 12.2.6

COHERENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The results for women and men are clearly heterogeneous. The heterogeneity of the results along gender lines, unless supported by a biological explanation, argues against causality.	(F1) The results are homogeneous when stratified by gender. The results for men are very clearly distributed about an OR of 1.15 (on a log scale), with 50% of the studies being in an interval between 1 and 1.2.	(C1) The results for women are clearly consistent with no effect. Although the results for men are more consistently elevated, they do not appear to be randomly distributed about a clear maximum-likelihood value. The mode is about 1, but there is a clear tail of elevated risks, without a corresponding tail of ORs lower than 1. Since the results refer to different clinical endpoints, this asymmetry should not be seen as inconsistent with a true effect. Although a clear pattern is not seen, the authors of the study suggest that cancers of the reproductive system and other hormone-mediated cancers are more clearly associated with EMF exposure. This, or similar theories, may explain the skewed distribution of the results.
	(F2) This is a study on multiple endpoints. There is no reason to expect homogenous results.	(C2) Since this evaluation is based on a single study, there is no way to determine whether the internal discrepancies are more likely to be due artifact or reflect real differences between endpoint and gender susceptibility. This must be regarded as a hypothesis-generating study.

TABLE 12.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no dose-response trend. On the contrary, the risk estimates for the medium-exposure group are usually higher than those for the high-exposure group	(F1) Theoretical data show that misclassification of exposure may increase risk estimate in intermediate exposure category (Dosemeci et al., 1990), (DelPizzo & Salzberg, 1992).	(C1) The pattern of the highest risk estimates appearing in the medium exposure group has been observed in many other occupational studies and has been attributed to misclassification. Nevertheless, the absence of a trend must affect the credibility of the data.

TABLE 12.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
N.A.	N.A.	N.A.

TABLE 12.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 12.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 12.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 12.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 12.2.13

SPECIFICITY AND ASSOCIATIONS WITH OTHER DISEASES		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 12.2.14

SUMMARY TABLE FOR THE DISEASES CONSIDERED HERE			
	HOW LIKELY IS THIS PATTERN OF EVIDENCE UNDER:		
	THE "NO EFFECT" HYPOTHESIS	THE CAUSAL HYPOTHESIS	EFFECT ON CONFIDENCE
Chance.	Possible	Possible	No impact
Bias.	Possible	Possible	No impact
Confounding.	Possible	Possible	No impact
Combined chance, bias, confounding.	Possible	Possible	No Impact
Strength of association.	Possible	Possible	No impact
Consistency.	Very likely for women Unlikely for men	Unlikely for women Very likely for men	Lowers prior confidence that EMFs increase the risk of all cancers in women Increases our confidence substantially that EMFs increase the risk of many cancers in men
Coherence.	Possible	Possible	Decreases the confidence of EMF as a broadband cancer risk in women. Increases the confidence in EMF as a risk factor for many cancers in men.
Dose response.	Possible	Possible	No impact
Coherence/visibility.	Possible	Possible	No impact
Experimental evidence.	Unlikely	Possible	Increases confidence
Plausibility.	Possible	Possible	No impact
Analogy.	Possible	Possible	No impact
Temporality.	Possible	Possible	No impact
Specificity and associations with other Diseases.	Possible	Likely	No impact or slight increase

12.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

12.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

REVIEWER 1 (DELPIZZO)

All cancers

Degree of Certainty: After eliminating the cancers evaluated individually in this document, there are more risk estimates > 1 than < 1, but not enough to rule out chance as an explanation. Although Floderus's results raise interesting hypotheses to explore (see pro and con arguments above), they do not provide evidence that EMFs are a broadband cancer risk. For Reviewer 1 the evaluation is: "strongly believe that EMFs do not add to the risk" of all cancers. For the purpose of decision analysis, numerical values of 0 to 10 are defensible with a median estimate of 6 out of 100.

IARC Classification: "inadequate."

REVIEWER 2 (NEUTRA)

Degree of Certainty: The pattern of associations does not suggest that all types of cancer are associated with EMF-related jobs. In women the number of cancers with associations above the null is about the same as the associations below the null. In men there are somewhat more cancers with associations above the null than expected, but not all cancers are elevated. This evidence has moved the degree of certainty to about 3 out of 100, with a range from 1 to 10. The evidence for the cancers that were above the null, other than those already discussed, is not extensive enough to move confidence above the prior confidence for those conditions.

IARC Classification: The animal, mechanistic and epidemiological evidence does not point towards EMFs as a universal carcinogen, so the evidence is "inadequate" to implicate EMFs in this way.

REVIEWER 3 (LEE)

Degree of Certainty: The human evidence of the other cancers is based mainly on one study where very weak associations for surrogate occupational exposures, mostly among men, were found. Hence, Reviewer 3's prior for a weak relative risk is slightly increased by a weak positive-association pattern across studies and by the positive association found for childhood leukemia and adult brain cancer. However, this reviewer's prior is considerably decreased by the fact that the evidence is based on one study assessing multiple conditions. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "improbable that it is a cause" category. The range of uncertainty about the evidence using this reviewer's median prior is 4 to 7 with a median at 3.

IARC Classification: The human evidence is weak (based on one study) where chance, bias, and confounding cannot be ruled out. Also, the animal evidence is lacking and there is no sound mechanistic rationale. Given this, the evidence, as a whole, is sufficient for a classification of "not classifiable."

12.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIEWER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY IN CAUSALITY FOR POLICY ANALYSIS
				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
Do EMFs increase the risk of all cancers?	1	3	Strongly believe not	
	2	3	Strongly believe not	
	3	3	Strongly believe not	

12.4 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 12.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 12.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 12.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 12.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 12.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 12.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
Not applicable.	Not applicable.

TABLE 12.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 12.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
None, until present study is replicated.	None.

TABLE 12.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
None.	None.

TABLE 12.4.10

CAPABILITY OF CHANGING ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are no similar studies in progress; therefore, it is not envisaged that this evaluation can be changed in the foreseeable future.	None.

TABLE 12.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Very likely.	None for now.

13.0 MISCARRIAGE

STATEMENT TO THE PUBLIC

The reviewers expressed their judgments using two distinct sets of guidelines to evaluate the evidence:

- ***Using the traditional guidelines of the International Agency for Research on Cancer (IARC), they considered EMFs as a "possible risk" for miscarriage, category 2B. (IARC itself only evaluates cancer and did not discuss miscarriage. The National Institutes for Environmental Health Sciences classified the evidence as "inadequate.")***
- ***Using the Guidelines developed especially for the California EMF program, all of the reviewers were "close to the dividing line between believing or not believing" that high residential or occupational EMFs cause some degree of increased risk of miscarriage.***

There are several reasons for the differences between the DHS reviewers and those of NIEHS. First, the two large miscarriage studies by Lee et al. and Li et al. had not yet come out at the time of the NIEHS review. Second, the three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them. While rodent and chicken egg studies provide little or no support for EMF effects, some studies on early-model higher emitting video display terminals (VDTs) and two new epidemiology studies in humans suggest that EMFs might cause a substantial proportion of miscarriages. Miscarriages are common in any case (about 10 per 100 clinically diagnosed pregnancies) and the theoretical added risk for an EMF-exposed pregnant woman might be an additional 10 per 100 pregnancies according to these two studies. If truly causal this could clearly be of concern to individuals and regulators. However, the type of EMF exposures implicated by these two new epidemiological studies (short, very high exposures) probably come from being within a few inches of some appliances and unusual configurations of wiring in walls and grounded plumbing, and only rarely from power lines. Since the majority of us come into contact with non-obvious sources of these fields on a daily basis, it may not be possible to avoid the majority of such exposures in modern life, even if we avoided the obvious sources like appliances.

Seventy-five percent of the women in the studies had at least one of these brief high exposures during a given day. Even one exposure a day, if experienced regularly during pregnancy, seemed to increase the risk of miscarriage. Nonetheless, the majority of pregnant women with such exposures did NOT miscarry.

The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the added personal risk suggested by the epidemiological studies was "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. The three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar: The differences in certainty between the three reviewers arises primarily from how sure they were that they could rule out study flaws or other explanatory agents and how much the evidence on one disease influenced certainty in the findings for other diseases.

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Spontaneous Abortion				0 5 10 1 5 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

13.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

TABLE 13.1.1 VDT AND SPONTANEOUS ABORTION STUDIES

STUDY NAME, INFORMATION	DESCRIPTION	STUDY NUMBER	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Ericson & Kallen, 1986a)	>20 hrs/week	1	1.20	0.90	1.70
(Ericson & Kallen, 1986b)	High	2	1.1	0.9	1.2
(McDonald, Cherry & Delorme, 1986)	30 hrs vs. none	3	1.1	0.9	1.4
(Goldhaber, Polen & Hiatt, 1988)	>20 hrs/week	4	1.8	1.2	2.8
(McDonald, 1988)	>15 hrs vs. none	5	1.23	1.1	1.4
(Bryant & Love, 1989)	>20 hrs/week	6	1.1	0.6	2
(Windham et al., 1990)	>=20 hrs/week	7	1.3	0.9	1.8
(Nielsen & Brandt, 1990)	21-30 hrs/week	8	1.12	0.76	1.65
(Roman et al., 1992)	>=21 hrs/week	9	0.9	0.5	1.6
(Lindbohm et al., 1992)	Measurement of VDT models	10	3.40	1.40	8.60
(Schnorr et al., 1991)	High model vs. low model, >=25 hrs	11	1.00	0.61	1.64

Figure 13.1.1 and Table 13.1.1 show the reported relative risks (RRs) of spontaneous abortions (SAB) conveyed by VDT use from 11 studies. The first 9 studies assessed exposure as hours of use, the 11th study (Schnorr, 1991) compared users of two different types of VDTs where one was incorrectly assumed to emit higher low frequency fields than the other, and the 10th study (Lindbohm, 1992) actually assigned exposure based on the laboratory measurements of the user's VDT model. Nine out of 11 VDT studies were above an RR of 1.0 (p = 0.03) while 4 out of 11 were above an RR 1.2 (p = 0.16). Only 1 of the 11 studies had an RR above 1.5. The pattern associated with VDT use and miscarriage is slightly above the "no-effect" RR.

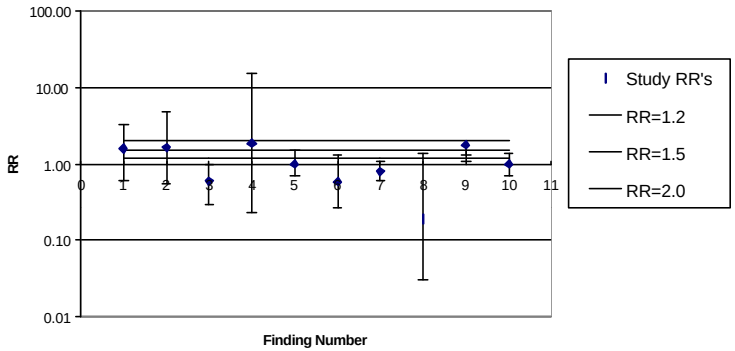


Figure 13.1.2 Electric Bed Heater and Home Cable Heat and Spontaneous Abortions Studies

TABLE 13.1.2 ELECTRIC BED HEATER AND HOME CABLE HEAT AND SPONTANEOUS ABORTION STUDIES

STUDY NUMBER	REFERENCE	FINDING NUMBER	EXPOSURE	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
1	(Lee et al., 2000)	1	Electric blanket	High setting	1.60	0.60	3.30
2	(Belanger et al., 1998)	2	Electric blanket	High setting	1.65	0.56	4.86
1	(Lee et al., 2000)	3	Electric blanket	>= 6 hrs	0.60	0.30	1.00
2	(Belanger et al., 1998)	4	Electric blanket	>= 8 hrs	1.87	0.23	15.48
1	(Lee et al., 2000)	5	Water bed	High setting	1.00	0.70	1.50
2	(Belanger et al., 1998)	6	Waterbed	High setting	0.59	0.27	1.30
1	(Lee et al., 2000)	7	Waterbed	>= 8 hrs	0.80	0.60	1.10
2	(Belanger et al., 1998)	8	Waterbed	>= 8 hrs	0.19	0.03	1.40
3	(Wertheimer & Leeper, 1989)	9	Electric bed heater	Use	1.80	1.10	1.30
3	(Wertheimer & Leeper, 1986)	10	Home cable heat	Own	1.00	0.70	1.40

Figure 13.1.2 and Table 13.1.2 show the reported RR of SAB conveyed by home electric bed heaters (3 studies) and home electric cable heat (1 study). No matter how one evaluates these electrical devices (e.g., grouped by setting; grouped by hours of use) the pattern is inconsistent.

Figure 13.1.2 SAB and Residential Spot Measurements and Wirecodes

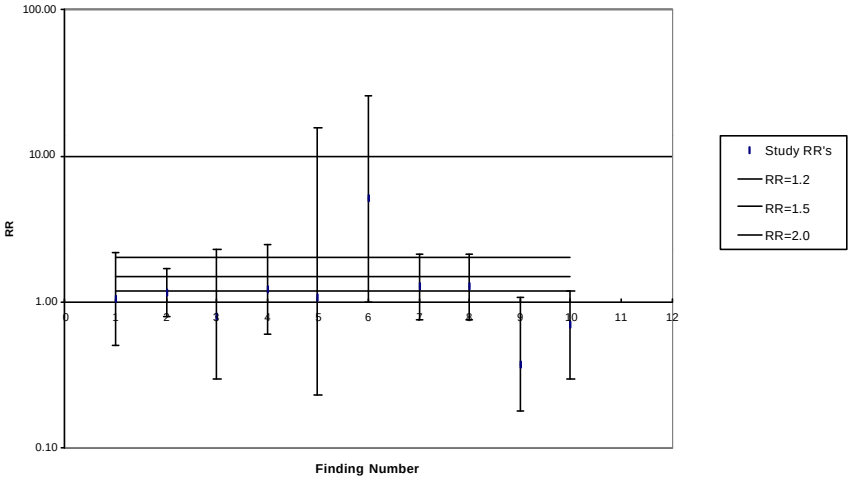


TABLE 13.1.3 SAB AND RESIDENTIAL SPOT MEASUREMENTS AND WIRE CODES

STUDY NUMBER	REFERENCE	FINDING NUMBER	EXPOSURE	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
1	(Lee et al., 2000)	1	Inside Spots	>= 2.0 mG	1.05	0.51	2.19
2	(Li et al., 2002)	2	Inside Spots	>= 0.4 mG	1.15	0.79	1.68
3	(Savitz, 1994)	3	Inside Spots	>= 2 mG	0.80	0.30	2.30
1	(Lee et al., 2000)	4	Front Door Spots	>= 2.0 mG	1.22	0.60	2.49
2	(Li et al., 2002)	5	Front Door Spots	>= 0.55 mG	1.07	0.23	15.48
4	(Juutilainen et al., 1993)	6	Front Door Spots	>= 6.3 mG	5.09	1.00	26.00
1	(Lee et al., 2000)	7	Wire Code	Vh vs. Buried	1.27	0.76	2.14
2	(Li et al., 2002)	8	Wire Code	Vh vs. Buried	1.27	0.76	2.14
5	(Belanger et al., 1998)	9	Wire Code	Vh vs. Buried	0.37	0.18	1.09
3	(Savitz, 1994)	10	Wire Code	High vs. Low	0.70	0.30	1.18

Figure 13.1.3 and Table 13.1.3 show the reported RR of SAB conveyed by residential magnetic field estimates (wire codes and home area measurements). Overall, the pattern is inconsistent for these studies. Only one study found a moderate RR for a high front door measure; this study assessed pre-clinical spontaneous abortions while the others assessed clinical spontaneous abortions.

Figure 13.1.4 and Table 13.1.4 show the progression of RRs from lowest to highest quartile of the 24-hour personal maximum magnetic field exposures for the two studies (Lee, 2000b) and (Li 2000) that assessed the relationship of personal magnetic field measures and SAB. Lee and coworkers found a trend for progressively higher RRs with higher quartiles using measures below the 25th percentile value as the reference exposure while Li and coworkers found a plateau effect above the 25th percentile value.

How do these two studies relate to the many previous studies? The fact that wire code in these studies was NOT associated with maximum field (it is the rare power line, which delivers magnetic fields as high as 16 mG) makes it understandable that wire codes were also not clearly associated with miscarriage. The TWA was moderately correlated with maximum field, and the TWA was only weakly associated with miscarriage as with those found for some of the VDT and electric bed heater studies. Perhaps the predominance of RRs above 1.0 found for the VDT studies is reflecting an association with maximum fields and its EMF correlates, or some systematic bias.

Figure 13.1.3
Personal Maximum Dose Response and Spontaneous Abortions

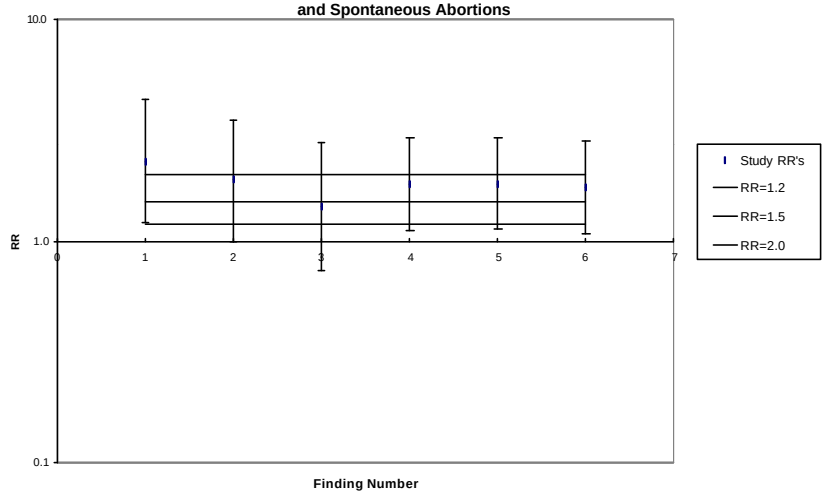


TABLE 13.1.4 PERSONAL MAXIMUM DOSE-RESPONSE AND SPONTANEOUS ABORTION

FINDING NUMBER	REFERENCE	FINDING NUMBER	EXPOSURE	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
1	(Lee et al., 2000)	1	Personal Max	35.05 +	2.30	1.21	4.36
2	(Lee et al., 2000)	2	Personal Max	23.42 – < 35.05	1.90	1.00	3.50
3	(Lee et al., 2000)	3	Personal Max	14.31 – < 23.43	1.44	0.74	2.80
4	(Li et al., 2002)	4	Personal Max	49 +	1.81	1.12	2.95
5	(Li et al., 2002)	5	Personal Max	27 – < 49	1.83	1.14	2.96
6	(Li et al., 2002)	6	Personal Max	16 – < 27	1.76	1.08	2.86

TABLE 13.1.5 ADJUSTED ODDS RATIO (OR) OR RELATIVE RISK (RR) AND 95% CONFIDENCE INTERVAL (C.I.) OF THE ASSOCIATION BETWEEN TOTAL 24-HOUR PERSONAL MAGNETIC FIELD RATE OF CHANGE METRIC (RCM), MAXIMUM (MAX.) VALUE, AND TIME WEIGHTED-AVERAGE (TWA) OF SPONTANEOUS ABORTION BY QUALITIES FOR THE TWO PERSONAL MEASUREMENT STUDIES

Lee et al.					**Li et. al.**				
Max Value		Number	Percent	Adjusted OR * (95% C.I.)	**Max Value**		Number	Percent	Adjusted RR (95% C.I.)
35.05+	Case	39.0	29.8	2.30 (1.21-4.36)	49 +	Case	42	17.7	1.81 (1.12-2.95)
	Control	115.0	23.8			Control	196	82.4	
23.42 – < 35.05	Case	38.0	29.0	1.90 (1.00-3.51)	27-49	Case	48	19.8	1.83 (1.14-2.96)
	Control	115.0	23.8			Control	195	80.3	
14.31 – < 23.43	Case	33.0	25.2	1.44 (0.74-2.80)	16-27	Case	42	17.8	1.76 (1.08-2.86)
	Control	121.0	25.1			Control	194	82.2	
<14.31	Case	21.0	16.0	1.00 (Reference)	< 16	Case	27	10.7	1.00 (Reference)
	Control	132.0	23.8			Control	225	89.3	
RCM Value		Number	Percent	Adjusted OR * (95% C.I.)					
0.94+	Case	46.0	35.1	3.08 (1.59-5.95)					
	Control	109.0	22.5						
0.62 – < 0.94	Case	37.0	28.2	2.29 (1.19-4.40)					
	Control	118.0	24.4						
0.43 – < 0.62	Case	31.0	23.7	1.53 (0.768-3.05)					
	Control	126.0	26.0						
<0.43	Case	17.0	13.0	1.00 (Reference)					
	Control	131.0	23.8						
TWA		Number	Percent	Adjusted OR * (95% C.I.)					
1.28 +	Case	35.0	26.7	1.68 (0.87-3.23)					
	Control	123.0	25.5						
0.93 – < 1.28	Case	37.0	28.2	1.74 (0.92-3.30)					
	Control	114.0	23.6						
0.72 – < 0.93	Case	36.0	27.5	1.73 (0.91-3.26)					
	Control	122.0	25.3						
< 0.72	Case	23.0	17.6	1.00 (Reference)					
	Control	124.0	25.7						

* Adjusted for: maternal age, interview at gestation, coffee consumption at conception, income, race, and Kaiser facility
**Adjusted for: each of the variables listed above and the other personal metric

TABLE 13.1.6 SUMMARY OF SPONTANEOUS ABORTION STUDIES

STUDY NUMBER	REFERENCE	MEASURE TYPE	EXPOSURE	ODDS RATIO	LOWER CL	UPPER CL
1	(Lee et al., 2002)	TWA Personal	1.28 +	1.68	0.87	3.23
		TWA Personal	0.93 – < 1.28	1.74	0.92	3.30
		TWA Personal	0.72 – < 0.93	1.73	0.91	3.26
2	(Li et al., 2002)	TWA Personal	0.44	1.20	0.80	1.80
1	(Lee et al., 2002)	Max Value Personal	49 +	2.30	1.21	4.36
		Max Value Personal	21 – < 49	1.90	1.00	3.51
		Max Value Personal	16 – < 27	1.44	0.74	2.80
2	(Li et al., 2002)	Max Value Personal	35.05 +	1.81	1.12	2.95
		Max Value Personal	23.42 – < 35.05	1.83	1.14	2.96
		Max Value Personal	14.31 – < 23.43	1.76	1.08	2.86
1	(Lee et al., 2002)	RCM Personal	0.94 +	3.08	1.59	5.95
		RCM Personal	0.62 – < 0.94	2.29	1.19	4.40
		RCM Personal	0.42 – < o.62	1.53	0.77	3.05
1	(Lee et al., 2002)	Inside Spots	<0.43	1.05	0.51	2.19
2	(Li et al., 2002)	Inside Spots	0.44	1.15	0.79	1.68
3	(Savitz, 1994)	Inside Spots	2.0	0.80	0.30	2.30
1	(Lee et al., 2002)	Front Door Spots	2.0	1.22	0.60	2.49
2	(Li et al., 2002)	Front Door Spots	0.55 mG	1.07	0.74	1.54
3	(Juutilainen et al., 1993)	Front Door Spots	6.3	5.09	1.00	26.00
1	(Lee et al., 2002)	Wire Code	VHCC	1.27	0.74	2.20
			OHCC	0.94	0.58	1.51
			OLCC	1.01	0.65	1.57

TABLE 13.1.6 SUMMARY OF SPONTANEOUS ABORTION STUDIES (CONT.)

STUDY NUMBER	REFERENCE	MEASURE TYPE	EXPOSURE	ODDS RATIO	LOWER CL	UPPER CL
2	(Li et al., 2002)	Wire code	VHCC	1.27	0.76	2.14
			OHCC	0.95	0.61	1.48
			OLCC	0.95	0.60	1.49
			VLCC	1.42	0.76	2.66
4	(Belanger et al., 1998)	Wire code	VHCC	0.37	0.18	1.09
3	(Savitz, 1994)	Wire code	High	0.70	0.30	1.18
3			Med	0.60	0.30	1.10
5	(Lee et al., 2000)	Electric blanket setting	Low	0.50	0.30	0.90
			Med	1.00	0.50	1.80
			High	1.60	0.60	3.30
4	(Belanger et al., 1998)	Electric blanket setting	None	1.00	1.00	1.00
			Daily low	1.34	0.47	3.86
			Daily high	1.65	0.56	4.86
5	(Lee et al., 2000)	Electric blanket hours	1	1.40	0.70	3.10
			2-5	0.70	0.30	2.00
			6+	0.60	0.30	1.00
4	(Belanger et al., 1998)	Electric blanket hours	None	1.00	1.00	1.00
			<8	1.45	0.63	3.25
			8	1.87	0.23	15.48
5	(Lee et al., 2000)	Waterbed setting	Low	1.00	0.60	1.80
			Med	6.20	0.40	0.90
			High	1.00	0.70	1.50

TABLE 13.1.6 SUMMARY OF SPONTANEOUS ABORTION STUDIES (CONT.)

STUDY NUMBER	REFERENCE	MEASURE TYPE	EXPOSURE	ODDS RATIO	LOWER CL	UPPER CL
4	(Belanger et al., 1998)	Waterbed setting	None	1.00	1.00	1.00
			Daily Low	0.70	0.27	1.77
			Daily High	0.59	0.27	1.30
5	(Lee et al., 2000)	Waterbed hours	<8	0.60	0.30	1.10
			8	0.80	0.60	1.10
4	(Belanger et al., 1998)	Waterbed hours	None	1.00	1.00	1.00
			<8	0.77	0.40	1.47
			8	0.19	0.03	1.40
6	(Lindbohm et al., 1992)	VDT, MF flux density	<0.4uT	1.00	1.00	1.00
			0.4-0.9	1.90	0.90	3.90
			>0.9	3.40	1.40	8.60
7	(Schnorr et al., 1991)	VDT Hours	None	1.00	1.00	1.00
			1-25	1.04	0.61	1.79
			25+	1.00	0.61	1.64
8	(Ericson & Kallen, 1986a)	VDT hours	>20 hrs/ week	1.20	0.90	1.70
9	(Ericson & Kallen, 1986b)	VDT hours	High	1.1	0.9	1.2
10	(McDonald et al., 1986)	VDT hours	30 hrs vs. none	1.1	0.9	1.4
11	(Goldhaber et al., 1988)	VDT hours	>20 hrs/ week	1.8	1.2	2.8
12	(McDonald, 1988)	VDT hours	>15 hrs vs none	1.23	1.1	1.4
13	(Bryant & Love, 1989)	VDT hours	>20 hrs/ week	1.1	0.6	2
14	(Windham et al., 1990)	VDT hours	20 hrs/week	1.3	0.9	1.8
15	(Nielsen & Brandt, 1990)	VDT hours	21-30 hrs/week	1.12	0.76	1.65
17	(Roman et al., 1992)	VDT hours	21 hrs/week	0.9	0.5	1.6

13.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 13.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the VDT, wire code, and the electric bed heater study results are not statistically significant.	(F1) Although not all the positive VDT studies were significant, the number of studies above a relative risk of 1.0 (9 out of 11 VDT) showed a significant pattern (p= 0.03). Given the different populations and indirect methods of assessing VDT use, not all studies are expected to be significant.	(C1) Chance alone is an unlikely explanation for the consistent positive associations for the VDT studies and the significant positive results of the two personal measurement studies where the studies had sufficient power to assess weak to moderate positive associations.
(A2) Many of these studies, especially the studies assessing personal measurements, have multiple comparisons and more than one way of dichotomizing the distributions of the exposures examined. This makes significant "p-values" less impressive.	(F2) For the two personal measurement studies (Lee, 2002), (Li, 2002), all comparisons were based on *a prior* hypothesis. The positive associations found were significant and consistent with each other. Furthermore, Lee et al. (Lee, 2000) reported Chi Square for trend p-values of less than 0.001 for the personal magnetic field and maximum and rate of change metric (RCM) values; this is unlikely to be explained by multiple comparisons of three personal metrics.	
(A3) The Li (Li et al., 2002) study used a post hoc cutpoint of 16 mG.	(F3) Examination of the cumulative distributions of the maximum field in the two personal measurement studies (Lee, 2002), (Li, 2002) and the RCM in the Lee (Lee, 2000) study does not suggest that results would be very sensitive to the choice of cutpoints. Li's 16 mG was the 25th percentile for the cohort.	

TABLE 13.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The VDT studies may be the result of recall bias; women self-reported VDT use some time after the index pregnancy was complete. It is highly likely that women who had a spontaneous abortion were more likely to report VDT use than those who had live births, since the event of an abortion may trigger better recall of VDT use.	(F1) Recall bias is a definite possibility for most of these VDT studies. Non-differential misclassification bias may also play a major role in all these VDT studies under-estimating the true effects since VDT use is a very crude estimate of exposure during the first trimester.	(C1) If there is any bias in these studies, it is downward because of non-differential exposure misclassification, which also will distort dose response relationships. Recall bias is possible in the VDT studies.
(A2) Both of the personal measurement studies, (Lee, 2002) and (Li et al., 2002), had low participation response rates. This leaves more room for potential differential participation of cases and non-cases with regard to EMF exposure.	(F2) Studies like the two personal measurement studies require substantial subject cooperation and thus have high non-participation rates (Lee et al., 2002; Li et al., 2002). However it is unlikely that participants could know enough about EMF sources that produce brief high fields to differentially influence the decisions of cases and non-cases to enter Lee's case control study. It is even less likely that women in Li's (Li et al., 2002) prospective cohort study, who had not yet miscarried would differentially enter the study on the basis of their future miscarriage status and present brief high magnetic field exposure.	(C2) The personal measurement studies taken closer to the relevant time period give associations for TWA similar to those in the VDT studies and stronger associations for Max and RCM. Measuring one day out of a pregnancy will still produce exposure misclassification particularly for unstable measures like Max and RCM.
(A3) Half the miscarriages in Li's allegedly prospective study (Li et al., 2002) had already occurred when the magnetic field measurements were taken. These miscarriage cases COULD have decided to cooperate with the study based on their EMF exposure and thus biased the study. Indeed, when analysis was restricted to measurements taken before the miscarriage the association between miscarriage and EMF exposure was not statistically significant. That proves that bias had indeed occurred.	(F3) Li (Li et al., 2002) presents the associations between Maximum Field and miscarriage for early and late miscarriages for cases who had not yet miscarried and who had already miscarried at the time of measurement. The associations respectively are similar, an adjusted RR of 5.6 and 6.1 for <10 week gestation and a RR of 1.7 and 1.6 for gestations $\geq$ 10 weeks gestation. The sample size of the before measurements was small; smaller numbers result in wider confidence intervals. But the data show similar associations regardless of whether the miscarriage occurred before or after the measurements. This does not suggest that substantial selection bias occurred in the Li study.	(C3) Each of the two studies assessed selection bias and the results support little or no selection bias.

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A4) Lee's (Lee et al., 2002) study demonstrated some selection bias for wire code; cases with high current wires were more likely to enter the study than cases with lower wire code homes. This inflated the apparent association between wire code and miscarriage. This probably explains the apparent association between miscarriage and maximum fields or RCM.	(F4) There *was* a selection bias, which slightly inflated the wire code association with miscarriage, but not enough to be statistically significant. But wire code was not associated with maximum field or RCM so the slight selection bias on wire code could not explain the associations between miscarriage and maximum field or RCM. When one examines the associations between miscarriage and Max and RCM in Lee's prospective sub-study where selection bias could not have taken place, the associations are similar to those observed in the larger nested case control study. This does not support the hypothesis that selection bias occurred.	(C4) Recall bias is not a problem for the two personal measurement studies and the prospective electric bed heater studies, and the evaluation of selection bias in Lee (2002) and Li (2002) does not suggest much selection bias if any.
(A5) Lee (Lee et al., 2002) showed very low correlation between Max field and RCM at weeks 12 and 30. How could anything so unstable be validly measured on only one day? This must be due to selection bias.	(F5) In Li's (Li et al., 2002) study the association was really restricted to those measured on "typical" days. Lee's (Lee, 2002) poor correlations were with typical and atypical days taken together. If these measures are too unstable to predict disease, how can they be stable enough to predict participation in a study?	(C5) If maximum field and RCM on "typical" days are indeed unstable and poorly correlated, this could suggest that the associations observed are underestimates of the true effect.
	(F6) One should not use selection bias as a default explanation without evidence to support it.	

TABLE 13.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A weak to moderate confounder would easily "explain" the apparent positive associations found for the VDT and personal measurement studies since the effect measures in these studies are very close to one.	(F1) A hypothetical confounder could explain the weaker VDT associations but there is no specific evidence for this.	(C1) All studies with relative risks close to 1.00 are vulnerable to confounding regardless of the direction of the association. But this reasoning should not be used to routinely explain away positive associations close to the resolving power of the studies.
(A2) There are only a few known risk factors for spontaneous abortions making it difficult to control for the many unknown factors in the analysis.	(F2) Many of these studies, especially the personal measurement studies, adequately assessed known confounders and the positive associations remained.	(C2) For the studies where the exposure was objectively assessed, the positive associations were moderate and less likely to be explained by confounders.
	(F3) The personal measurement studies found moderate associations for some of their analyses; strong confounders would be needed to explain away these associations. No such confounders have been found even though strong confounders would more likely be known than not known.	(C3) Known risk factors did not explain away the personal magnetic field associations.

TABLE 13.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) For the studies assessing sources believed to emit strong fields, such as the VDT and electric bed heaters, those studies showing positive associations found weak associations that are easily due to chance, bias, or confounding. Electric blankets should deliver maximum fields and high RCMs yet no dramatic risks have been documented.	(F1) Surrogate measures such as those used in the VDT and electric bed heater studies may suggest a risk that is not large enough to be easily detected by epidemiological studies due to random misclassification. Hence, they are expected to covey weaker relative risks than studies that measure the appropriate exposure metric directly. One of the electric bed heater studies (Lee et al., 2000) found that most of the women used an electric blanket on a low setting and exposures from low setting blankets were similar to background levels. Retinal doses from even high settings were low. VDTs may have emitted much weaker fields in the late 90s than they did in the 80s when most VDT studies were done, hence later studies would not be expected to show stronger associations.	(C1) Associations close to the resolution power of epidemiological associations (such as the VDT studies and electric bed heater studies) may reflect a true effect or bias or confounding. They should not be assumed to be due to bias or confounding without some evidence to support that hypothesis. See bias and confounding.
(A2) Also, evidence is lacking for a strong association between a woman's long-term residential exposure (assessed as wire codes) and spontaneous abortions.	(F2) Wire codes are a proxy for magnetic field exposure and may not capture the biological agent of the EMF mixture. The Lee (Lee et al., 2002) study found that the wire code was moderately associated with the magnetic field TWA but not associated with the maximum value or the rate of change metric, the measures found to be positively associated with spontaneous abortions.	(C2) The modest associations found for the personal measurement studies (Lee, 2002) and (Li, 2002) remained even after confounding and bias were taken into account. These two studies demonstrate consistent moderate associations between spontaneous abortions and maximum and RCM values with narrow confidence intervals.
(A3) Although the personal measurement studies (Lee, 2002), (Li, 2002) have modest associations, they are within the range of vulnerability to bias and confounding.	(F3) The strength of the consistent positive association found for the personal measures in the Li (Li 2002) and Lee (Lee 2000) studies, while moderate has narrow confidence limits. The association between Max and miscarriage was greater than 2.0 in early miscarriages.	(C3) The earlier studies based on questionnaires about VDT use and electrical bed heater use at medium/high settings gave results suggesting an effect near to the resolution power of the studies. This was compatible with the association seen in the personal measurement studies with TWA, the measure most comparable to the surrogates used in the VDT studies.

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A4) Also, for the two personal measurement studies, a weaker non-significant association was found for the personal 24-hour magnetic field TWA. This is the metric which, when examined at the 90th percentile, has been associated with some cancers and hence expected to be strongly associated with miscarriage.		(C4) The cancer studies have not evaluated the association with maximum field so it is hard to make comparisons.
(A5) Even the personal measurement studies have RR less than 2.00. "Real science" ignores such associations.		(C5) Some of the RR reported in Lee (2002) and Li (2002) are well above 2.00 but this is not a magic number in any case.

TABLE 13.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) To evaluate a causal association, only studies with statistically significant associations that are consistent across studies should be considered. The overall pattern of studies does not show a consistent statistically significant positive association.	(F1) Out of 11 major VDT studies assessing spontaneous abortions, 9 had relative risks slightly above one. A sign test reveals a low probability (.03) of this representing a chance pattern.	(C1) There is a greater tendency for relative risk estimates to be greater than 1.0 than less than 1.0, indicating a slight consistency across the VDT studies.
(A2) The very small, non-significant positive association pattern observed for the VDT studies should be interpreted with caution; the same bias occurring in multiple studies could produce an apparent but spurious consistency.	(F2) Although there are only two personal measurement studies, both show consistent results.	(C2) Both the personal measurement studies found relative risks above 1.0 for the magnetic field maximum levels.
(A3) Consistency can not be evaluated for the personal measurement studies since there are only two studies.		(C3) The bed heater studies are not consistent.

TABLE 13.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There appears to be a heterogeneous, overall pattern across studies. The results of the electric bed heater studies were inconsistent as well as the results of studies assessing spot or area measures.	(F1) The VDT studies, overall, reveal a weak positive association. The lack of homogeneity for the bed heater and area measurement studies most probably reflects the differences in assessing the exposure (as a self reported use obtained using different definitions of use or area measures obtained at different times) and in the differences in the study population.	(C1) The pattern of the VDT results is suggestive of a homogenous, positive association.
(A2) Homogeneity cannot be evaluated for the personal measurement studies since there were are only two studies.	(F2) Both the two personal measurement studies (Li et al., 2002) and (Lee et al., 2002), are homogenous in that showed a statistically significant positive association for the personal magnetic field maximum exposure and a weaker for the personal magnetic field TWA exposure.	(C2) The homogenous findings of the personal measurement studies increase confidence in a causal association.
	(F3) If EMF acts in combination with other agents it might appear heterogeneous if those other agents were not always present equally in the various studies.	

TABLE 13.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The likelihood of a causal relation is strengthened if a dose-response effect (gradient) is found. No gradient is found for the VDT and electric bed heater studies.	(F1) The studies using surrogate estimates of exposure may not have adequately categorized the exposure into high to low exposure groups. The electric bed heater studies used hours of use and setting to categorize high to low exposure. The retrospective personal measurement study (Lee et al., 2002) indicated that this categorization probably did not distinguish the use of high exposure bed heaters from low exposure ones.	(C1) The evidence suggests an increase with increase in exposure for the studies where high to low exposure categorization was based on measurements, (e.g., between exposed and non-exposed).
(A2) Even for the prospective personal measurement study (Li et al., 2002) where the measurements were obtained at the biologically critical time, an orderly monotonic increase in risk was not found for an increase in exposure; this decreases the possibility of a causal association.	(F2) Most of the VDT studies only used hours worked as a means to categorize more exposure. In the one study where measured VDT exposure was used to categorize the devices into emitting high to low exposures, a clear dose response was observed (Lindbohm et al., 1992).	(C2) The Lee (Lee et al., 2002) study shows a progressive increase of risk with dose while the Li (Li et al., 2002) study does not. This may be due to the exposure misclassification for the two associated metrics.
	(F3) In the retrospective personal measurement study (Lee et al., 2002), a clear dose response was found for two personal 24-hour exposure metrics (maximum value and the RCM).	

TABLE 13.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The personal measurement studies suggest risks of spontaneous abortion double when women experience the population's median for the maximum magnetic field. But the electric blanket studies do not show a doubling of risk at high settings or with prolonged use. It's not coherent.	(F1) The exposure delivered by electric blankets to different parts of the body varies. A lot to the skin, less to the uterus, and very little to the retina (Lee et al., 2000). It is not clear what, if any, target body site responds to magnetic fields to increase the risk of miscarriage. This could explain the apparent lack of coherence. The electric bed heater studies (Lee et al., 2000), (Belanger et al., 1998) both reported a significant and non-significant doubling of risk at high settings, respectively.	(C1) The lack of coherence with the electric blanket heater studies is acknowledged, but may have explanations as discussed.
(A2) The personal measurement studies suggest that 30 to 40 % of the background rate of miscarriages would be due to maximum magnetic field exposures. Why did we not notice this when electricity was introduced or subsequently as the use of appliances increased?	(F2) Miscarriages are not routinely monitored; as electricity use increased, a 30 to 40 % increase in rates could have been easily missed.	(C2) Increases in miscarriage rates could easily have been missed over time due a lack of a systematic reporting system.
(A3) The chance encounter with a maximum field would vary from day to day. It is puzzling that a "typical" day would be any more likely to capture this than an atypical day.	(F3) There are points of internal coherence in the personal measurement studies. Li (Li et al., 2002) shows a larger effect when analysis is restricted to "typical days" (e.g., when the measured exposure is more likely to reflect typical exposure), and a larger effect for women with a history of infertility or previous miscarriages. Both studies found a larger effect for earlier miscarriages.	(C3) The internal coherence of the studies is supportive of a causal association.
(A4) The personal maximum magnetic fields finding of the two personal measurement studies (Lee et al., 2002),(Li et al., 2002) are not coherent. One shows a monotonic dose response (Lee et al., 2002) while the other (Li et al., 2002) does not.		(C4) The fact that a stronger association with metrics that are less stable than the TWA is surprising. It is possible that a person who "typically" takes the electrical subway or usually enters some high exposure environment gets a range of maximum fields that they would not see on an atypical day where they did not do this.

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
		(C5) The lack of coherence in the shape of the dose response between the two measurement studies is acknowledged but may be due to the different exposure distributions of the two studies and hence different exposure reference levels. Li (Li et al., 2002) found higher exposures than Lee (Lee et al., 2002).

TABLE 13.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no clear evidence from animal studies of an association of EMF exposure and spontaneous abortions. Chick bioassays are variable and have little regulatory weight.	(F1) A number of laboratory studies have reported alterations in the development of chick embryos exposed to EMFs. These mostly used pulsed fields similar to the "maximum peaks" associated with spontaneous abortions in the two personal measurement studies (Lee et al., 2002), (Li et al., 2002). Those mammalian studies that reported no associations all used steady high fields. The chick studies suggest biological effect at levels encountered in residential environments.	(C1) The evidence is not sufficiently extensive or clear. See Generic discussion.

TABLE 13.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The melatonin hypothesis advanced by some lacks consistent experimental evidence that EMFs alter mammalian melatonin or that changes in melatonin increase the risk of spontaneous abortion.	(F1) Epidemiological studies by Burch (Burch, 1998; Burch, 1999) and Kaune (Kaune, Davis & Stevens, 1997) suggest a melatonin effect on humans, particularly with variable fields. Melatonin is linked to menstrual cycle hormones (Cagnacci & Volpe, 1996) and these relate to the menstrual cycle and conceivably to spontaneous abortions.	(C1) Biological mechanism arguments are still speculative. If links in mechanistic causal chain were all elucidated confidence would be boosted. Lack of a clear mechanistic understanding does not decrease the reviewers' confidence since clear mechanisms are not always available when epidemiological associations are first demonstrated.

TABLE 13.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" Chapter.		

TABLE 13.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The retrospective personal measurement study (Lee et al., 2002) measured exposure after the women in the cases had their miscarriages and while the controls were in their last gestation of pregnancy. Perhaps the cases reverted to a more active pre-pregnancy behavior far different from the current behavior of the controls due to their advanced pregnancy status. As a result, controls may experience lower EMF exposures than cases and than they would have experienced while not pregnant. This would explain the positive associations found.	(F1) The retrospective measurement study (Lee et al., 2002) also contained a pilot study based on measurements taken early in pregnancy and before any miscarriages. This study shows similar associations as the retrospective part of the study, albeit with wide confidence limits. This argues against a problem with temporality.	(C1) Tests of internal coherence in the two studies argue against a temporality problem.
(A2) Measurements were obtained after the miscarriage for 60% of the prospective measurement (Li et al., 2002) study. These cases could have changed behavior from their behavior while pregnant. This may bias the result upward as described in A1. The association was no longer significant from the measurements obtained prospectively.	(F2) The pattern of associations in the Li (Li et al., 2002) study is similar for the prospective and retrospective measurements. The same associations, which are statistically significant when the two types of measurements are combined, have wider confidence limits when the retrospective and prospective measurements are observed separately. (See discussion under Bias.)	
(A3) In the Li (Li et al., 2002) study, nauseated women destined to deliver a healthy baby may have stayed put and experienced a lower rate of change metric and fewer maximum fields than the women whose embryo as getting ready to be aborted.	(F3) In a letter to the editor Li, (Li & Neutra, 2002) provides data showing no association between nausea or vomiting and maximum field.	

TABLE 13.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" Chapter.		

TABLE 13.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The lack of associations with birth defects and other reproductive endpoints decreases the credibility of the positive results of the two personal measurement studies.	(F1) The quality and timing of exposure assessment for the other reproductive endpoints is not as good as the two personal measurement studies (Lee et al., 2002), (Li et al., 2002). Also, it is difficult to compare the spontaneous abortion results with the other reproductive endpoint findings since these endpoint are very heterogeneous and the methods of exposure assessment is very different across studies. They are much less frequent than miscarriage.	(C1) The lack of associations in the weak first generation studies of other reproductive endpoints does not carry much weight.
(A2) The positive findings found for the cancer study should not influence the credibility of the EMF and spontaneous abortion association since these conditions are not related to spontaneous abortions.	(F2) Given that it is not known that a specific mechanism applies to some endpoints associated with EMF and not to SAB, the existence of other associations should increase confidence to some degree.	(C2) The associations with other disease endpoints carry some weight.

TABLE 13.2.15

SUMMARY TABLE FOR MISCARRIAGE			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	"NO-EFFECT" HYPOTHESIS	CAUSAL HYPOTHESIS	HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?
Chance not an easy explanation.	Less possible	More possible	Increase
Bias recall possible for VDT studies and random misclassification (bias toward the null), if any, in the personal measurement studies of Lee and Li.	Possible	More possible	No impact or slight increase
Confounding adequate for known risk factors, slight possibility for unknown risk factors.	Possible	More possible	No impact or slight increase
Combined effect of bias, confounding, and chance.	Possible	Possible	No impact
Strength of Association: (1) moderate, although not large enough to rule out unspecified bias or confounding.	Less possible	Possible	No impact or slight increase
Consistency found for VDT studies and two personal measurement studies.	Less possible	More possible	Increase
Homogeneity for personal measurement studies; heterogeneous with most residential studies.	Possible	More possible	Slight increase
Dose: response clear with one personal measurement study (other threshold effect) and VDT study that obtained a range of exposure.	Possible	More possible	Slight increase
Coherence/visibility: lack of surveillance system for SABs to adequately assess time trends and high exposure is rare so population impact would not be obvious.	Possible	Possible	No impact
Experimental Evidence: null animal studies.	More possible	Possible	No impact or slight decrease
Plausibility: melatonin hypothesis, not tested.	Possible	Possible	No impact
No analogy.	Possible	Possible	No impact
Specificity: see generic discussion.	Possible	Possible	No impact
Based mainly on two studies.	More possible	Less possible	Decrease

13.3 Posterior (Updated) Degree of Certainty and IARC Classification

13.3.1 Statements of Individual Reviewers

Reviewer 1 (DelPizzo)

Degree of Certainty: The epidemiological evidence consists of two separate groups of studies investigating what can reasonably be defined as two distinct research hypotheses:

a) Is EMF exposure an epidemiologically detectable risk factor for spontaneous abortion (SAB) (e.g., with a relative risk of at least 1.2)?

b) Is EMF exposure resulting from VDT work a risk factor for SAB?

The reason why the two hypotheses cannot be combined is that, compared to residential and other occupational settings regarded as in the upper percentiles of average exposure EMF, exposure from VDT work varies from very weak to negligible, due both to the limited exposure time and to the historical trend toward lower emission levels.

Therefore, for the purpose of evaluating the hypothesis, which is the subject of this evaluation, the VDT studies can be regarded as a strengthening only type of evidence. That is, it is permissible to pool VDT and residential studies to determine the likelihood of the results under the null hypothesis (if EMF is not a risk factor, both strong and weak exposures should yield results symmetrically distributed around the null).

However, it is not permissible to use studies of exposure lower than that of interest in our context to determine if this exposure imparts a risk above a given minimum.

With this premise, Reviewer 1 judges the pattern of results is unlikely under the hypothesis of no effect. Additional confidence is derived by the analogy with the childhood leukemia assessment and the replicated animal and *in vitro* studies at low exposure levels. As noted elsewhere, their significance is not that of experimental evidence directly supporting the hypothesis, but that of an argument against the belief that EMF levels are too weak to affect.

Reviewer 1 has not relied on the Lee (Lee 2002) and Li (Li 2002) reports of associations between maximum exposure and SAB because this metric was not the reviewers' *a priori hypothesis.* However, these recent results confirm Reviewer 1's evaluation and beg for further investigations.

In qualitative terms, this reviewer is "close to the dividing line between believing and not believing" that VDTs and EMFs increase the risk of miscarriage to some degree.

For the purpose of decision analysis, Reviewer 1 believes that numerical values of 20 to 75 are defensible, with a median value of 56.

IARC Classification: 2B, possible human risk.

Reviewer 2 (Neutra)

Degree of Certainty: Over the last two decades there have been a series of VDT studies with inadequate exposure assessments showing somewhat consistent but not homogenous results, yet which suggested the possibility of an EMF effect just above the resolution power of the studies. The two large studies by Lee (Lee et al., 2002) and Li (Li et al., 2002) were based on 24-hour personal measurements taken during one day of pregnancy. They do not show a clear association with the average of instantaneous fields but both show associations with the maximum field experienced during the day that are somewhat above the resolution power of the studies. The similar associations seen in these two well-conducted studies are deemed unlikely to be due to chance or confounding with selection bias a possibility in the first study and a remote possibility in the second study. The null mammalian reproductive studies based on steady 60 Hz fields may not be relevant, while the controversial chick studies using pulsed fields may be relevant but did not affect this reviewers confidence much. The very suggestive evidence from only two studies combined with the very weak evidence from the lower quality previous studies of VDTs increased this reviewer's degree of certainty well above the prior. This would best be characterized as "close to the dividing line between believing and not believing" with a median estimate of 51 and a range from 20 to 70.

IARC Classification: The lack of support from mammalian pathology and clear mechanistic explanation, in the face of only two state-of-the-art epidemiological studies and a series of weaker studies compatible with a weak association with average magnetic fields would qualify this as an IARC 2B possible abortifacient based on "limited epidemiological evidence."

Reviewer 3 (Lee)

For evaluating the human evidence, Reviewer 3's posterior is increased considerably from her prior by the results of the two well-conducted personal measurement studies based on the studies' strength of the relative risks, dose response, and threshold effects, as well as the temporal relationship between exposure and effect, the adequate assessment of confounding, the adequate assessment of exposure, and the consistency of the study results. The pre-clinical study assessing the association of area measurements and miscarriage (Juutilainen et al., 1993) and the VDT studies, as a group, support the positive associations of these two personal measurement studies. The pre-clinical study found a positive association and the VDT studies, and overall show a slight consistent positive association. The home electric heater studies reveal an inconsistent pattern and hence do not contribute to the body of evidence for or against a causal association**.**

However, Reviewer 3's posterior is slightly decreased by the lack of animal pathology evidence. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "close to the dividing line between believing and not believing" category with a median value of 59 and a range of 30 to 85.

IARC Classification: Although the human evidence is mainly based on two personal measurement studies, these studies make it easy to rule out chance, bias, and confounding. The other studies using surrogate exposure measures provide some background support. Although a rational biological hypothesis and mechanism have been proposed, there is no animal evidence to support the proposal. Hence, EMF belongs to the lower end of Group 2B, "possible" risk.

13.3.2 SUMMARY OF THE THREE REVIEWER'S CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Spontaneous Abortion				0 5 10 1 5 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	
	2	2B	Close to dividing line	
	3	2B	Close to dividing line	

13.4 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 13.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Li and Lee suggest that changes in fields and brief high fields may be important.	(I1) If true, would focus on avoiding brief high exposures.

TABLE 13.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) For the personal magnetic field maximum levels, the results from Li and coworkers (Li et al., 2002) suggests a plateau after 16 mG, while the maximum results from Lee and coworkers (Lee et al., 2002) suggests a dose response. (C2) Neither provides evidence for a lower threshold of effect.	(I1) Unclear at this time.

TABLE 13.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Both Li (Li et al., 2002) and Lee (Lee et al., 2002) provide evidence of effects from daytime exposure. (C2) Nighttime exposures are lower but there is a suggestion of effects from these exposures too. (C3) There is some suggestion for more effect early in pregnancy.	(I1) No basis for difference between night and day recommendations.

TABLE 13.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 13.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Similar size to maternal age, race, and other known risk factors. (C2) Large population attributable risk if causal.	(I1) Relative size is irrelevant to policy, which is driven by absolute added risk and prevalence of exposure. May be relevant to risk communication.

TABLE 13.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1,000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The added risk in the exposed group, if true, could be far larger than these benchmarks.	(I1) Of regulatory concern, if true.

TABLE 13.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Earlier studies did not address this. Lee (Lee et al., 2002) and Li (Li et al., 2002) looked for effect modification by race and income in their logistic regression models and found no significant terms for this. However, both studies are based on populations that are members of the Kaiser Permanente Medical Program health plan and hence represent a working population, not the general pregnant population, with perhaps a wider range of variability on ethnicity and social class.	No impact.

TABLE 13.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The earlier VDT studies were mostly subject to recall bias and had crude assessment of exposure. (C2) The electric bed heater studies only used surrogate assessment of exposure that may not reflect a person's personal nighttime exposure. (C3) Both VDTs and electric bed heaters have been re-engineered to give off lower magnetic fields in the mid 90s. (C4) The personal measurement studies (Lee et al., 2002) and (Li et al., 2002) are relatively large, expensive state-of-the-art epidemiological studies. Larger prospective studies with measurements on multiple days of pregnancy, with sub-studies to identify source of maximum fields would be ideal but expensive and perhaps not feasible because they would require unprecedented subject cooperation.	(I1) Requires research funding, which is not currently likely. (I2) Requires policy on how many further studies (if any) are needed.

TABLE 13.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Not aware of other studies in pipeline.	(I1) Risk management decisions for at least a decade will need to rely on what's available.

TABLE 13.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Using chick bioassay to explore bioactive exposure conditions might be useful. (C2) Further analysis of two personal measurement studies (Lee et al., 2002), (Li et al., 2002) to better understand exposure conditions could be useful. (C3) Using insights from the above to guide mammalian bioassays and further epidemiology could be useful.	(I1) Research funding and direction.

13.5 CONCLUSIONS ON POLICY-RELEVANT SCIENTIFIC ISSUES

13.5.1 DOSE-RESPONSE ISSUES

There is a clear, orderly, monotonic increase in risk with increase in personal magnetic field maximum exposures in one personal measurement study (Lee et al., 2002), while a plateau effect was found for the other study (Li et al., 2002). In the one VDT study (Lindbohm et al., 1992) where the VDT models were categorized into high to low EMF sources by laboratory measurements of the models used, a clear dose response was observed. For both of the personal measurement studies, an increased risk was noted around the 25th percentile value. Hence, if true, about 75% of pregnant women would experience an exposure associated with an increased risk of miscarriage. The exposure could account for a substantial proportion of the background rate of spontaneous abortion.

13.5.2

The added risk EMF poses on miscarriage, if real, is of regulatory concern as described above. The two personal measurement studies suggest that change in magnetic fields and brief high fields may be an important influence on miscarriage risk. This will require policy to direct funding for future studies to understand the nature of the exposure, to evaluate the sources of such fields, and to decide whether or not to pursue methods for mitigation.

14.0 OTHER REPRODUCTIVE AND DEVELOPMENTAL STUDIES

STATEMENT TO THE PUBLIC

The DHS reviewers used two different guidelines to evaluate the evidence:

- *Using the guidelines that the International Agency for Research on Cancer uses to assess cancer risks, they considered the evidence as "inadequate" to implicate EMFs. A recent National Institutes of Environmental Health Sciences workgroup reached the same conclusions.*
- *Using the Guidelines developed especially for the California EMF Program, they concluded that they "strongly believe that EMFs do not increase the risk" of reproductive and developmental abnormalities other than miscarriage.*

For use in policy analyses, the DHS reviewers were required to provide a numerical "degree of certainty on a scale from 0 to 100. They represented their best judgment with a little "x" and the range of their confidence with a shaded bar. These are presented below:

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Other Reproductive				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Strongly believe not	
	2	3	Strongly believe not	
	3	3	Strongly believe not	

14.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 14.1.1 VDT Studies and Other Reproductive Adverse Effects (not Congenital Anomalies)

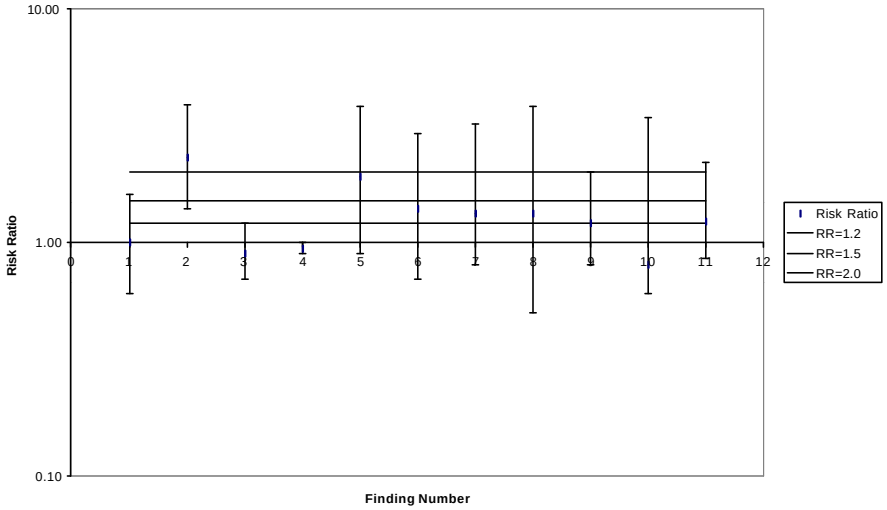


TABLE 14.1.1 STUDIES AND OTHER REPRODUCTIVE ADVERSE EFFECTS (NOT CONGENITAL ANOMALIES)

STUDY NUMBER	REFERENCE	FINDING NUMBER	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
1	(Kurppa, 1985)	1	VDT 4+ hrs/wk	1.00	0.60	1.60
1	(Ericson & Kallen, 1986a)	2	VDT 20+ hrs/wk	2.30	1.40	3.90
3	(Ericson & Kallen, 1986b)	3	VDT High	0.90	0.70	1.20
4	(McDonald et al., 1986)	4	Any VDT use	0.94	0.90	1.00
5	(Westerholm, 1987)	5	VDT, 15 + hrs/wk	1.90	0.90	3.80

TABLE 14.1.1 STUDIES AND OTHER REPRODUCTIVE ADVERSE EFFECTS (NOT CONGENITAL ANOMALIES) [CONT.]

STUDY NUMBER	REFERENCE	FINDING NUMBER	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
6	(Goldhaber et al., 1988)	6	VDT, 20+ hrs/wk	1.40	0.70	2.90
7	(Brandt, 1990)	7	VDT, 31+ hrs /wk	1.32	0.80	3.20
8	(Tikkanen, 1990)	8	VDT, 20+ hrs/wk	1.32	0.50	3.80
9	(Bjerkedal, 1987)	9	Any VDT use	1.20	0.80	2.00
10	(Rodriguez-Pinilla, 1995)	10	Any VDT use	0.80	0.60	3.40
11	(Li, Checkoway & Mueller, 1995)	11	VDT, 45+ hrs/wk	1.23	0.85	2.20

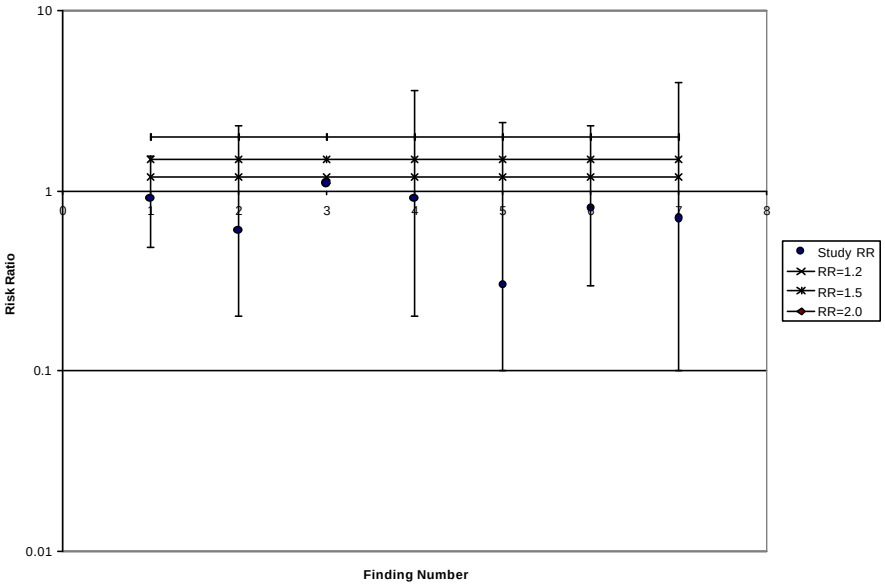


Figure 14.1.2 Residential Studies and Other Reproductive Effects (not Congenital Anomalies)

TABLE 14.1.2 RESIDENTIAL AND OTHER REPRODUCTIVE ADVERSE EFFECTS (NOT CONGENITAL ANOMALIES) STUDIES

STUDY NUMBER	REFERENCE	FINDING NUMBER	OUTCOME	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
1	(Dlugosz et al., 1992)	1	NTD	Electric blanket use	0.9	0.49	1.57
1	(Dlugosz et al., 1992)	2	IUGR	Home spot >1.0 mG cutpoint	0.6	0.2	2.3
1	(Wertheimer & Leeper, 1986)	3	Birthweight<2500	Electric Blanket and Water Bed	1.1	1.1	1.1
2	(Bracken et al., 1995)	4	Birthweight<2500	Home spot >1.0 mG cutpoint	0.9	0.2	3.6
3	(Savitz, 1994)	5	Birthweight<2500	Home spot >0.2 mT cutpoint	0.3	0.1	2.4
3	(Savitz, 1994)	6	Perinatal death	Home spot >0.2 mT cutpoint	0.8	0.3	2.3
3	(Savitz, 1994)	7	Early delivery	Home spot >0.2 mT cutpoint	0.7	0.1	4

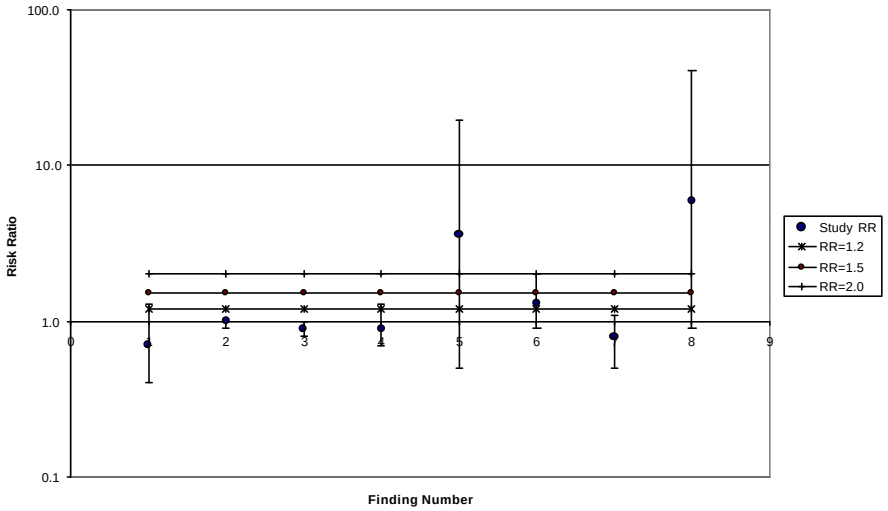


Figure 14.1.3 Occupational Studies and Other Reproductive Effects (not Congenital Anomalies)

TABLE 14.1.3 OCCUPATIONAL AND OTHER REPRODUCTIVE ADVERSE EFFECTS (NOT CONGENITAL ANOMALIES) STUDIES

STUDY	REFERENCE	FINDING NUMBER	OUTCOME	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
1	(Knave et al., 1979)	1	M:F sex ratio	Male EMF occupation	0.70	0.40	1.30
2	(Irgens et al., 1997)	2	M:F sex ratio	Male EMF occupation	1.00	0.90	1.00
2	(Irgens et al., 1997)	3	M:F sex ratio	Female EMF occupation	0.90	0.80	1.00
3	(Tornqvist, 1998)	4	M:F sex ratio	Male EMF occupation	0.90	0.70	1.30
4	(Nordstrom, Birke & Gustavsson, 1983)	5	Perinatal death	Male EMF occupation	3.60	0.50	19.7
3	(Tornqvist, 1998)	6	Perinatal death	Male EMF occupation	1.30	0.90	2.00
3	(Tornqvist, 1998)	7	Birthweight<2500	Male EMF occupation	0.80	0.50	1.10
5	(Buiatti et al., 1984)	8	Male infertility	Male EMF occupation	5.90	0.90	40.2

Figures and Tables 14.1.1-14.1.3 show the reported relative risks of adverse reproductive conditions other than congenital anomalies and spontaneous abortions. Figure 1 and Table 1 are VDT studies. Figure 2 and Table 2 are residential studies. Figure 3 and Table 3 are occupational studies. Overall, there is no pattern of relative risks greater than 1.0, 1.2, or 1.5 for either type of condition or type of exposure. There are about the same number of studies with relative risks above 1.0 and 1.2 as below 1.0 and 1.2 (VDT studies, 7 and 6 out of 11 ($p = 0.16$, $p = 0.23$); residential studies, 7 and 5 out of 12 ($p = 0.19$ for both); occupational studies, 3 out of 8 for both ($p = 0.22$). Very few studies had relative risks above 1.5.

Figure 14.1.4 VDT and Congenital Anomalies Studies

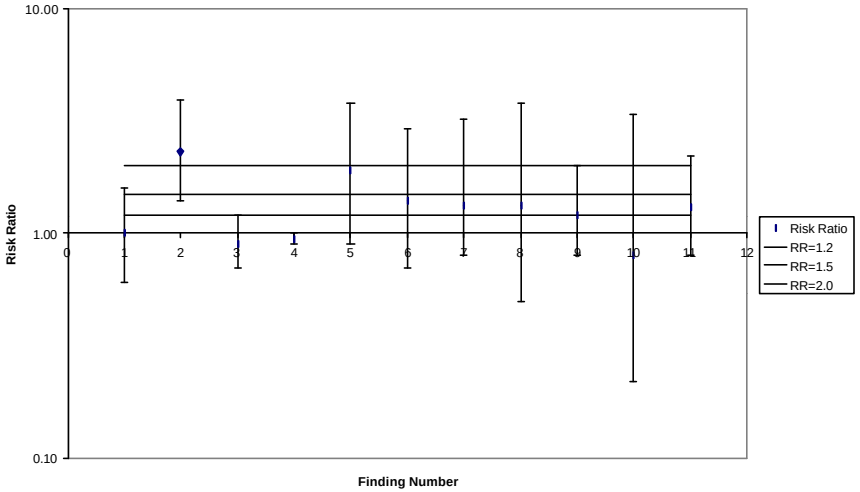


TABLE 14.1.4 VDT AND CONGENITAL ANOMALIES STUDIES

REFERENCE	FINDING NUMBER	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
(Kurppa, 1985)	1	VDT 4+ hrs/wk	1.00	0.60	1.60
(Ericson & Kallen, 1986a)	2	VDT 20+ hrs/wk	2.30	1.40	3.90
(Ericson & Kallen, 1986b)	3	VDT high	0.90	0.70	1.20
(McDonald et al., 1986)	4	Any VDT use	0.94	0.90	1.00
(Westerholm, 1987)	5	VDT, 15+ hrs/wk	1.90	0.90	3.80
(Goldhaber et al., 1988)	6	VDT, 20+ hrs/wk	1.40	0.70	2.90
(Brandt, 1990)	7	VDT, 31+ hrs /wk	1.32	0.80	3.20
(Tikkanen, 1990)	8	VDT, 20+ hrs/wk	1.32	0.50	3.80
(Bjerkedal, 1987)	9	Any VDT use	1.20	0.80	2.00
(Rodriguez-Pinilla, 1995)	10	Any VDT use	0.80	0.22	3.40
(Li et al., 1995)	11	VDT, 45+ hrs/wk	1.30	0.80	2.20

Figure 14.1.5 Residential and Congenital Anomalies Studies

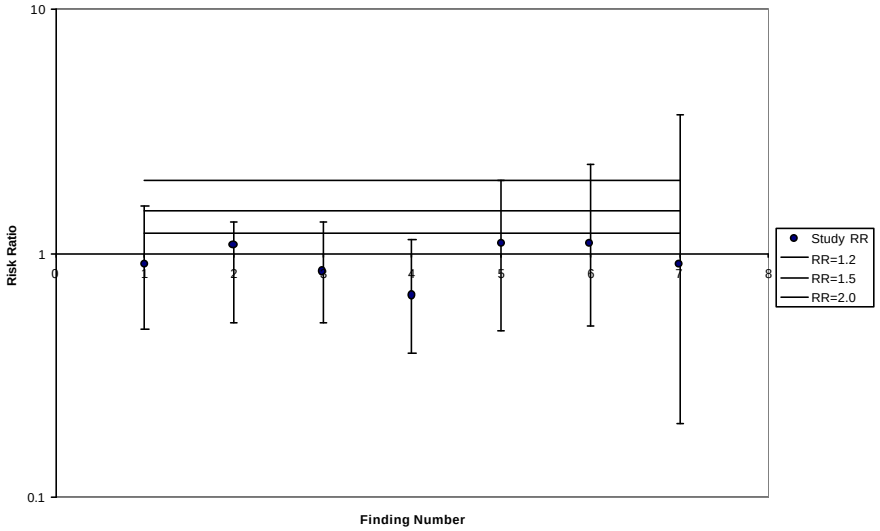


TABLE 14.1.5 RESIDENTIAL CONGENITAL ANOMALIES STUDIES

REFERENCE	FINDING NUMBER	OUTCOME	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
(Dlugosz et al., 1992)	1	NTD	Electric blanket use	0.9	0.49	1.57
(Dlugosz et al., 1992)	2	NTD	Waterbed use	1.08	0.52	1.35
(Dlugosz et al., 1992)	3	Oral cleft	Electric blanket use	0.84	0.52	1.35
(Dlugosz et al., 1992)	4	Oral cleft	Waterbed use	0.67	0.39	1.14
(Milunsky et al., 1992)	5	NTD	Electric blanket use	1.1	0.48	2
(Li et al., 1995)	6	Urinary tract defect	Electric blanket use	1.1	0.5	2.3
(Li et al., 1995)	7	Urinary tract defect	Waterbed use	0.9	0.2	3.7
(Robert et al., 1996)	8	All abnormalities	High voltage lines	0.95	0.45	3.22

Figure 14.1.6 EMF Occupational and Congenital Anomalies Studies

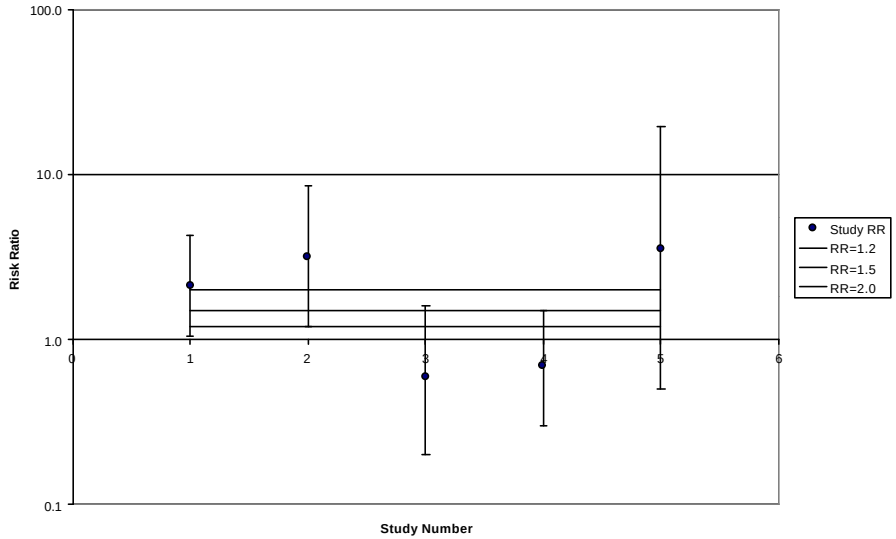


TABLE 14.1.6 OCCUPATIONAL CONGENITAL ANOMALIES STUDIES

STUDY	REFERENCE	FINDING NUMBER	OUTCOME	EXPOSURE	ESTIMATED RISK RATIO	LOWER CL	UPPER CL
1	(Spitz & Johnson, 1985)	1	Congenital Anomalies	Male EMF occupation	2.13	1.05	4.35
2	(Nordstrom et al., 1983)	2	Congenital Anomalies	Male EMF occupation	3.2	1.2	8.6
3	(Bunin et al., 1990)	3	Neuroblastoma	Male EMF occupation	0.60	0.20	1.60
4	(Tornqvist, 1998)	4	Congenital Anomalies	Male EMF occupation	0.70	0.30	1.50
5	(Nordstrom et al., 1983)	5	Perinatal death	Male EMF occupation	3.60	0.50	19.7

Figures and Tables 14.1.4-14.1.6 show the reported relative risks of congenital anomalies. Figure 4 and Table 4 are VDT studies. Figure 5 and Table 5 are residential studies. Figure 6 and Table 6 are occupational studies. Overall, there is no pattern of relative risks greater than 1.0, 1.2, or 1.5 across types of exposure. For the VDT studies, there are about the same number of studies with relative risks above 1.0 and 1.2 as below 1.0 and 1.2 (6 and 5 out of 11; p = 0.23 for both). Only 1 out 11 studies had a relative risk above 1.5. For the residential studies, 3 out of 7 (p = 0.27) had relative risks above 1.0 and no studies had relative risks greater than 1.2. For the occupational studies, the same 3 out of 5 studies had moderate relatives above 1.0, 1.2, 1.5, and 2.0 (p = 0.31).

14.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 14.2.1 OTHER REPRODUCTIVE AND DEVELOPMENTAL STUDIES

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The positive findings are due to chance regardless of the adverse reproductive condition. Only 2 findings out of 31 were significantly above 1.0.	(F1) All four of the electric bed heater findings assessing low birth weight and growth retardation were above 1.0 resulting in a one-sided p-value of 0.06 (Wertheimer & Leeper, 1986), (Bracken et al., 1995).	(C1) Overall, chance cannot be ruled out as an explanation for the observed positive results.

TABLE 14.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the case-control studies are associated with observational bias resulting in the observed positive results.	(F1) Most of the studies used crude assessment of exposure resulting in non-random misclassification and a bias toward the null.	(C1) Non-random misclassification is the major concern resulting in the dilution of an effect, if an effect is present.
(A2) For the positive congenital abnormality studies, only those conditions that were positive may have been presented since a number of conditions were generally assessed.	(F2) There are only two studies that have assessed magnetic fields directly (Savitz, 1994), (Bracken et al., 1995). However, these were not based on personal measures but on area measures resulting in misclassification toward the null.	

TABLE 14.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Ergonomics and occupational stress from VDT use may have confounded the positive VDT studies.	(F1) It is inappropriate to invoke cofounders that have not been identified; there is no evidence regarding the relationship of VDT use and occupational stress and adverse reproductive conditions.	(C1) Unknown confounders may either bias an association upward or downward. Therefore, no impact.
(A2) If there is an association, it is due to some factor other than EMF related to the surrogate measures used in these studies (such as stress from VDT use or heat from electric bed heater use), since the two studies assessing direct measures (Savitz, 1994), (Bracken et al., 1995) found no associations.	(F2) Confounding was adequately assessed for the few known risk factors of the various endpoints regardless of the main purpose of the study.	(C2) A surrogate measure for EMF such as self-reported electric bed heater use and VDT use may be correlated with another risk factor/exposure unrelated to EMF. However, no such candidates have been adequately identified and explored.
	(F3) Not much can be inferred from the measurement studies since there were only two studies using area measures rather than personal exposures (Savitz, 1994), (Bracken et al., 1995).	

TABLE 14.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) All associations are weak (most are below a relative risk of 1.2) and hence could be due to bias or confounding.	(F1) Non-random exposure misclassification bias is the main problem, which in turns weakens an association if one exists.	(C1) It is possible that non-random misclassification is the reason for the no to very weak associations observed since very crude assessments of exposures were used for all but two studies. The true relative risk may be larger and therefore less vulnerable to bias and confounding.
(A2) The two studies using area magnetic field measures (Savitz, 1994), (Bracken et al., 1995) found a non-significant negative effect to little or no effect where a stronger association is expected.	(F2) Weak, positive associations were found for the overnight magnetic field measurements (Bracken et al., 1995).	(C2) Even evaluating the studies by endpoint, only weak positive associations are observed for those endpoints with more than two studies.
	(F3) Li et al. (Li et al., 1995) found a strong association for urinary tract anomalies and electric blanket users in a subset of women who had a history of sub-fertility	(C3) However, there is a lack of measurement studies to assess if the weak positive studies using surrogate estimates reflect a true association and if the two measurement studies reflect a non-causal relationship. Although very few studies find relative risks above 1.2, this is to be expected.

TABLE 14.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Only the significant associations should be assessed. Overall, out of 52 findings, only 2 studies found significantly positive results for unrelated conditions, a VDT exposure and low birth weight finding (Savitz, 1994) and a paternal occupation and congenital malformation finding (Ericson & Kallen, 1986b).	(F1) There is a slight suggestion of consistency for the electric bed heater studies of low birth weight and growth retardation, as well as VDTs and congenital; but as a group, they are not significantly positive.	(C1) Such inconsistency is expected across very heterogeneous studies.
	(F2) Although the two area measurement studies reported inconsistent results, a consistently positive association may emerge if more area measurement studies were conducted.	(C2) Even for those subgroups where more findings are above 1.0 than below 1.0, chance is a credible explanation of the pattern of evidence.

TABLE 14.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The 2 out of 11 VDT and congenital anomaly studies (Ericson & Kallen, 1986b), (Westerholm, 1987) revealing the largest risks did not restrict analyses to specific phenotypic subgroup, thus increasing the probability these findings are due to chance.	(F1) Due to the considerable heterogeneity of the body of evidence with respect to exposure estimate and endpoint, studies with homogenous endpoints and exposure estimates should be evaluated. For low birth weight and growth retardation, all 4 findings showed relative risks above 1.0 resulting in a low probability ($p = 0.06$) that this is due to chance. Also, for the VDT and congenital anomaly studies, 7 of the 11 findings reported relative risks above 1.0 resulting in a 16% probability of being due to chance.	(C1) Grouping the findings into more homogenous endpoints and/or exposure estimate groups does not reveal any strong consistencies within any of the subgroups.
(A2) In general all the associations are not significant where effects range from weakly protective to weakly negative.	(F2) Some of the VDT and congenital anomalies studies reveal elevated risks. This is to be expected due to the heterogeneous nature of congenital anomalies in terms or their etiology and timing of exposure.	(C2) It is difficult to infer a causal or non-causal association due to the heterogeneity of the group as a whole and the small number of studies available for each individual endpoint.
(A3) The findings with direct exposure measures did not have the strongest relative risks.		

TABLE 14.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The VDT studies assessing greater hours of use or "high" use show little or no association.	(F1) The studies using surrogate measures to assess exposure also used very crude assessments of "increased exposure." The assumption of electric bed heaters emitted as a source for high fields and greater hours on a VDT resulting in "more" exposure has not been demonstrated in these and other studies.	(C1) Evidence is lacking to evaluate dose response; most studies did not evaluate risk at various levels of the exposure estimate.

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A2) Studies assessing electric bed heaters, a source of strong nighttime exposures, found associations close to 1.0.		

TABLE 14.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The prevalence of VDT use among working women has increased considerably over time. However, a corresponding increase in adverse reproductive effects is not apparent.	(F1) An apparent increase in adverse reproductive effects with increasing VDT use is not expected due to the heterogeneity of the group, and its association with different etiologies and the lack of sufficient surveillance systems to report these conditions.	(C1) Large, sophisticated studies assessing exposure over time and at the critical time would be needed to address visibility; no such studies have been established.
(A2) A stronger association for studies with direct measures of exposures compared to studies using surrogate measures of exposure was not found.	(F2) There are not enough studies assessing direct EMF measures to evaluate if these exposures result in stronger risks.	
(A3) Among the congenital anomaly studies, one would expect stronger associations for studies focusing on one or two anomalies compared to those studies grouping all anomalies together. The two studies showing the largest elevated risk (Ericson & Kallen, 1986b), (Westerholm, 1987) grouped anomalies.		

TABLE 14.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The results of teratogenic and reproductive effects in mammalian systems are generally negative.	(F1) A number of laboratory studies have reported alterations in the development of chicken embryos exposed to EMF.	(C1) The lack of positive animal studies decrease the confidence only slightly.
	(F2) Animal bioassays of one aspect of a complex mixture are not highly sensitive and may not be linear in risk at high dose resulting in inconsistent and perhaps null results. Null results do not decrease the confidence as much as positive results increase the confidence.	

TABLE 14.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
No evidentiary base.	No evidentiary base.	(C1) A generally accepted mechanism for biologic effects on reproduction does not currently exits.

TABLE 14.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 14.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 14.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 14.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No biologic reason to consider the associations with other diseases when evaluating the relationship associated with adverse reproductive effects.	(F1) Given that there is an association with spontaneous abortions, it is reasonable to assume that fetuses that are subject to exposure may be damaged even though they survive to term.	(C1) There is some relevance especially with spontaneous abortions.
	(F2) Associations with other diseases will strengthen confidence of causation since EMF is a mixture of components that may influence different biological processes resulting in ill health.	

TABLE 14.2.15

SUMMARY TABLE FOR OTHER REPRODUCTIVE DEVELOPMENTAL CONDITIONS			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance is feasible.	More possible	Possible	Decrease
Bias mainly random misclassification thereby diluting an effect if there is one.	Possible	Possible	No impact
Confounding by unspecified confounders.	Possible	Possible	No impact
Combined chance, bias, and confounding.	More Possible	Possible	Slight decrease
Strength of association (1) not large enough to rule out unspecified bias or confounding.	More possible	Possible	No impact or slight decrease
Consistency: not easily detectable.	More possible	Possible	No impact or slight decrease
Homogeneity: heterogeneous even in similarly grouped endpoints.	More possible	Possible	No impact or slight decrease
Dose response difficult to evaluate due to lacking evidence.	Possible	Possible	No impact
Coherence/visibility difficult to evaluate due to heterogeneous nature of endpoints.	Possible	Possible	No impact
Experimental evidence: animal bioassays are basically negative.	More possible	Possible	No impact or slight decrease
Plausibility: a generally accepted mechanism not defined.	Possible	Possible	No impact
Analogy: see generic discussion.	Possible	Possible	No impact
Specificity: see generic discussion, SAB association.	More possible	Possible	No impact or slight decrease

14.3 POSTERIOR (UPDATED) DEGREE OF CERTAINTY AND IARC CLASSIFICATION

14.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

Reviewer 1 (DelPizzo)

Degree of Certainty: The human evidence is inconsistent. This reviewer's evaluation of the hypothesis "strongly believe that it is not a cause." For the purpose of decision analysis, Reviewer 1 believes that numerical values of 0 to 10 are appropriate, with the median value to be 5.

IARC Classification: "inadequate" (Class 3).

Reviewer 2 (Neutra)

Degree of certainty: The quality of the exposure assessment in most of the studies of other reproductive outcomes has left a good deal to be desired. The studies have been inconsistent and the pattern is compatible with chance. If the studies had powerful designs, the largely null results would have pulled this reviewer's posterior confidence substantially below the prior, but as it is, the posterior confidence is modestly lower than the prior. Reviewer 2 would characterize the degree of certainty as "Strongly Believe that EMFs do NOT increase the risk of reproductive or developmental problems other than miscarriage to any degree" with a median certainty of 2 and a range from 0.5 to 5.

IARC Classification: The evidence is "inadequate" to implicate EMFs as a reproductive toxicant and would fall in Group 3.

Reviewer 3 (Lee)

Degree of Certainty: The human evidence of the other reproductive and developmental conditions is based on a heterogeneous group of studies with respect to type of condition and exposure assessment making it difficult to evaluate this body of evidence. This reviewer's posterior for a weak relative risk is decreased from her prior by a random association pattern across studies, the heterogeneity of the body of evidence, the fact that bias and confounding cannot be ruled out, and the lack of plausibility evidence. Hence, Reviewer 3's posterior degree of certainty for purposes of the policy analysis falls within the "strongly believe that it is NOT a cause" category with a median value of 5 and a range from 2 to 10.

IARC Classification: The human evidence is inadequate where most studies are susceptible to biases and confounding due to the crude exposure estimates. The overall relative risks are weak where chance cannot be ruled out as an explanation. The heterogeneity of the types of conditions assessed make it difficult to adequately evaluate the causal relationship of any one condition. Hence, exposure is not classifiable and is consistent with Group 3.

14.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Other Reproductive				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Strongly believe not	
	2	3	Strongly believe not	
	3	3	Strongly believe not	

14.4 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 14.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 14.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 14.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 14.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 14.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Hard to evaluate due to the heterogeneity of the group and lack of major risk factors associated with most of the group's endpoints.	None.

TABLE 14.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1,000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Lack of evidence to evaluate, but based on the surrogate measure studies, the relative would be very small and not comparable.	No impact.

TABLE 14.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 14.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There is considerable room for improvement in the studies published. Future studies should evaluate direct measures of exposure at various levels and timing periods on more homogenous outcome groups, and ascertain potential risk factors as well as other sources of EMF exposures.	(I1) Results from carefully controlled studies assessing at least the more common endpoint would have a considerable impact on policy.

TABLE 14.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
None known to date.	

TABLE 14.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
See "Room for Improvement" above.	

14.5 CONCLUSIONS OF POLICY-RELEVANT SCIENTIFIC ISSUES

14.5.1 DOSE-RESPONSE ISSUES

The evidentiary base is not sufficient to answer questions about special vulnerabilities, biological windows, thresholds, plateaus, etc.

14.5.2 RESEARCH POLICY

The studies, as a whole, are too heterogeneous with respect to endpoint and exposure assessment to adequately define policy one way or another. It is worth investing in future research for at least the low birth weight and intrauterine growth retardation outcomes due to the positive findings with personal measurements and spontaneous abortions. There is a need for studies—assessing personal exposures from both residential and occupational sources—that are large enough to have the power to evaluate various homogenous subgroups and assess timing of exposure. When exposure conditions are better understood, mechanistic studies should be considered as well since the experimental work to date offers little direction for future epidemiological studies.

15.0 AMYOTROPHIC LATERAL SCLEROSIS (ALS)

STATEMENT TO THE PUBLIC

Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease)

The reviewers used two distinct sets of guidelines to evaluate the evidence:

- *Using the guidelines that the International Agency for Research on Cancer uses to assess cancer risks, they considered the evidence to warrant a "possible (2B)" cause of ALS on the basis of limited epidemiology. A work group convened by the National Institutes of Environmental Health Sciences considered the evidence "inadequate" (Group 3). The British National Radiological Protection Board noted a consistent epidemiological association with high-exposure electrical occupations but speculated that it might be due to shocks.*

- *Using Guidelines developed specifically for the California EMF Program, the DHS reviewers were all "close to the dividing line between believing and not believing" that EMFs increased the risk of ALS to some degree.*

The DHS scientists are more inclined to believe that EMF exposure increased the risk of ALS than were the majority of the members of scientific committees convened to evaluate the scientific literature by the NIEHS in 1998, and by the NRPB in 2001. There are several reasons for these differences. The three DHS scientists thought there were reasons why animal and test tube experiments might have failed to pick up a mechanism or a health problem; hence, the absence of much support from such animal and test tube studies did not reduce their confidence much or lead them to strongly distrust epidemiological evidence from statistical studies in human populations. They therefore had more faith in the quality of the epidemiological studies in human populations and hence gave more credence to them.

Lou Gehrig's Disease has a low incidence with rates around 1/100,000 a year. Even doubling such rates and accumulating them over a lifetime leaves accumulated lifetime risks less than 1/1,000. Thus the vast majority (99.9%) of highly-exposed people would still not contract this disease. Furthermore, calculations suggest that the fraction of all cases of this condition that one could attribute to EMFs would be no more than a few percent of the total cases (if any). However, if EMFs do contribute to the cause of these conditions, even the low fractions of attributable cases and the size of accumulated lifetime risk of highly exposed individuals could be of concern to regulators. Indeed, when deemed a real cause, estimated lifetime risks smaller than these (1/100,000) have triggered regulatory evaluation and, sometimes, actual regulation of chemical agents such as airborne benzene. The uncommon, accumulated high-EMF exposures implicated by the evidence about these conditions come from unusual configurations of wiring in walls, grounded plumbing, nearby power lines, and exposure from some jobs in electrical occupations. There are ways to avoid these uncommon accumulated exposures by maintaining a distance from some appliances, changes in home wiring and plumbing, and power lines. However, to put things in perspective, individual decisions about things like buying a house or choosing a jogging route should involve the consideration of certain risks, such as those from traffic, fire, flood, and crime, as well as the uncertain comparable risks from EMFs.

The EMF Program's policy analysis required each of the three DHS scientists to express in numbers their individual professional judgments that the range of added personal risks suggested by the epidemiological studies were "real." They did this as a numerical "degree of certainty" on a scale of 0 to 100. For the conditions with the most suggestive evidence of EMF risk, the three scientists each came up with a graph that depicts their best judgments with a little "x" and the margin of uncertainty with a shaded bar:

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
ALS (Lou Gehrig's Disease)					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	9	
	2	2B	Close to dividing line	21	
	3	2B	Close to dividing line	11	

15.1 EPIDEMIOLOGICAL EVIDENCE

Figure 15.1 ALS RRs

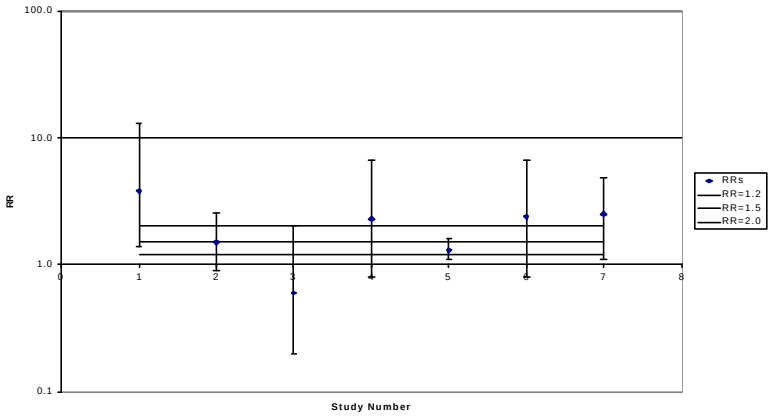


Figure 15.1 and Table 15.1 display the seven studies which deal with electrical occupation or estimated magnetic field exposure and the occurrence of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's Disease). The graph shows the relative risks reported in the seven studies. Ahlbom (Ahlbom, 2001) calculated the meta-analytic summary relative risks for all seven, the clinic based studies, the mortality based studies and the two utility cohort studies which assigned magnetic field exposure based on a job-activity matrix. For all seven studies the meta-analytic summary RR was 1.5 (1.2-1.7). For the two utility cohort studies it was 2.7 (1.4-5.0). Thus the evidence suggests an association between ALS and working in an electric occupation, or having a job within a utility company with a high magnetic field exposure. Six of seven studies report RR above 1.0 (P=.055). Given the small number of studies, the fact that 86% of the relative risks are above 1.0 does not achieve conventional statistical significance.

TABLE 15.1.1

STUDY NUMBER	REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
1	(Deapen & Henderson, 1986)	Study population: not specified. Cases: ALS society, US in 1979. Controls: friends	Questionnaire: electrical occup 3 yr prior to diagnosis.	CC	678 cases (19 electr occ) 518 controls (5 electr. occ.)	3.8 1.4-13.0
2	(Gunnarsson, 1991)	Male population of Sweden 1970-83. Cases: Deaths with ALS as underlying or contributing cause in mortality registry. Controls: Random sample from population.	Job title in census 1960: electricity worker.	CC	1067 cases (32 exposed) 1005 controls	1.5 0.9-2.6
3	(Gunnarsson, 1992)	Male population of central and southern Sweden in 1990. Cases: Patients with MND in neurological departments. Controls: Random sample from population.	Questionnaire: electricity work and exposure to MF.	CC	58 cases (4 MF exposure) 189 controls	0.6 (MF exp) 0.2-2.0
4	(Davanipour et al., 1997)	Study base: not specified. Cases: ALS	Questionnaire about occupational history:	CC	28 cases	2.3

STUDY NUMBER	REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
		patients at outpatient clinic in southern California. Controls: relatives.	EMF exposure assessed by hygienist. Cumulative (E1) and average (E2) exposure.		32 controls cut off: 75th percentile, of case distribution	0.8-6.6 average (E2)
5	(Savitz, Loomis & Chiu-Kit, 1998b)	Male population in 25 states, US, 1985-91. Cases: deaths from ALS. Controls: Deaths from other causes.	Job title on death cert.: electrical occupation in aggregate and individual jobs.	CC	114 cases in electr. occup. in aggregate	1.3 1.1-1.6
6	(Savitz et al., 1998a)	Male employees at five US utility companies 1950-1988. Cases: deaths with ALS mentioned on death certificate, identified through multiple tracking sources.	Measurements and employment records. Combination of duration and EMF index.	Cohort	9 cases with >20 years in exposed occup.	2.4 0.8-6.7
7	(Johansen & Olsen, 1998a)	Male employees in Danish utility companies observed during 1974-1993. Cases: deaths from ALS in mortality registry.	Employment records and JEM: estimated average exposure level.	Cohort	21236 males in cohort. 14 (9 exposed) cases	2.5 1.1-4.8

15.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 15.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all the associations are above 1.00 or statistically significant.	(F1) The narrow confidence limits in the meta-analytic summaries and the low likelihood of this pattern of evidence by chance leans away from chance as an explanation.	(C1) A non-chance explanation must be sought.
(A2) Each of the studies have small numbers of exposed cases.	(F2) There are 18 exposed cases in the two cohort studies and 175 “exposed” cases in the other studies.	

TABLE 15.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The case-control studies are subject to recall bias. All studies are subject to the authors presenting only the strongest associations of the many generated during analysis. For example in the Savitz, Checkoway (Savitz et al., 1998a) study, there was no association with ALS for durations less than 20 years and no dose response with duration of occupation.	(F1) Like the electric shock and trauma associations in questionnaire-based case control studies, electrical occupation is subject to recall bias. But two large occupational cohort studies and a case control study objectively assessing EMF exposure show a higher ALS rate and an association with high EMF work. Even if one were to discard the Savitz, Checkoway (Savitz et al., 1998a) study as gerrimandered, the Johansen (Johansen & Olsen, 1998a) study remains.	(C1) Bias upward is not a big concern in this evidentiary base. Bias downward might be a problem.
	(F2) If there is any consistent bias it is non-differential measurement error which would tend to obscure associations.	

TABLE 15.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One doubts that electrical occupation or high-EMF electrical work is associated with ALS. Johansen (Johansen & Olsen, 1998a) showed that fatal electric shock was associated with high-EMF jobs. Serious non-lethal shocks should be more common in high-EMF jobs also.	(F1) Since high amperage is often associated with high voltage, it is not surprising that high magnetic field jobs would have a higher probability of death among those shocked. It does not follow that the frequency of shocks would be greater.	(C1) The evidentiary base to describe the frequency of shocks and link them to EMF exposure in an objective way is non-existent, so any link between magnetic field and shock exposure is speculative.
(A2) If it is, then the association is not due to magnetic fields but to the delayed effect of many shocks experienced in those jobs. Experimental work shows that shocks, not EMF exposure is responsible for acute vascular trauma.	(F2) Kondo (Kondo & Tsubaki, 1981) and Gunnarson (Gunnarsson, 1992) showed weak protective associations with shock. The other studies (Deapen & Henderson, 1986), (Savettieri et al., 1991), (Cruz et al., 1999) were of borderline statistical significance, so by conservative criteria 5 out of 6 studies were null. Four out of 6 studies had ORs larger than 1.00.	(C2) The reported associations with ALS based on objective assessments of magnetic field are of about the same strength as those conveyed by subjectively recalled shock history in the general public.
(A3) (Kurtzke, 1980) and others have shown association between ALS and physical injury many years before. Electrical trauma may also have delayed effects.	(F3) All these studies rely on recall.	(C3) One would need to believe that virtually all high EMF electrical workers had experienced shocks which rendered them unconscious during their work life, or that common minor shocks carry the same risk as major shocks, for shocks to explain the magnetic field association with ALS. This seems implausible on the face of it but needs to be evaluated.
(A4) (Deapen & Henderson, 1986), (Gallager, 1987), (Cruz et al., 1999), and (Savettieri et al., 1991) showed associations between ALS and self reported electrical shock, often years before.	(F4) The ORs conveyed by shock leading to uncosciousness in (Deapen & Henderson, 1986) is 2.8 (1.0-9.9). The ORs conveyed by high EMF work excluding 3 out of 19 workers with shock is 3.3 (1.1-10.3) Shock to unconsciousness does not explain the EMF association. One needs to postulate that virtually all high EMF workers have received lesser shocks which conveyed more risk than shock to unconsciousness. [Cruz 1999 #1460] reports a RR	(C4) A similar concern, as voiced in C3, would apply to contact currents as a confounder of magnetic fields.

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
	= 0.7 (0.5-1.1) from multiple non-injury shocks.	
(A5) Gunnarsson (1992) reports an association with solvent exposure RR = 15.6 (2.8-87.0). This has not been ruled out as a confounder.	(F5) Gunnarson had 58 cases and 189 controls. McGuire (McGuire et al., 1997) with 174 cases and 348 controls reports a solvent exposure RR for males of 1.3 (0.7-2.3). This is too weak to explain EMF association.	(C5) For the same reason it is also implausible that the history of physical trauma or solvent use in high-EMF workers could explain the association. The 60-year-old literature (Alexander, 1938) in shock pathology relates to acute not delayed effects.

TABLE 15.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The associations are modest and could be due to bias.	(F1) Associations of 2.5 and 3.0 are not so easy to dismiss by invoking bias or confounding.	(C1) We do not put much weight on bias as a default explanation without specific evidence.
		(C2) The utility study associations are not so small and are not subject to recall or selection bias.
		(C3) Exposure misclassification could lead to downward bias.

TABLE 15.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One should only pay attention to statistically significant associations. Of 7 studies of electrical work or magnetic field exposure, only 3 were significant and the ORs ranged from 1.3 to 3.8.	(F1) One should look at the general pattern among 7 studies. Six reported ORs above 1.00.	(C1) There is a recurrent finding of relative risks moderately above the resolution power of the studies suggesting an association between electrical work and jobs with high magnetic fields and the occurrence of ALS.

TABLE 15.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all the associations are statistically significant.	(F1) All the studies are compatible with a RR of 1.5.	(C1) The heterogeneity in the 86% of studies with RRs above 1.0 is not great and has a reasonable explanation.
(A2) Estimates of association vary with no clear central tendency.	(F2) The small heterogeneity has a reasonable explanation. The studies with the crudest exposure had lowest RR, those with the highest propensity to selection bias had the highest RR, and the occupational studies with good exposure assessment had associations in between with pooled RR = 2.7 (1.4-5.0).	

TABLE 15.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Only 3 of the 7 studies allow the reviewers to look at magnetic field exposure from job-exposure matrices.	(F1) All three studies that ranked jobs by exposure show increasing risk with EMF exposure, but confidence intervals are wide.	(C1) The evidentiary base is not voluminous and the size of the studies are not sufficient to get a clear picture of dose response, but the pattern of evidence is more what one would expect if something about high EMF jobs, held for a long time, caused ALS.
(A2) Davanipour (Davanipour et al., 1997) shows no statistically significant associations for the whole group.	(F2) When the (Johansen & Olsen, 1998a) upper two categories of exposure are combined the SMR is 2.5 (1.1-4.8).	
(A3) Johansen (Johansen & Olsen, 1998a) shows no statistically significant associations for the entire group.	(F3) For both Davanipour (Davanipour et al., 1997) and Savitz (Savitz, 1998), a stronger dose response is seen in persons who have worked for at least 20 years. The associations (high to low) are respectively 5.5 (1.3-22.5) and 2.4 (0.7-8.0).	
(A4) There is no statistically significant dose response. This should pull down confidence a lot that something about high-EMF work (much less the EMF mixture itself) causes ALS.	(F4) In Savitz (Savitz et al., 1998a), only the 20-year exposure group displayed associations with narrow confidence limits. The other durations of occupation displayed associations with wide confidence limits and with no obvious pattern.	
(A5) Savitz (Savitz et al., 1998a) reports only the results for greater than 20 years exposure, the 10-20 year group shows some protection from EMF exposure.		

TABLE 15.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Electricity is everywhere. Why have we not seen an obvious epidemic of ALS?	(F1) Both exposures to strong EMF and ALS are rare events. The rate of ALS in the highly exposed group is only a few cases per hundred thousand.	(C1) If real, this would take sophisticated studies to detect and would not be obvious.

TABLE 15.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
No evidentiary base.	No evidentiary base.	(C1) There are no EMF animal bioassays for ALS.
		(C2) Experiments showing bioeffects at high EMF levels increases somewhat the credibility of EMF effects in general.

TABLE 15.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no known physical induction mechanism nor a chain of mechanisms leading from exposure to pathology.	(F1) It takes a while to figure out the causal processes underlying observations.	(C1) The lack of a mechanism does not pull confidence down as much as the presence would pull it up.

TABLE 15.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 15.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 15.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 15.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No mechanistic reason to pay attention to associations with other diseases.	(F1) Association with Alzheimer's, depression/suicide, and arrhythmic death suggest neurological effects. (F2) Association with other diseases strengthens confidence in EMF mixture bioeffects.	(C1) Has some relevance.

TABLE 15.2.15

SUMMARY TABLE FOR ALS			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance highly unlikely according to meta-analysis.	Unlikely		A non-chance explanation is needed
Upward bias not suggested. Cohort studies most likely free of bias report RR of 2.7 (1.4-5.0).	Unlikely	Possible	Slight increase
Confounding by shocks proposed but not highly credible.	More Possible	Possible	No impact or slight decrease
Combined bias, confounding, and chance.	Possible	Possible	Slight decrease
Strength of association does not fully exceed plausible bias or confounding.	More Possible	Possible	No impact or slight decrease
Consistency of association: 86% of RR above 1.0 (probability = 0.055).	Unlikely	Possible	Some increase
Dose response suggestive but not clear.	Possible	More possible	No impact or slight increase
Coherent with national and temporal trend.	Possible	Possible	No impact
Experimental: No EMF bioasays.	NA	NA	No impact
Plausibility: No mechanistic explanation.	Possible	Possible	No impact
No analogy.	Possible	Possible	No impact
Temporality.	NA	NA	No impact
Specificity: effect not restricted to subtype, other disease associations.	Possible	Possible	No impact, slight increase

15.3 Posterior (Updated) Degree of Certainty and IARC Classification

15.3.1 Statements of Individual Reviewers

Reviewer 1 (DelPizzo)

Degree of Certainty: The epidemiological studies present a fairly consistent pattern, with 6 out of 7 studies reporting RR > 1. The meta-analysis suggests that these results are not due to chance. It is this reviewer's judgment that the results are not likely to be due to bias or confounding, given the diversity of the studies' populations and design. The credibility of the hypothesis of hazard is boosted by the high degree of certainty attributed to other associations and the weakness of the arguments for an alternative explanation. In this reviewer's judgement, an appropriate evaluation is "close to the dividing line between believing and not believing" that EMFs increase the risk of ALS to some degree. For decision analysis purposes, the reviewer would use values between 20 and 80, with a median of 55.

IARC Classification: 2B, possible human hazard.

Reviewer 2 (Neutra)

Degree of Certainty: An association somewhat above the resolution power of the studies that shows up with moderate consistency in studies with and without the likelihood of upward bias and without an obvious confounder pulls up one's initial degree of certainty quite a bit despite the lack of analogous agents and a biological explanation. To give credence to the possibility of shocks or contact currents as the true agent to explain this association requires that the association with magnetic field exposure be quite strong and that these shocks be known to produce a larger association with ALS than magnetic fields do. The evidence for either of these assertions is weak to absent. This reviewer would characterize degree of certainty as "close to the dividing line between believing and not believing" that EMFs increase the risk of ALS to some degree. For the purposes of the decision model, a median degree of certainty of 52 ranging from 20 to 65.

IARC Classification: An IARC Classification of "Possible 2B" would be warranted by the fairly consistent epidemiological studies, tempered by the residual uncertainty as to whether magnetic fields are the responsible agent, and the lack of animal models or mechanistic explanations of the phenomenon. One could argue that the two utility cohort studies provide confirmation of the Deapen (Deapen & Henderson, 1986) and Davanipour (Davanipour et al., 1997) and Savitz death certificate study (1998a) that something about electrical occupations conveys risk, much in the way that IARC sometimes lists occupation in an industry as a cause for cancer and that the occupation (as opposed to magnetic fields in the occupations) warrants a 2A classification on the basis of consistent epidemiological evidence in humans.

Reviewer 3 (Lee)

Degree of Certainty: The human evidence of the ALS studies is based on seven occupational studies that differ considerably in design. This reviewer's posterior is increased over the prior due to the consistent associations mostly above a RR of 1.0. However, the posterior is slightly decreased for a lack of a dose response and the fact that confounding and bias cannot be ruled out. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "close to the dividing line between believing and not believing" that EMFs increase the risk of ALS to some degree category with median of 55 and a range of 20 to 75.

IARC Classification: The human evidence is modest but not consistent with chance explaining the body of evidence. Bias and confounding cannot be ruled out. Also, the animal evidence is inadequate, and there is no sound mechanistic rationale. Nonetheless, the evidence as a whole is sufficient for a Group 2B "possible human hazard."

15.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
ALS (Lou Gehrig's Disease)					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	9	
	2	2B	Close to dividing line	21	
	3	2B	Close to dividing line	11	

15.4 QUESTIONS RELEVANT TO DOSE RESPONSE AND POLICY

TABLE 15.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 15.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Davanipour (Davanipour et al., 1997) and Savitz (Savitz et al., 1998a) show an upward trend in risks with microtesla-years with no threshold or plateau in those with 20+ years of work. Johansen (Johansen & Olsen, 1998) shows the same for all workers. (C2) Only 3 studies are relevant. No suggestion of threshold or plateau.	(I1) Cannot provide "safe" dose or much dose-response information.

TABLE 15.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base. Primarily daytime long-term exposure.	None.

TABLE 15.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) To the extent there is any evidence (Savitz and Davanipour), it suggests an interval between exposure and disease around 20 years, the kind of interval seen in studies of the delayed effect of trauma and not the shorter intervals claimed for cancer induction in EMFs. (C2) Not all disease processes initiated by EMFs would have the same induction period.	None.

TABLE 15.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Similar to other reported associations (McGuire et al., 1997) as to size and frequency of occurrence. Not really relevant in any case.	None.

TABLE 15.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1,000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) With annual mortality of 1/100,000 (Kurtzke, 1980) and RR of 2.7, the 40-year added risk in workers, if real, might not reach the 1/1,000 benchmark, but would exceed the 1/100,000 environmental *de minimis* bench mark 85	(I1) Could be of environmental regulatory interest but might be considered *de minimis* from an occupational regulatory point of view.

TABLE 15.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 15.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are no known confounders that were not dealt with or are credible alternative explanations in the cohort studies. They are sophisticated occupational studies and they agree with the case-control studies. (C2) The case-control studies leave a lot to be desired. The cohort studies are sophisticated and of good quality. Future study could explicitly deal with shocks and trauma and their association with EMF exposure and with a more modern approach to the histopathology of major and minor shocks.	(I1) While ALS is so rare that it is probably a *de minimis* risk from a regulatory point of view, a JEM exposure study could address the shock and contact-current hypotheses for this and other diseases. A mechanistic understanding of this association might be relevant to the association with other diseases.

TABLE 15.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO CHANGE ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A population case-control study by Nelson et al. will be looking at electric shocks but not EMFs per se. (C2) An incidence study of ALS and EMFs by Johansen is pending.	(I1) Not likely to change assessment.

TABLE 15.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A better JEM exposure study in electrical workers and in the general population could address the hypothesis that contact currents or small shocks are correlated with measured magnetic fields. This could lead to reanalysis of other studies and suggest exposure conditions for experimental studies. The association between EMFs and ALS is unlikely to be explained in one or two iterations of study.	(I1) Results of initial research would be needed to anticipate progress. Current assessment likely to remain for a decade at least.

15.5 CONCLUSIONS ON POLICY-RELEVANT SCIENTIFIC ISSUES

15.5.1 DOSE RESPONSE

Something about electrical occupations and aspects of those occupations that are associated with magnetic fields is associated with ALS. Shocks have been proposed as an explanation, and contact currents could also be invoked although there is no direct evidentiary basis for associating shocks, contact currents, and magnetic fields. Other aspects or non-TWA summary exposure metrics have not be invoked as an explanation. Decades of exposure with long induction period may be important. The evidentiary base is not present to discuss thresholds or plateaus, or biological windows of vulnerability or social or ethnic vulnerability or exposure.

15.5.2 RESEARCH POLICY

ALS is a rare disease and an association, if real, might not translate into an absolute risk which was above *de minimis* bench marks for occupational exposures. A job exposure matrix examining shocks, contact currents, and electric and magnetic fields with various summary exposure metrics might help resolve the shock vs. magnetic field explanations for ALS, if applied to the existing data bases. Clarity in this rare disease might have implications for more common diseases associated with EMF exposures.

16.0 ALZHEIMER'S DISEASE

STATEMENT TO THE PUBLIC

Alzheimer's Disease)

The reviewers used two distinct sets of guidelines to evaluate the evidence:

- *Using the guidelines that the International Agency for Research on Cancer uses to assess cancer risks, they considered the evidence as "inadequate" to implicate EMFs. This was similar to conclusions by work groups of NIEHS in 1998 and of NRPB in 2002.*
- *Using the Guidelines developed especially for the California EMF Program one DHS reviewer was "close to the dividing line between believing and not believing" that exposure to EMFs at home or work could add to an individual's lifetime risk of contracting Alzheimer's disease and the other two were "prone not to believe" that EMFs conveyed any risk for this disease.*

The reviewers graphed their degree of certainty for the purposes of policy analysis as follows:

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Alzheimer's				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

16.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 16.1 Relative Risks Reported In Alzheimer's EMF Studies

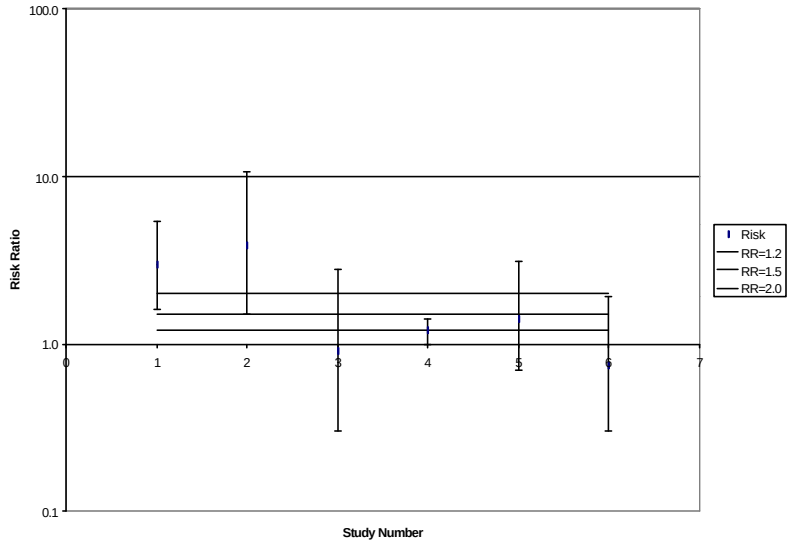


TABLE 16.1.1 KEY TO FIGURE 16.1.1

STUDY	NO	INDIVIDUAL ODDS RATIO	LOWER CL	UPPER CL
(Sobel et al., 1995)	1	3.00	1.60	5.40
(Sobel et al., 1996)	2	3.90	1.50	10.60
(Feychting et al., 1998b)	3	0.90	0.30	2.80
(Savitz et al., 1998b)	4	1.20	1.00	1.40
(Savitz et al., 1998a)	5	1.40	0.70	3.10
(Graves et al., 1999)	6	0.74	0.30	1.90

TABLE 16.1.2 DESCRIPTION OF ALZHEIMER'S STUDIES.

REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
(Sobel et al., 1995)	Study population: not specified. Cases: 3 series of AD patients examined, 1977-1993, at one neurological clinic in the US and 2 in Finland. Controls: 3 series: 1) vascular dementia patients; 2) patients without neurological disease; 3) neighborhood controls.	Interview data on primary occupation. Classification into high/medium vs. low EMF exposure.	CC	386 cases (36 exposed) 475 controls (16 exposed)	3.0 1.6-5.4
(Sobel et al., 1996)	Study population not specified. Cases: patients with probable or definite AD treated at AD medical center in California, US Controls: patients who were cognitively impaired or demented.	Statewide data form information on primary occupation. Classification into high/medium vs. low	CC	326 cases 152 controls	3.9 1.5-10.6
(Feychting et al., 1998b)	Study population: sub sample of the Swedish Twin Registry. Cases: identified through a screening and evaluation procedure. Controls: intact twins with 1 twin in each of 2 control groups where both were eligible.	Interviews. Primary and last occupation. Classification into 3 levels, based on JEM, highest > 0.2 μT.	CC	55 cases 228 and 238 controls	0.9 (primary) 0.3-2.8 (similar with other control group)
(Savitz et al., 1998b)	Male population in 25 states, US, 1985-1991. Cases: deaths from AD. Controls: deaths from other causes.	Job title on death certificate: electrical occupation in aggregate and individual jobs.	CC	256 cases in electrical occupation in aggregate	1.2 1.0-1.4
(Savitz et al., 1998a)	Male employees at 5 US utility companies, 1950-1988. Cases: deaths with AD mentioned on death certificate, identified through multiple tracking sources.	Measurements and employment records. Combination of duration and EMF index.	Cohort	16 cases with > 20 years in exposed occupation	1.4 0.7-3.0

REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
(Graves et al., 1999)	Members of a Seattle, WA, HMO. Cases of AD using NIH criteria. Healthy controls matched on age & sex.	Complete job and job title history. Each title assigned one of 3 ranks: 0 = background; 1 = intermittent; 2 = prolonged high fields	CC	89 controls 89 cases	0.74 0.29-1.92

Four out of the six studies have ORs above 1.00 (p = 0.23). Ahlbom (Ahlbom, 2001) calculates a summary OR for the two clinic-based Sobel studies of 3.2 (1.9-5.4). There seems to be true heterogeneity in these studies, related to the study design. The evidence is discussed below.

16.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 16.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Of the six studies reviewed, only two showed a statistically significant association. The others show no statistically significant effect.	(F1) Of the six studies reviewed, four showed RRs above 1.0; and, if one counts Feychting's RR of 2.7 for "last occupation," five of six reported RRs above 1.00. The cumulative binomial probability of this is 0.09, not conventionally significant, but also unlikely by chance.	(C1) One can argue about the pattern of the entire data, depending on whether one focuses on EMF as a cause of all dementias or specifically of Alzheimer's. However, at least some of these studies cannot be easily dismissed as due to chance.
(A2) The population-based studies show no statistically significant results.	(F2) It helps to see the overall pattern of association. Ahlbom (2001) also combined clinic-based studies (OR = 3.2; 95% CI: 1.9-5.4) and the pre-1999 population-based studies (OR = 1.2; 95% CI: 0.7-2.3) for a more refined look.	
(A3) One should not pool results of studies with different study designs, such as those considered here.	(F3) For all dementias, Feychting (Feychting et al., 1998b) reports an RR of 3.8 (1.4-10.2) for high EMF "last" occupations.	
(A4) One should not lump all dementia and Alzheimer's, or primary occupation and last occupation, in analyzing studies.		
(A5) The small Graves (Graves et al., 1999) study, which suggests a protective effect, emphasizes the randomness of the pattern of results.		

TABLE 16.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The two studies with the statistically significant RRs used clinic-based controls, which are subject to selection bias.	(F1) While clinic-based case control studies have a generically greater probability of bias, as alleged in A1 and A2, there is no identifiable scenario which would predict such a bias for clinics in both California and Finland. The association with last occupation (which on average lasted a long time) found in Feychting's (Feychting et al., 1998b) population studies suggests that bias is NOT the explanation.	(C1) The strongest associations were in the bias-prone clinic-based case-control studies. The small Feychting study, with good systematic diagnosis and population control groups, suggests an association between both dementia and Alzheimer's dementia (NS) and the last occupation (median duration 25 years). Bias cannot be ruled out from the strongest studies. The small Graves study, within a defined cohort, is inconsistent with the Sobel studies. However, the Graves study defined exposure differently.
(A2) Feychting (Feychting et al., 1998b) and Graves (Graves et al., 1999) drew cases and controls from defined populations and had careful diagnostic criteria for cases. They did not show large associations with usual occupation. This suggests that there is a problem with the two studies that used clinic-based controls.	(F2) Different definitions of "electrical occupation" will have different prevalence rates. One needs to compare cases and controls using the same definition. This was done in each of these studies.	
(A3) The subtle differences in the proportion of cases and controls with occupations whose average fields exceed 2 mG are small, compared to the differences in control groups in the various studies. These are around 3%-5% for Sobel (Sobel et al., 1995), (Sobel et al., 1996), 20% for Feychting (Feychting et al., 1998b) about 7% for Savitz (1998), and about 22% for Graves (Graves et al., 1999).		

TABLE 16.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One does not know all the causes of Alzheimer's and cannot control for them.	(F1) Known correlates were adjusted for in these studies.	(C1) There is little or no evidence to suggest confounding as a problem here.
(A2) Shocks and contact currents, not magnetic fields, might be the explanation.	(F2) The evidentiary base linking shocks and contact currents to Alzheimer's and magnetic fields is absent.	(C2) Alzheimer's is not well enough understood for one to be sure everything has been controlled for.

TABLE 16.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The associations are not so large that unspecified bias or confounding could be ruled out as an explanation	(F1) The Sobel (Sobel et al., 1995), (Sobel et al., 1996) associations are quite large.	(C1) Clinic-based studies such as those of Sobel, while well above the resolution power of the population studies, are more subject to selection bias. The population studies have ORs closer to 1.0 and are more vulnerable to unspecified bias.

TABLE 16.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is inconsistency in the population-based and clinic-based studies.	(F1) The clinic-based studies show strong associations. This should boost our confidence.	(C1) The Feychting (Feychting et al., 1998b) and Graves (Graves et al., 1999) studies are drawn from an identified population and have good diagnostic criteria but are small. They show associations with Alzheimer's that are below the null while Sobel's studies (Sobel et al., 1995), (Sobel et al., 1996), with clear diagnostic criteria, have associations well above the null. The rest of the studies have less-exact diagnoses and weaker associations. There is something here, but it is inconsistent.
(A2) The population-based studies have a weak to null association and make one worry about bias.		(C2) Examining the pattern of ORs, the binomial conditional probability of the observed ORs, given the hypothesis that the true OR is 1.0, is 0.34. The results are not consistent.

TABLE 16.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The Sobel (Sobel et al., 1995), (Sobel et al., 1996) studies are the only positive studies. The other four are non-supportive.	(F1) With the exception of Graves (Graves et al., 1999), which used a different exposure approach, the studies are not completely null.	(C1) There is a lack of homogeneity in results from the studies in non-null results, a lack that seems correlated with study design. Sobel's two clinic-based studies provide larger effects than the other studies.

TABLE 16.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is not a clear monotonic dose response in any of the studies.	(F1) The study designs did not provide a good chance to demonstrate a clear dose response.	(C1) The studies would not be expected to show a clear dose response because the exposure assessment was not refined. This criterion is not very helpful in this context.

TABLE 16.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) If EMFs causes Alzheimer's, why has there been no epidemic of Alzheimer's?	(F1) There is an epidemic.	(C1) There is no consensus that the age-specific incidence of Alzheimer's is increasing. Although, as the population ages, the number of CASES is increasing.
		(C2) The occupations in the Sobel (Sobel et al., 1995), (Sobel et al., 1996) studies are infrequent enough that they would not affect the overall Alzheimer's rates much. The smaller associations in the other studies also would not affect the overall prevalence much.

TABLE 16.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
No evidentiary base.	No evidentiary base.	(C1) No animal pathology studies with EMF.

TABLE 16.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no reason to believe that EMFs influence Alzheimer's.	(F1) Some experiments suggest EMF effects on calcium transport, and calcium transport plays a role in Alzheimer's.	(C1) The evidence linking EMFs to calcium and immune function is still contested, so mechanistic explanations are still speculative.
	(F2) Some experiments suggest that EMFs affect immune response, and immune response may be important in Alzheimer's.	

TABLE 16.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
None.	None.	See Generic Issues chapter.

TABLE 16.2.12

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One of Sobel's comparison groups (Sobel et al., 1995) consisted of patients with other dementias, and the relative risk between these to groups of patients was similar to that between Alzheimer's patients and healthy controls. That would suggest that EMFs don't do not cause non-Alzheimer's dementia. However, Feychting (Feychting et al., 1998b) shows the strongest association between electrical occupation and non-Alzheimer's dementia. Thus, there is inconsistency as to which disease is associated.	(F1) There were only 70 subjects in the Sobel control group. When compared to the 299 non-dementia controls, there IS a weak association, 1.3 (0.3-5.3) for primary occupation exposure above 2 mG.	(C1) The lack of consistency between studies—as to whether the association is with Alzheimer's alone, other dementias alone, or all dementias—may reflect the small numbers in the available studies.
	(F2) Feychting had 28 vascular dementia cases and 27 Alzheimer's cases. For vascular dementia, primary occupations with exposures above 2 mG conveyed an OR of 3.8 (0.65-28). For Alzheimer's, primary occupations conveyed an OR of 0.8 (0.3-2.3), and last occupations, an OR of 2.7 (0.9-7.8).	(C2) Feychting's data suggest that both conditions may be affected.

TABLE 16.2.13

SUMMARY TABLE FOR ALZHEIMER'S			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance: not an easy explanation.	Unlikely		Slight increase
Bias: in clinic-based studies might be an explanation.	More possible	Possible	No impact or slight decrease
Confounding by unspecified confounders, or shocks or contact currents.	More possible	Possible	No impact or slight decrease
Combined chance, bias and confounding.	More possible	Possible	No impact or slight decrease
Strength of association: (1) not large enough to rule out unspecified bias or confounding.	More possible	Possible	No impact or slight decrease
Consistency: four out of six studies had ORs above the null.	Unlikely	More possible	No impact or slight increase
Homogeneity: heterogeneous results by study design.	More possible	Possible	No impact or slight decrease
Dose response: not clear, in studies which had little chance of showing it.	Possible	Possible	No impact or slight decrease
Coherence/visibility: high exposure is rare so population impact would not be obvious.	Possible	Possible	No impact
Experimental evidence: no evidentiary base.	N.A.	N.A.	No impact

TABLE 16.2.13 (CONT.)

SUMMARY TABLE FOR ALZHEIMER'S			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Plausibility: calcium transport and immune effects evidence not strong.	Possible	Possible	No impact
No analogy.	Possible	Possible	No impact
Specificity: some confusion as to association with Alzheimer's or vascular dementia.	More possible	Possible	No impact or slight decrease

16.3 IARC CLASSIFICATION AND CERTAINTY OF CAUSALITY

16.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

REVIEWER 1 (DELPIZZO)

Degree of Certainty: The human evidence is very limited and not very consistent. This reviewer's prior is increased a little by the existence of other associations and experiments showing that EMFs can be biologically active, but the posterior level of confidence remains: "close to the dividing line of believing and not believing." For policy analysis purposes, this reviewer would use a median value of 40, with an uncertainty range of 25-55.

IARC Classification: Inadequate evidence.

REVIEWER 2 (NEUTRA)

Degree of Certainty: While there is fragmentary mechanistic evidence related to calcium transport, melatonin rhythms, etc., there is not a coherent mechanistic explanation, nor are there relevant animal pathology studies in this domain. This does not pull confidence down much below the prior degree of certainty, but it does not increase confidence either. There are two clinic-based studies, of the sort that traditionally has been considered subject to selection bias, which show associations well above the resolution power of the epidemiology. There is some weak support from an occupational study and a death certificate study. Two small population-based studies with good diagnostic criteria and job histories are not fully supportive. Taken together, the new information boosts the posterior confidence only moderately above the prior. This leaves this reviewer "prone not to believe" that EMFs increase the risk of Alzheimer's. For policy analysis, this reviewer would use a median of 20 and a range of confidence from 2 to 70.

IARC Classification: The lack of mechanistic and animal support and the heterogeneous epidemiology would lead to an IARC classification of evidence "inadequate" to characterize EMFs as a cause of Alzheimer's Disease.

REVIEWER 3 (LEE)

Degree of Certainty: The human evidence of the Alzheimer's studies is based on a small number of heterogeneous studies consisting of two clinical studies, subject to selection bias, which show positive associations; two non-supportive cohort studies; and support from an occupational and death certificate study. Overall, there is a consistently weak positive association across studies, which slightly increases this

reviewer's posterior over the prior. However, the posterior is slightly decreased by the heterogeneity of the studies, a lack of dose response, and the small number of studies contributing to the body of evidence. Hence, the posterior degree of certainty could be described as "prone not to believe" with a median of 15 and a range of 0.5 to 65.

IARC Classification: "inadequate."

16.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Alzheimer's				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

16.4 QUESTIONS RELEVANT TO DOSE AND THE STATE OF THE SCIENCE

TABLE 16.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Feychting (Feychting et al., 1998b) showed some association of EMFs with last job while Savitz (Savitz,1998) showed somewhat more association with exposures 20 years prior to diagnosis.	None.

TABLE 16.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The associations are similar in magnitude to those with known risk factors other than the genetic factors.	(I1) Not relevant to policy, perhaps to risk communication.

TABLE 16.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Despite the late onset of Alzheimer's, the high late incidence means that epidemiologically detectable RRs translate into a greater than 1/1,000 lifetime risk, if real.	(I1) Could be of regulatory interest if true.

TABLE 16.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Diagnosis, job history, exposure assessment, and sample size could be improved.	(I1) Suggest value of further study.

TABLE 16.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO CHANGE ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are large case-control studies in California by Sobel and in Washington state by Kukel; a death certificate study by Noonan in Colorado; and a blood amyloid beta study by Noonan and Reif in Colorado.	(I1) Could modify confidence but probably not resolve uncertainty.

TABLE 16.4.10

CAPABILITY OF CHANGING ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Unlikely to resolve issue.	None.

TABLE 16.4.11

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Better exposure assessment, in electrical jobs, including other occupational exposures such as contact currents and shocks. Larger, well funded residential case control studies, with refined exposure assessment. Such data could help resolve the question and could provide information to define exposure conditions of experimental studies. (C2) This policy-relevant disease has a small evidentiary base and would benefit from adequately funded studies.	(I1) Alzheimer's is a common condition. If it were related to EMFs, that would be important in policy formation.

16.5 CONCLUSIONS ABOUT DOSE AND THE STATE OF THE SCIENCE

16.5.1 DOSE-RESPONSE ISSUES

The evidentiary base is not sufficient to answer questions about special vulnerabilities, biological windows, thresholds, and plateaus.

16.5.2 RESEARCH POLICY

Alzheimer's becomes a common disease in the last decades of life and is devastating to patients and their families. As such, it would be an important factor in EMF policy if the degree of certainty that it caused this disease were increased. There are a number of suggestive studies. A careful exposure study of magnetic fields, electric fields, contact currents and shocks in work environments and in the residential environment, along with large well-conducted case control studies are warranted. When exposure conditions are better understood, mechanistic studies should be considered as well.

17.0 HEART DISEASE AND EMF EXPOSURE: EVIDENCE

STATEMENT TO THE PUBLIC

Heart disease

The reviewers used two distinct sets of guidelines to evaluate the evidence:

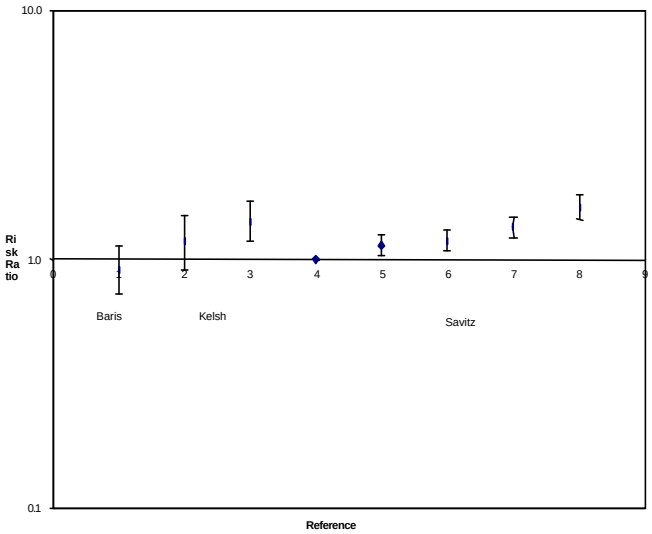
- *Using the guidelines that the International Agency for Research on Cancer uses to assess cancer risks, they considered the evidence as "inadequate" to implicate EMFs. This is the same conclusion reached by the workgroup of the National Institutes of Environmental Health Sciences in 1998*
- *Using the Guidelines developed especially for the California EMF Program, one of the reviewers was "close to the dividing line between believing and not believing" and two were "prone not to believe" that exposure to EMFs at home or work increases the risk of heart attack to any degree.*

They graphed their degree of certainty as follows:

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Heart				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

17.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 17.1.1 Heart Disease



There are three occupational studies that are relevant to this association. The relative risks reported in these studies are shown in Figure 17.1, the key for which is presented in Table 17.1. More details about the studies are given in Table 17.1.1. The study by Baris (Baris et al., 1996a) compared cardiovascular mortality in persons with exposures above and below the median magnetic field, electrical field and pulsed electrical exposures. No excess risk was demonstrated. Kelsh (Kelsh, 1997) examined cardiovascular mortality in broad job categories. Although non-administrative categories showed modest increases of risk relative to those of the administrative group, the categories containing jobs with the highest exposures did not show the highest relative risks. The third study by Savitz (Savitz et al., 1999) focused on deaths due to arrhythmia and acute myocardial infarction, a subgroup that was hypothesized to be vulnerable to interference in autonomic control of heart rate. A study by Sastre (Sastre, Cook & Graham, 1998) had suggested that EMFs might influence heart rate variability, and Tsuji (Tsuji et al., 1996) had demonstrated higher incidence of myocardial infarction in those with lower heart rate variability in the Framingham cohort. The Savitz (Savitz et al., 1999) study showed an association between length of employment in high-exposure jobs and estimated microtesla–years (μT-yrs) of exposure for this subgroup, but not from more chronic forms of cardiovascular disease resulting in death. These are modest but very precise associations. Two out of three studies with odds ratios above 1.0 could have easily occurred by chance. The discussion of these three studies and their impact on degree of certainty follows.

TABLE 17.1 KEY TO THE FIGURE

STUDY	EXPOSURE DEFINITION	REFERENCE NUMBER	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Baris et al., 1996a)	< 0.16 μT vs. > 0.16 μT	1	0.91	0.73	1.14
(Kelsh, 1997)	Management & professional	2	1.19	0.91	1.50
	Linemen	3	1.42	1.18	1.71
(Savitz et al., 1999)	0-0.6 μT-years	4	1.00	1.00	1.00
	0.6 to < 1.2	5	1.14	1.04	1.26
	1.2 to < 2.0	6	1.19	1.08	1.31
	2.0 to < 4.3	7	1.35	1.22	1.48
	> 4.3	8	1.62	1.45	1.82

TABLE 17.1.1 EPIDEMIOLOGICAL STUDIES OF HEART DISEASE MORTALITY WITH FULL SHIFT MEASUREMENTS OF MAGNETIC FIELDS

REFERENCE	STUDY POPULATION	EXPOSURE METHOD	MAGNETIC FIELD EXPOSURES	CASES	OR (CI)
(Baris et al., 1996a), Cohort mortality study	21,744 Hydro Quebec male utility workers employed an average 12.9 years. Employed between 1970 and 1988. All circulatory disease deaths.	JEMs from 2,066 workweek EMF measurements (50/60 Hz magnetic and electric fields, and pulsed EMF) applied to last job held. Also compared blue-collar and white-collar workers.	< 0.16 μT vs. > 0.16 μT. < 5.76 volts/meter vs. > 5.76 < 23.7 ppm vs. > 23.7 ppm	180 vs. 137 187 vs. 130 249 vs. 68	0.91 (0.73-1.14) 0.76 (0.61-0.95) 0.87 (0.66-1.14)
(Kelsh, 1997) Cohort mortality study	40,335 Southern California Edison utility workers. Mortality determined from 1960-88. SMRs were compared to general population. RRs were also obtained by comparing other utility jobs to administrative staff. Tracked "major cardiovascular" deaths.	Assigned each subject to the job category that he or she had occupied for the longest time while working for the company.	Management/ Professional Service/Labor Linemen Meter Reader/Field Service Plant Operations Trade/Craft Administrative/ Technical Total	103 82 217 25 130 216 223 996	1.19 (0.91-1.5) 1.48 (1.15-1.91) 1.42 (1.18-1.71) 1.71 (1.13-2.58) 1.56 (1.26-1.94) 1.43 (1.19-1.73) 1.00 reference
(Savitz et al., 1999) Cohort mortality study	138,905 men employed for > 6 months in 5 electric utilities, followed for mortality from 1950-86. Deaths due to arrhythmia, acute myocardial infarction, atherosclerosis, and chronic coronary heart disease, examined separately on basis of *a priori* hypothesis from a human experiment by Sastre (Sastre et al., 1998) related to autonomic control of heart rate.	Cumulative magnetic field exposure estimated from job history, plus JEM based on 2841 magnetic field measurements. JEM constructed for 28 occupational categories, collapsed into 5 exposure categories for TWA. Years employed observed for "exposed occupations": electricians, linemen, and power plant operators.	0- 0.6 μT-yrs 0.6-1.2 1.2-< 2.0 2.0-< 4.3 > 4.3 Total	1,031 852 899 946 510 Slope: RR/μT-yr 4,238	1.00 1.14 (1.04-1.26) 1.19 (1.08-1.31) 1.35 (1.22-1.48) 1.62 (1.45-1.82) 1.04 (1.03-1.06)

17.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 17.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Savitz (Savitz & Loomis, 1995), Baris (Baris et al., 1996a), and Kelsh (Kelsh, 1997) all showed that mortality from heart disease in all utility workers was lower than in the general public.	(F1) The Savitz (Savitz et al., 1999) study has more than 2 million person-years of observation and hundreds of thousands of person-years and hundreds of cases in each exposure category. The probability by chance alone would be extremely small for finding the RR of 1.14 (1.04-1.26) for the next-to-the-lowest exposure category of 6-12 mG-yrs, or for the association reported for the highest category of > 43 mG-yrs (RR = 1.62; CI:1.45-1.82).	(C1) While the RRs are not much above the usual resolution power of typical epidemiological studies, the Savitz (Savitz et al., 1999) study is so large that chance is a vanishingly small explanation of the pattern. This leaves bias, confounding, or causality as possible explanations.
(A2) Baris (Baris et al., 1996a) demonstrated no difference between cardiovascular disease in blue- and white-collar workers or in workers with occupational exposure to high magnetic fields, electric fields, or pulsed electric fields.	(F2) Savitz (Savitz et al., 1999) reanalyzed their data and found that the 65% of deaths due to acute MI or arrhythmia showed a statistically significant, monotonically increasing dose response between mG-yrs of magnetic field exposure and RR. Judging by the confidence intervals, this is very unlikely to be due to chance.	(C2) The healthy worker effect will tend to produce a lower cardiovascular death rate in utility workers as compared to the general population. Savitz (Savitz et al., 1999) had *a priori* reasons to propose that only the acute and arrhythmic infarctions should be sensitive to magnetic fields and the association Savitz demonstrated has not been duplicated elsewhere. It is highly unlikely to be due to chance.

TABLE 17.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Since the relative risks reported by Savitz (Savitz et al., 1999) are less than 2.5, they might be due to bias.	(F1) This study was not subject to selection bias or recall bias. It was subject to measurement bias that, on average, would have biased the associations toward the null.	(C1) No one has invoked a plausible bias to explain this association.

TABLE 17.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Magnetic field exposure might be associated with other risk factors for cardiovascular death, such as smoking, blood lipids, stress, etc.	(F1) These risk factors do not convey RRs much above the ones observed for magnetic fields. It is not plausible that they could explain away these associations. There are two pieces of evidence which argue against smoking as a plausible confounder. Lung cancer, which is largely driven by smoking, was not associated with magnetic fields in Savitz. Atherosclerotic heart disease is associated with smoking but was not associated with magnetic fields in the Savitz study. The association is limited to acute MI and arrhythmic MI.	(C1) Confounding, while not compelling (there is no reason to suspect that lipid profiles are associated with magnetic fields), has not been ruled out in this study.
(A2) Magnetic field exposure might be confounded with spark and contact current exposure.	(F2) There is not any evidentiary base to link shocks and contact currents to magnetic fields or to heart rate variability.	(C2) One needs to invoke risk factors associated with magnetic field exposure and ONLY sudden and arrhythmic cardiac death. This, too, has not been ruled out.

TABLE 17.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) None of the reported associations are so large that bias or confounding could not be invoked as an alternate explanation	(F1) There are associations with both duration of employment for high exposure groups and μT-yrs of exposure. No specific biases or confounders have been postulated to explain this.	(C1) One is reluctant to discount RRs barely above the resolution power of epidemiological studies routinely if they come from large, well-conducted studies, which is the case with Savitz. This may reflect reality. However, the danger of confounding cannot be ruled out.
	(F2) If exposure misclassification were corrected, the true association might be larger and less vulnerable to bias.	

TABLE 17.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One should never rely on one study, such as Savitz (Savitz et al., 1999), even if statistically significant.	(F1) Although Savitz (Savitz et al., 1999) may not be fully convincing on its own, the fact that two studies out of three indicate a risk increase is not very likely under the null hypothesis (p = 0.125).	(C1) With only three studies in the literature, consistency is not a very powerful argument for either the null or the alternative hypothesis.

TABLE 17.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The overall cardiovascular mortality in utility workers is lower than average. In Baris (Baris et al., 1996a), even blue-collar workers had lower than average mortality and no difference as to magnetic field exposure.	(F1) Baris (Baris et al., 1996a) examined all heart disease mortality, while Savitz examined arrhythmic and acute infarction deaths separately. Examining all deaths would have diluted Baris' results. This might explain her null results.	(C1) Kelsh (Kelsh, 1997) and Baris (Baris et al., 1996a) report differing results when examining all cardiovascular deaths, while Savitz reports associations with magnetic fields and with duration of occupation for arrhythmic and acute infarctions.
(A2) If Savitz (Savitz et al., 1999) is right, 65% of these deaths were due to arrhythmic or acute infarctions and the impact of magnetic fields should have been visible.	(F2) Baris dichotomized magnetic field exposure at the median exposure, including persons at risk in the reference group; hence, lessening the chance of seeing an association. Savitz began demonstrating excess risk in the second quintile of exposure. Kelsh (Kelsh, 1997) did see some increased risk for all types of cardiovascular deaths in high magnetic field jobs in the utility industry.	(C2) The smaller studies of Kelsh (36,000 workers) and Baris (22,000 workers) disagree with each other. But Kelsh is compatible with Savitz (139,000 workers).

TABLE 17.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) When Baris (Baris et al., 1996a), Kelsh (Kelsh, 1997), and Savitz (Savitz et al., 1999) are taken together, there is no clear dose response.	(F1) Savitz (Savitz et al., 1999) defines disease differently and is much larger than the other two. The 376, 625, and 507 acute myocardial infarctions, respectively, in electricians, linemen and power plant operators show an orderly increase of risk with increasing duration of employment; and the 4238 acute myocardial infarctions show an orderly increase in risk with increasing mG-years of exposure.	(C1) The only study to examine the subset of heart disease that is believed to be sensitive to the governance of the conduction system, acute myocardial infarction, shows an orderly dose response in three independent high-exposure jobs within the utility industry.
(A2) Kelsh (Kelsh, 1997) shows higher cardiovascular mortality for a variety of jobs, but the greatest RRs are not for the jobs that are the most highly exposed, linemen and plant operators.	(F2) Kelsh's job categories are quite broad and may have obscured differences.	(C2) RR/μT–yr = 1.04 (1.03-1.06).

TABLE 17.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A dramatic increase in cardiovascular death should have been seen when electricity was introduced and, afterward, as electricity use increased.	(F1) Before electrification, there was virtually no accumulated exposure. Now 75% of the population has a 24-hour TWA of .7 mG or more and would accumulate at least 49 mG-years over a 70-year lifetime. The data from Savitz suggests that a subset of CHD deaths would have increased by a factor of 1.41. The reviewers calculate that the total CHD rate might have increased by a factor of 1.21. This is not a dramatic change within the context of the change in dietary and other risk factors over the 20th century.	(C1) The Savitz (Savitz et al., 1999) data suggest the possibility that residential and occupational exposures could accumulate to produce epidemiologically detectable effects, yet these would not have dramatically changed overall CHD death rates.
	(F2) The coherence of dose response in three independent occupations in the Savitz (Savitz et al., 1999) utility study commands attention.	(C2) The internal coherence of the Savitz findings with regard to duration of employment and risk in three high-exposure jobs, and the association with mG-years for various lag times, increases the confidence somewhat.

TABLE 17.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is only one study showing an effect on heart rate variability (Sastre et al., 1998), and a replication study had not been reported by June 2000, the deadline for this evaluation.	(F1) Sastre (Sastre et al., 1998) showed an effect of 200 mG on heart rate variability in humans. Decreased heart rate variability has been associated with increased risk of cardiac events (Tsuji et al., 1996), (Martin, 1987).	(C1) The experimental evidence is scanty but suggestive.
	(F2) Various experimental results of bioeffects at high levels of EMF increase the credibility of the hypothesis that EMFs may interfere with living organisms.	

TABLE 17.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Even if EMFs produced transient effects on heart rate variability, the mechanism for long term exposures would have no theoretical basis.	(F1) Continual perturbation of the autonomic control of cardiac rhythm might produce permanent changes	(C1) The evidentiary base is scanty and insufficient to support or refute hypotheses.

TABLE 17.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
	NA	NA

TABLE 17.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not an issue.	(F1) Not an issue.	(C1) Not an issue.

TABLE 17.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Death certificate diagnoses are not reliable; the rationale for separating arrhythmic and acute infarctions from other infarctions or cardiac deaths is not very compelling.	(F1) The *a priori* specification of death certificate rubrics produced the predicted differential effect of mG-yrs of exposure.	(C1) The *a priori* predicted effect on a subset of CHD deaths increases confidence somewhat.
	(F2) The non-differential misclassification of disease and exposure should not have produced the kind of orderly dose response seen in the Savitz study.	

TABLE 17.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Statistical associations with cancers, miscarriage, or ALS should not be relevant to associations with CHD mortality.	(F1) While these diseases have different etiologies, the ability to cause one disease should boost the credibility of EMFs causing other diseases.	(C1) The associations with other diseases have some effect.

TABLE 17.2.15

SUMMARY TABLE FOR HEART DISEASE			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance: highly unlikely.	Unlikely		Increase
Upward bias: not suggested.	Possible	Possible	No impact
Confounding: a remote possibility.	More possible	Possible	No impact or slight decrease
Combination of bias, confounding and chance	More Possible	Possible	Slight decrease
Strength of association: does not exceed plausible confounding or bias.	More possible	Possible	No impact or slight decrease
Consistency: two studies out of three indicate a risk.	Possible	Possible	No effect
Homogeneity: Baris's results appear to be inconsistent with others.	More possible	Possible	No impact or slight decrease
Dose response: monotonic for duration and μ-T years in a large study.	Unlikely	Likely	Substantial Increase
Coherence: in several jobs and predicted invisibility in national rates.	Unlikely	Possible	Slight Increase
Experimental evidence: in Sastre study.	Possible	More possible	No impact or slight increase
Plausibility: lack of strong mechanistic explanation.	Possible	Possible	None
Analogy.	Possible	Possible	None
Temporality: not a problem.	Possible	Possible	None
Specificity of association: with arrhythmia's and acute MI. Other disease associations.	Possible	More possible	No impact or slight increase
Only one study shows orderly association.	More possible	Possible	No impact to substantial decrease

17.3 IARC CLASSIFICATION AND CERTAINTY OF CAUSALITY

17.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

REVIEWER 1 (DELPIZZO)

Degree of Certainty: With two smaller studies suggesting opposite conclusions, the evaluation is based on a single, though very large, study. The prior is boosted by a very clear monotonic dose-response relationship. In the opinion of Reviewer 1, the combined pattern of evidence is considerably more likely to occur if the association is causal than if EMFs were really harmless. Reviewer 1 is "close to the dividing line between believing and not believing." He has a confidence range of 25 to 55 and a median value of 42.

IARC Classification: Inadequate evidence.

REVIEWER 2 (NEUTRA)

Degree of Certainty: A small, human experiment (Sastre et al., 1998), unreplicated by deadline for this evaluation (June 2000), suggests that EMFs might affect autonomic control of heart rate in a way that might increase the risk of sudden cardiac death. This hypothesis is tested in a very large, state-of-the-art, retrospective cohort study by Savitz (Savitz et al., 1999). It shows a monotonic dose response with tight confidence intervals for duration of work in highly exposed workers, but for μT-years of exposure, only for the hypothesized subtypes of cardiac mortality, arrhythmic deaths and acute myocardial infarction. Overall, cardiac mortality is lower than the general population, as expected for healthy workers. The more routine comparison of total cardiac mortality showed no increased mortality in one study by Baris (Baris et al., 1996a). The Baris study compared all cardiac deaths in persons above and below the median and may have been too crude a comparison, which may well mask an effect in the upper few percent of the exposure distribution. Another study by Kelsh (Kelsh, 1997) showed some differences between exposed and unexposed occupations for all cardiac deaths combined.

All of these studies are state-of-the-art occupational mortality studies, with careful job exposure matrices. The very large Savitz study was the only one analyzed so as to specifically address the autonomic hypothesis. Its specificity, coherence, monotonic dose response, and statistical precision all go to provide a pattern of evidence extremely unlikely to be due to chance. But it is only one study. Could there be a confounder? State-of-the-art retrospective occupational cohort studies, such as this one, have not been able to collect confounding information on the subjects. Heart disease is a well-studied endpoint and there are many recognized risk factors. Smoking is an unlikely confounder, since lung cancer and atherosclerotic heart disease (strongly determined by smoking) were not associated with magnetic field exposure in the Savitz study. Shocks or contact currents, or other aspects of the EMF mixture, cannot be ruled out but have little supportive evidence.

Any confounder would have to be specifically related to arrhythmic and sudden cardiac death but not to other heart disease deaths. Other than non-differential exposure misclassification, which on average would tend to underestimate risk but could rarely increase apparent risk in a single study, bias seems unlikely. The good quality and very large size of the Savitz study makes chance an extremely unlikely explanation of its findings, but Reviewer 2's degree of certainty was pulled down by there being only one really relevant study and by the possibility of confounding.

Despite this, Reviewer 2 was moved by the evidence above the prior degree of certainty. Given the reviewer's initial degree of certainty for the range of effect that contains what has subsequently been observed, and all the streams of evidence, this reviewer has a posterior degree of certainty which one could characterize as "prone not to believe" that EMFs can increase the risk of heart attack. On a scale from 0 to 100, he has a wide range of uncertainty from 8 to 60 and a median estimate of 30. This is the degree of certainty that something about the EMF mixture, probably magnetic fields, is related to arrhythmic or acute myocardial infarction.

IARC Classification: Because there is only one study that properly analyzes the data and because there is no relevant animal experimental evidentiary base or strong mechanistic evidentiary base, Reviewer 2 would classify the heart disease evidence with an IARC classification of "inadequate" evidence to associate EMFs with arrhythmic or acute myocardial death.

REVIEWER 3 (LEE)

The human evidence of the heart disease studies are based on three studies, all occupation mortality studies, where only one study was large enough to assess a dose response and subtypes (Savitz et al., 1999). One study (Baris et al., 1996a) found no excess cardiovascular mortality. Overall, the consistent increased apparent risk just above the resolution power of two studies, as well as the evidence of a dose response, increases Reviewer 3's posterior above the prior. The fact that

confounding and other biases are a possible explanation and that only three studies contribute to the body of evidence decreases the posterior somewhat. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "prone not to believe" that EMFs increase the risk of heart attack to any degree. The degree of certainty centers around 25, with a range of 10 to 55

IARC Classification: The human evidence is weak, since it is based on three studies with only one sufficiently large study. Hence, chance, bias, and confounding cannot be ruled out. Also, the animal evidence is lacking, and there is no sound mechanistic rationale. Given this, the evidence as a whole is sufficient for a classification of "inadequate" evidence.

17.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Heart Disease				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

17.4 QUESTIONS RELEVANT TO DOSE AND THE STATE OF THE SCIENCE

The following tables deal with evidence relevant to potentially bioactive aspects of the EMF mixture, the shape of dose-response curves (if any), evidence for unfair vulnerability or exposure (if any), and the state of the science.

TABLE 17.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Magnetic fields might be confounded with shocks and contact currents. (C2) An elaborate job exposure matrix suggests that accumulated mG-years are predictive of risk. (C3) Long-term magnetic field exposure seems associated with risk. One cannot guarantee that a non-EMF confounder or another metric might be responsible for the association.	(I1) Some possibility that mitigating TWA would not affect risk.

TABLE 17.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidence suggesting a threshold. (C2) The effect of work-time exposure may add to the effect of other exposures. Averaging time may be shorter than 24 hours, so that "hits" at home add to "hits" at work. (C3) The data from Savitz suggest an association with 6-12 mG-years, within 5 years of exposure. Many occupations and residential settings could accumulate this kind of mG-year exposure.	(I1) If causal, these associations would affect a large proportion of population and could produce effects of regulatory concern.

TABLE 17.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) These are primarily daytime exposures. Not much is known about nighttime exposures. (C2) Not particularly helpful in demonstrating biological windows of vulnerability.	No impact.

TABLE 17.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Durations longer than 10 years and incubations as short as 5 years show associations in the Savitz (Savitz et al., 1999) study. (C2) The large numbers in the Savitz (Savitz et al., 1999) study allowed exploration of these issues. One sees stronger associations with longer exposure and effects within 5 years of the cessation of exposure.	(I1) If true, suggests that effects can show up within 5 years and can persist, and that prolonged exposure might increase risk. Could be relevant to work assignments and land use.

TABLE 17.4.5

EMFS COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) In the same ballpark as some of the recognized moderate risk factors. (C2) This is more relevant to risk perception than policy. Utilitarian policy is driven by the cost effectiveness of mitigation, not the effect relative to the effect of other factors.	No impact.

TABLE 17.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1,000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The average incidence of heart disease mortality is about 1/1,000, a 1.14 fold increase (the RR conveyed by the lowest Savitz exposure category sustained for 20 to 40 years of residence or occupation) would be more than the occupational regulatory benchmark of 1/1000 added lifetime risk or the environmental benchmark of 1/100,000. (C2) If true, these associations would convey lifetime theoretical risks of regulatory interest. (C3) There are about 17,000 sudden cardiac deaths in California each year. Even if EMFs accounted for only a few percent of these, the attributable cases would be in the hundreds per year because of this being a common event.	(I1) If true, could be of regulatory concern.

TABLE 17.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 17.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Savitz (Savitz et al., 1999) did not control for confounding. (C2) Confounders not likely to explain associations. (C3) One is reluctant to base policy on one study, but in a study this large, controlling for confounding is unlikely to be done.	(I1) Raises issue of how to verify large well-done study.

TABLE 17.4.9

NEW STUDIES IN PIPELINE AND THEIR ABILITY TO RESOLVE ISSUE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Re-analysis of the Kelsh (Kelsh, 1997) study and the Harrington (Harrington et al., 1997) study are underway. (C2) Kelsh-Sahl was one-quarter the size and Harrington was not much more than half the size of the Savitz (Savitz et al., 1999) study. They are unlikely to resolve this issue. (C3) If the Kelsh and Harrington studies confirmed the findings, they could strengthen the reviewers' conviction; if they do not, they would not cancel out Savitz. (C4) Nothing is now planned that would be likely to resolve this issue. (C5) A study by Graham (Graham, Cook & Sastre, 2000) came out after the June 2000 deadline. It did not confirm the Sastre (Sastre et al., 1998) experiment. The authors proposed testable reasons for these inconsistent results.	(I1) Will have some weight on interim actions and substantial weight on research directions.

TABLE 17.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Experiments using individual aspects of the EMF mixture may not be sensitive tests for the effect of the mixture itself. (C2) Experiments using actual environmental exposures may have a role. (C3) Job Exposure Matrix studies dealing with magnetic fields, electric fields, contact currents, shocks, and various summary exposure metrics will be needed to deal with suspected confounding with magnetic fields. (C4) Very large cohort studies or case-control studies are needed with refined diagnosis and sufficient numbers of highly exposed subjects. It would be helpful to explore supplementing existing CHD studies with occupational and residential histories. In cohort studies, prospective ascertainment of appliance use would be possible. (C5) Non-utility worker EMF exposures are likely to have different confounders than utility worker exposures, so that coherent results in other populations would increase confidence considerably and lack of confirmation would decrease it considerably.	(I1) The frequency of sudden cardiac death is so great that it is cost-beneficial to investigate it. (I2) The reported incubation period is short enough that this endpoint lends itself to study.

17.5 Conclusions About Dose and The State of the Science

17.5.1 Dose-Response Issues

Magnetic field exposure, or something associated with it, may influence acute MI deaths. The evidentiary base does not allow conclusions about which aspect of the mixture. The lower quintile categories of μT-years in workers overlaps with μT-years expected from residential exposures, but it is difficult to extrapolate to the general population.

The relative risks conveyed by these lower quintiles, if real, would translate to theoretical added lifetime risks above the 1/100,000 and 1/1,000 benchmarks that trigger regulatory action in the domain of carcinogens. Even if EMFs accounted for only a few percent of the 17,000 annual sudden cardiac deaths in California, this would be equivalent to hundreds of deaths per year. As years of exposure increase, the association becomes stronger. The data support a lag period of as short as 5 years.

17.5.2 Research Policy

An experiment by Graham (Graham et al., 2000), which came out after the deadline, does not confirm Sastre (Sastre et al., 1998). The re-analyses in the pipeline are of studies substantially smaller than the Savitz (Savitz et al., 1999) study. If they show similar results they would increase confidence; if they disagree they would not have the weight to cancel Savitz. For a common condition such as acute myocardial infarction, the value of information is high. Experimental studies and re-analysis of epidemiological studies should receive the highest research priority.

18.0 SUICIDE

STATEMENT TO THE PUBLIC

Suicide

The reviewers used two distinct sets of guidelines to evaluate the evidence:

- *Using the guidelines that the IARC uses to assess cancer risks, they considered the evidence as "inadequate" to implicate EMFs.*
- *Using the Guidelines developed especially for the California EMF Program, they all were "close to the dividing line between believing and not believing" that EMFs could increase the risk of suicide to any degree.*

The reviewers graphed their degree of certainty as follows:

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Suicide				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Close to dividing line	
	3	3	Close to dividing line	

18.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 18.1.1 Suicide

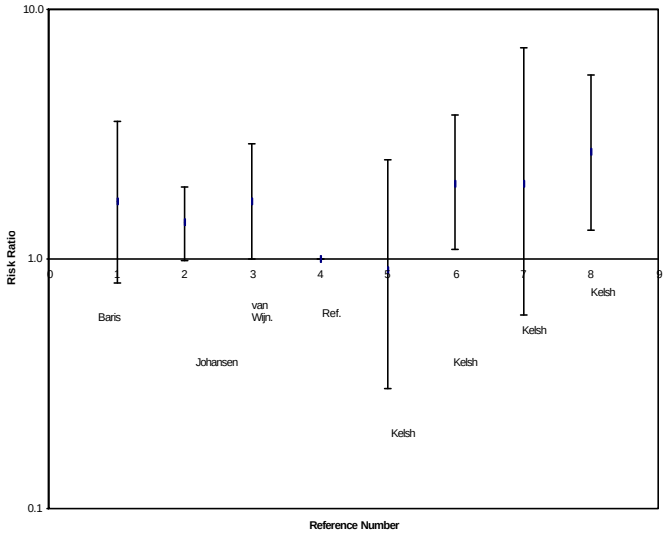


TABLE 18.1 KEY TO FIGURE 18.1.1

	EXPOSURE DEFINITION	REFERENCE NUMBER	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Baris et al., 1996b)	<0.16 μT vs. >0.16 μT	1	1.70	0.80	3.60
(Johansen & Olsen, 1998a)	< 0.09 μT vs. >1 μT	2	1.40	0.98	1.94
(van Wijngaarden et al., 2000)	> 0.12 μT yrs	3	1.70	1.00	2.90
(Kelsh, 1997)	Administration/technical	4	1.00	1.00	1.00
(Kelsh, 1997)	Management	5	0.90	0.30	2.50
(Kelsh, 1997)	Linemen	6	2.00	1.10	3.80
(Kelsh, 1997)	Meter readers	7	2.00	0.60	7.10
(Kelsh, 1997)	Plant operators	8	2.70	1.30	5.50

TABLE 18.1.2

REFERENCE	STUDY POPULATION	EXPOSURE METHOD	MAGNETIC FIELD EXPOSURES	CASES	OR (CI)
(Reichmanis et al., 1979)	Suicide victims and controls.	Estimates of residential exposure from power lines.		589	OR (not calculated) higher estimated and measured fields in cases' homes
(Perry, Reichmanis & Marino, 1981)	Suicide victims and controls.	Measurements in homes.			Higher measured fields
(McDowall, 1986)	Persons resident in vicinity of transmission lines in UK at time of 1971 census.	Home within 50 meters from substation or 30 meters from overhead line.		8	SMR = 0.75
(Baris & Armstrong, 1990)	Deaths in England and Wales during 1970-72 and 1979–83.	Job titles on death certificates. Electrical workers in aggregate as well as specific jobs. Proportional mortality study.	Job titles	495 suicide cases in electrical occupations	No increase for electrical workers.
(Johansen & Olsen, 1998a)	21,236 male employees in Danish utility companies observed during 1974-1993. There were 303,000 person-years of follow up. Cases: deaths from suicide in mortality registry.	Employment records and JEM: estimated average exposure level.	< 0.09 μT 0.1-0.29 μT 0.3-0.99 μT > 1.0 μT	21,236 males in cohort. 19 37 41 36	 SMR = 1.0 SMR = 0.8 SMR = 0.9 SMR = 1.4
(Baris et al., 1996a)	21,744 Hydro Quebec male utility workers employed an average 12.9 years. Employed between 1970 and 1988. All circulatory disease deaths.	JEMs from 2,066 workweek EMF measurements (50/60 Hz magnetic and electric fields, pulsed EMF) applied to last job held. Also compared blue-collar and white-collar workers.	< 0.16 μT vs. > 0.16 μT < 5.76 volts/meter vs. > 5.76 <23.7 ppm vs. > 23.7 ppm	11 vs. 20 11 vs. 20 19 vs. 12	1.7 (0.8-3.6) 1.6 (0.8-3.4) 1.3 (0.6-2.8)
(Baris et al., 1996b)	Case subcohort. Study of 49 suicides and 217 subjects from (Baris, 1996a) cohort study.	JEMs from 2,066 workweek EMF measurements (50/60 Hz magnetic and electric fields, pulsed EMF) applied to last job held. Also compared blue-collar and white-collar workers.	V/M-yrs geom. mean <23 23-40	 16 vs. 106 20 vs. 55	OR adjusted for SES, marriage and alcohol 1.0 3.1 (1.2-8.2)

REFERENCE	STUDY POPULATION	EXPOSURE METHOD	MAGNETIC FIELD EXPOSURES	CASES	OR (CI)
			40+ μT-yrs geom. mean < 1.25 1.25-2.1 > 2.1	13 vs. 54 26 vs. 107 8 vs. 54 15 vs. 54	2.2 (0.6-7.8) 1.0 1.3 (0.5-3.1) 1.9 (0.3-2.5)
(Kelsh, 1997)	Cohort mortality study. 40,335 Southern California Edison utility workers. Mortality determined from 1960-91. SMRs compared to general population and internal RR comparing other jobs to administrative staff. Tracked deaths for various endpoints, including suicide.	Assigned each subject to the job category that he or she had occupied for the longest time while working for the company.	 Linemen Plant Operators Meter Readers Management Admin./Technical	Case/pers.- yr 22/111,189 13/46,942 3/19,900 5/61,639 18/211,925	 2.0 (1.1-3.8) 2.7 (1.3- 5.5) 2.0 (0.6-7.1) 0.9 (0.3-2.5) Reference
(van Wijngaarden et al., 2000)	Cohort mortality study. 138,905 men employed for > 6 months in 5 electric utilities followed for mortality 1950-86. Deaths due to suicide.	Cumulative magnetic field exposure estimated from job history plus JEM based on 2,841 magnetic field measurements. JEM constructed for 28 occupational categories, collapsed into 5 exposure categories for TWA. "Recent exposures" shown here. Last 1-5 years also shows trend, but not past 10 to 20 or > 20 years.	0 μT-years 0-.029 .03-.049 .05-.11 > 0.12 Total	294 58 62 62 60 536	1.00 1.2 (0.8-1.9) 1.4 (0.9-2.3) 1.6 (1-2.7) 1.7 (1-2.9)

The reviewers reviewed eight epidemiological studies relating EMFs to suicide. The figure shows the four occupational studies that carried out internal comparisons as to magnetic fields or, in the case of Kelsh (Kelsh, 1997), job titles. In all these studies, the rate in utility workers was lower than that of the general population, but in all of them there was a pattern suggesting higher rates in the more highly exposed jobs. Only in the very large van Wijngaarden (van Wijngaarden et al., 2000) did this tendency nearly reach conventional statistical significance and display a monotonic dose response. The binomial probability of four out of four studies with ORs greater than 1.0 is 0.0625.

The discussion about bias and confounding in the occupational studies follows. The residential studies, the reviewers agree, provide inadequate evidence.

18.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 18.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of these studies do not reach statistical significance and should be disregarded.	(F1) One should attend to the pattern for all the data.	(C1) The monotonic upward trend in association size with dose in van Wijngaarden is unlikely to be a chance event, nor are the job associations in Kelsh (Kelsh, 1997). The trends in the smaller Johansen (Johansen & Olsen, 1998a) and Baris (Baris et al., 1996b) studies then catch one's attention and make chance less likely.

TABLE 18.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There might be biases.	(F1) The only likely bias in these cohort studies is non-differential measurement error, which would tend to obscure associations.	(C1) Upward bias is probably not much of an issue in these studies.

TABLE 18.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The people who do the high-exposure jobs are very different from the low-exposure office and managerial staff. These associations are probably due to confounders.	(F1) One can speculate about confounding, but one should not dismiss an association until one has shown that it is due to confounding.	(C1) Since these studies could not control for well-known confounders and since the jobs ARE occupied by different kinds of people, confounding needs to be addressed. One should not assume, however, that confounders explain the association as a default and let the matter rest.
(A2) Even the highly exposed categories of workers have lower-than-average suicide rates and lower-than-average proportional mortality for suicide Baris (Baris & Armstrong, 1990).	(F2) Baris (Baris et al., 1996b) controlled for SES, alcohol, and marital status; and this strengthened the association between suicide and electric and magnetic fields. Electric fields reached conventional statistical significance with an OR of 3.1 (1.1-8.2). van Wijngaarden (van Wijngaarden et al., 2000) found that controlling for SES and location were not important.	(C2) As was the case with cancers and heart disease, utility workers, like other healthy workers, had lower-than-average suicide rates, but there is some evidence for differential suicide and depression rates for high- and low-EMF jobs.
(A3) Much of the association reported by van Wijngaarden (van Wijngaarden et al., 2000) derives from recently retired or laid-off workers, few of whom had recent exposure. The effect was stronger in one western utility company. There must be some confounding to explain this strange pattern.	(F3) The healthy-worker effect predictably will give lower suicide rates in employed populations because the mentally ill are usually not recruited to run power generation plants or maintain transmission lines. It is the difference in suicide rates in highly-exposed and unexposed workers that should command our attention.	
(A4) When Baris (Baris et al., 1996b) controlled for mental disease, the weak association with magnetic fields went away.	(F4) Mental disease (mostly depression) was associated with high magnetic field and electric field jobs in Baris (Baris et al., 1996b) OR = 1.7 (0.6-4.7). Baris recognized that EMFs may cause the depression and the suicide. Controlling for mental disease is probably inappropriate since it may be on the causal path to suicide.	

TABLE 18.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) All of the reported associations are close enough to 1.0 to be easily explained by bias or confounding.	(F1) One should not ignore effects just because unspecified bias or confounding can be invoked.	(C1) Modest confounding could explain these associations.

TABLE 18.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is only one study with statistically significant associations with estimated magnetic field, and its association is not much above 1.0.	(F1) If one flipped four coins 100 times, all four would come up heads only six times.	(C1) Of four utility worker studies with internal comparisons, four had risk ratios above 1.0. This is a consistency whose probability slightly misses the conventional (but arbitrary) benchmark for statistical significance.
(A2) With only three magnetic field studies and four studies, if one counts Kelsh's job title descriptions, this pattern is easily due to chance. A probability of 0.0625 is bigger than the conventional benchmark of 0.05 and thus easily due to chance.		

TABLE 18.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Only one magnetic field study is statistically significant.	(F1) All three studies show effects close to RR = 1.5 for magnetic fields.	(C1) These large cohort studies with state-of-the-art exposure assessment show similar effects, but only the largest study had the power to achieve conventional statistical significance.
(A2) Johansen (Johansen & Olsen, 1998a) shows an association only at 1 μT, while Baris (Baris et al., 1996b) and van Wijngaarden (van Wijngaarden et al., 2000) show associations at 0.12-0.16 μT.	(F2) We may not have the power to resolve these differences.	(C2) The inconsistency of dose response does decrease confidence some.
(A3) Baris (Baris et al., 1996b) shows no associations with recent exposure, van Wijngaarden (van Wijngaarden et al., 2000) shows an association primarily with recent exposure.		
(A4) Baris (Baris et al., 1996b) shows little association with magnetic fields but shows an association with long-term electrical fields. This arises from multiple comparisons.		

TABLE 18.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Only van Wijngaarden (van Wijngaarden et al., 2000) shows dose response. Johansen (Johansen & Olsen, 1998a) had modest power but showed no dose response.	(F1) Johansen (Johansen & Olsen, 1998a) may not have had the power to show these associations, and it was an external, not internal, comparison.	(C1) There is some evidence for a monotonic dose response for magnetic fields but not electric fields.
	(F2) van Wijngaarden (van Wijngaarden et al., 2000) shows an orderly monotonic dose response for recent exposure.	
	(F3) Baris (Baris et al., 1996b) has a monotonic dose response for cumulative magnetic field exposure but not the statistical power to achieve significance.	

TABLE 18.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) An epidemic of suicides should have been seen when electricity was introduced.	(F1) The association is modest and with fairly high exposures. This effect would not have been obvious in temporal trends.	(C1) The effect would not have been visible without targeted studies.

TABLE 18.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The experimental evidence in humans and rodents for power frequency EMFs is mostly null.	(F1) Experiments may not have used the right aspect of the EMF mixture.	(C1) There have been no animal experiments on depression.
	(F2) Some experiments have suggested effects on sleep and behavior, and these are relevant to the nervous system and mood.	(C2) The experimental evidence for power frequency EMFs and melatonin is mostly non-supportive.
		(C3) Other experiments on behavioral endpoints are mildly supportive.

TABLE 18.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no demonstrated chain of causation from exposure to suicide.	(F1) There are some epidemiological studies suggesting an effect of the complete EMF mixture on melatonin (Wilson, Wright & Morris, 1990), (Burch et al., 1998), (Pfluger & Minder, 1996).	(C1) There is an established link between melatonin levels and depression, and the well-recognized increased risk of suicide in depressed persons. There is also some support, although not definitive, for the EMF mixture affecting melatonin in humans. Therefore, it is conceivable that EMF exposure could increase the risk of suicide.
(A2) McMahan (McMahan, Ericson & Meyer, 1994) and Verkasalo (Verkasalo et al., 1997) showed no association with mild depression. Savitz (Savitz, Boyle & Holmgreen, 1994) showed little association between depression and electrical occupation.	(F2) There are some epidemiological studies that suggest an association between the EMF mixture and depression (Poole et al., 1993); (Beale, 1998); (Bonhomme-Faivre et al., 1998a).	
	(F3) The healthy-worker effect may explain the Savitz (Savitz et al., 1994) findings. Savitz was not completely null in any case.	
	(F4) Melatonin has been used to predict the breast cancer/EMF association, too; and there is an overall association, at least for male breast cancer.	

TABLE 18.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no compelling analogy.	(F1) Seasonal affective disorder is thought to be due to light (another physical agent) and its effect on melatonin, among other possible mechanisms.	(C1) Not very influential to the reviewers.

TABLE 18.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See Generic Issues chapter.		

TABLE 18.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See Generic Issues chapter.		

TABLE 18.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The mechanisms of cancer, heart disease, ALS, and depression are quite different; shaky associations with these other diseases should not affect confidence about suicide.	(F1) Conditions that might be influenced by changes in melatonin are relevant to suicide.	(C1) Associations with other diseases increase confidence in this association slightly.

TABLE 18.2.15

SUMMARY TABLE FOR SUICIDE			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance: highly unlikely.	Unlikely		Moderate increase
Upward bias: not suggested.	Possible	Possible	None
Confounding: a possibility.	More possible	Possible	No impact or slight decrease
Combined chance, bias and confounding.	More possible	Possible	Slight decrease
Strength of association: does not exceed plausible confounding or bias.	More possible	Possible	No impact or slight decrease
Strength of association.	Unlikely	Possible	Moderate increase
Consistency of four internal comparison studies:	Possible	More possible	Slight increase
Dose response monotonic in van Wijngaarden and Baris (Baris et al., 1996b) but not Johansen (Johansen & Olsen, 1998a).	Possible	More possible	Slight to moderate increase
Coherence: invisibility in national rates.	Possible	Possible	No impact
Experimental evidence.	Possible	More possible	No impact or slight increase
Plausibility: melatonin and depression links.	Possible	Possible	No impact
Analogy.	Possible	Possible	No impact
Temporality: not a problem.	Possible	Possible	No impact
Specificity of association. Other diseases	Possible	Possible	No impact of slight increase

18.3 IARC Classification and Certainty of Causality

18.3.1 Statements of Individual Reviewers

Reviewer 1 (DelPizzo)

Degree of Certainty: The human evidence, consisting mainly of one large occupational study, tends to rule out chance as the explanation; but since many risk estimates come from the same study, the possibility of bias or confounding in this one study tainting the whole pattern of result must be considered. Nevertheless, additional support for the hypothesis of causality is offered by the hypothesis that melatonin suppression may contribute to depression and by the fact that other associations have been evaluated as likely to be causal. The arguments against causality are weak. In this reviewer's opinion, the combined pattern of the available evidence is more supportive than dismissive of the hypothesis. Since the evidence is so sparse that any conclusion must be tempered by large confidence intervals. Reviewer 1's assessment is: "close to the dividing line between believing and not believing" that EMFs increase the risk of suicide to some degree. For the purpose of decision analysis, Reviewer 1 would use a median of 49 with a range of 20 to 60.

IARC Classification: "Inadequate." With no animal pathology evidence possible, much more human evidence is required to make an assessment under these guidelines.

Reviewer 2 (Neutra)

Degree of Certainty: The appearance of associations between suicide and high-exposure jobs or estimated exposures within the large utility-industry cohort studies is quite suggestive to this reviewer and is somewhat increased by reported associations between the EMF mixture and melatonin levels, and some evidence about the EMF mixture and depression as measured in depression scales. The residential studies add only a very little to the impression, because of their designs. The possibility (but not a particularly strong one) of confounding factors, and the inconsistency between Johansen's (Johansen & Olsen, 1998a) reported dose response and that of van Wijngaarden (van Wijngaarden et al., 2000), pulls confidence downward. But, overall, this evidence moved the reviewer's confidence moderately upward from the prior.

This reviewer's degree of certainty in causality is best expressed as "close to the dividing line between believing and not believing" that EMFs increase the risk of suicide to some degree.For the purposes of the policy analyses, this reviewer would use a certainty score of 45 with a range from 15 to 70.

IARC Classification: The lack of definitive experimental and mechanistic evidence and the inability to rule out confounding in the large cohort studies would make this evidence "inadequate" to establish causality under the IARC scheme of classification.

Reviewer 3 (Lee)

Degree of Certainty: Overall, the relative likelihood of a consistently weak positive association increases the posterior over the prior. Some studies suggested dose response. However, the reviewer's posterior is limited by the fact that confounding cannot be ruled out, the heterogeneity of the studies, the lack of a clear dose response in all studies, and the small number of studies that contribute to the body of evidence. Hence, the posterior degree of certainty for purposes of the policy analysis is a score of 45 and a range of 15 to 80 thus "close to the dividing line between believing and not believing" that EMFs increase the risk of suicide to some degree.

IARC Classification: The human evidence is weak where chance, bias, and confounding cannot be ruled out. Also, the animal evidence is lacking and there is no sound mechanistic rationale. Given this, the evidence could be classified as "inadequate."

18.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Suicide				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Close to dividing line	
	3	3	Close to dividing line	

18.4 QUESTIONS RELEVANT TO DOSE AND THE STATE OF THE SCIENCE

The following questions address dose response and research policy issues.

TABLE 18.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Baris (Baris et al., 1996b) shows a statistically significant association with electric field but not with magnetic field, using a higher cutpoint than in the Baris (Baris et al., 1996a) study.	(I1) Some uncertainty about what aspect of EMF mixture is at work.

TABLE 18.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Baris (Baris et al., 1996b) suggest associations at levels that are experienced in the general population.	(I1) Implications for residential and occupational settings, if true.

TABLE 18.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base. Occupational studies are mostly daytime exposures, weak residential studies mostly nighttime.	None.

TABLE 18.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) van Wijngaarden (van Wijngaarden et al., 2000) suggests recent exposure within a year is important.	(I1) Effect would not be persistent, if true.

TABLE 18.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Similar to other modest risk factors.	No impact.

TABLE 18.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Suicide occurs at a rate of around 1/10,000 If this were increased by a factor of 1.5 over a 40-year work life or 70-year residential life, it would exceed the *de minimis* 1/1,000 and 1/100,000 benchmarks.	(I1) Could be of regulatory concern, if real.

TABLE 18.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	No impact.

TABLE 18.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Selection and exposure assessment are state of the art in these cohort studies. There is insufficient control for confounding, but it would be hard to obtain this information except in a prospective case-control study. A more refined assessment of induction period and examination of effect modification by age and other factors would be desirable.	(I1) Further studies could be done to resolve this issue.

TABLE 18.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are melatonin studies by Levallois in Quebec, Lee in California, and a depression study in pregnant women by Li in California, but no further suicide studies.	(I1) The pipeline studies are not likely to change current assessment much.

TABLE 18.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Prospective case-control studies of suicide related to transmission lines and within the utility industry could resolve the confounding issue. (C2) It would be important to know if post-partum depression or depression requiring hospitalization is associated with EMF mixture exposures. (C3) Clarifying the mechanism (if any) for suicide might be relevant to mechanisms (if any) for other diseases, even though suicide itself is rare enough that it alone might not have much influence in a cost-benefit-driven policy analysis.	(I1) Further research could clarify this body of evidence considerably.

18.5 Conclusions About Dose and the State of the Science

18.5.1 Dose Response

The evidentiary base is scanty for choosing aspects of the EMF mixtures or summary exposure metrics, determining biological windows of vulnerability, or special vulnerabilities in subgroups of the population. Both Baris (Baris et al., 1996b) and van Wijngaarden (van Wijngaarden et al., 2000) suggest the possibility of effects from exposures found in the general population as well as in utility workers. The interval from exposure to effect (if any) may be less than a year.

18.5.2 Research Policy

Although suicide is not so common that it alone would drive a cost-benefit-oriented policy, it has somewhat more mechanistic justification than the other conditions reviewed (but still not a strong support). There is substantial room for improvement in study design, and further study of suicide and serious depression (which is quite common and, if implicated, WOULD drive utilitarian policy) could provide policy-relevant information.

19.0 OTHER ADVERSE NON-CANCER HEALTH OUTCOMES

STATEMENT TO THE PUBLIC

Depression and Electrical Sensitivity

The reviewers found the evidence linking EMFs with depression and alleged electrical sensitivity to be "inadequate" and did not develop a degree of certainty for them different from their priors. This agreed with the assessment of the National Institutes of Environmental Health Sciences workgroup.

The reviewers found that the evidence pertaining to leukemia subtypes, CNS (except brain), lymphoma, cardiovascular disease (except acute myocardial infarction), and motor neuron disorders (other than ALS) was inadequate to carry out an evaluation. They also agreed with the NIEHS (1998) that the available evidence pertaining to depression and electrical sensitivity was "inadequate" to implicate electric or magnetic fields as causative agents. However, having the benefit of additional recent literature, the reviewers are in a position to offer a few caveats pertaining to these two endpoints

Depression: Ahlbom (Ahlbom, 2001) reviewed the literature related to depression, including the studies of Dowson (Dowson, 1988), Perry (Perry, Pearl & Binns, 1989), Poole (Poole et al., 1993), Savitz (Savitz et al., 1994), McMahan (McMahan et al., 1994), and Verkasalo (Verkasalo et al., 1997). Ahlbom concluded that the literature was inconsistent with Poole (Poole et al., 1993) (positive), and McMahan (McMahan et al., 1994) and Savitz (Savitz et al., 1994) (primarily null). He did not review the Beale (Beale, 1998) study, which came out after he had completed his review. Beale shows some relation between mood scales and magnetic field exposure to transmission lines. The reviewers remain close to their prior degree of certainty with regard to depression but believe that this is an area worthy of further study, particularly since it may shed mechanistic light on the EMF/suicide association.

Electrical Sensitivity: The reviewers conducted a study, as part of the California Department of Health Services routine random-digit-dial survey, to assess the prevalence of people who believe that they are unusually allergic or sensitive to electrical appliances or power lines. About 3% of 2,000 respondents alleged this sensitivity (see Appendix 3). A review of the literature (see Appendix 4), which includes a number of double-blind challenges of allegedly sensitive subjects, did not suggest that magnetic field exposure was responsible for the symptoms. There are some reports from the old Soviet Union of increased rates of symptomatic complaints in utility workers (Jerabek & et al., 1979), (Asanova & Rakov, 1975) and health complaints have been related to climactic and air ionizaton changes (Gad Sulman, 1980). Other aspects of the EMF mixture, such as contact currents, have not been systematically evaluated. If these complaints were to be linked causally to exposure to some part of the EMF mixture, one would need to ask how the pathophysiology of this syndrome was related to the pathophysiology of conditions like the leukemias, adult brain cancer, ALS, or miscarriage, which the authors of this document were inclined to believe to be linked to EMF exposure. The belief in electrical sensitivity led to changing jobs in 0.5% of Californians polled. Judging by anecdotal reports, an additional unknown number of people suffer from severe debilitating symptoms that they believe to be triggered by being close to appliances, power lines and the like. So this syndrome is impacting peoples' lives regardless of its etiology and requires further study. The null double-blind exposure studies have been criticized for not objectively selecting subjects or following their reactions long enough. If subjects could be found who reliably developed symptoms or physiological changes from EMF exposures that challenged biophysical assumptions under double-blind conditions, this would have implications for the interpretation of the literature pertaining to other health endpoints. Nonetheless the reviewers remain at their prior degree of certainty with regard to EMF and this self-defined syndrome.

20.0 ESTIMATING THE EXTENT OF THE POSSIBLE PROBLEM.

20.1 POTENTIAL ANNUAL NUMBERS OF DEATHS ATTRIBUTABLE TO EMFS

Two recent review articles calculated the proportion of all childhood leukemia cases that might be attributed to the rare highest residential EMF exposures. This was estimated to be around 3%. With about 100 childhood leukemia deaths per year, this would translate to about 3 deaths in California per year attributable to EMFs. The evidence does not permit similar direct calculations for the other reviewed conditions. However, suppose that only 1% of the conditions that were considered in this evaluation (minus those that the three reviewers "strongly believed" were not caused by EMFs) could be attributed to EMF exposure. The numbers of attributable cases could still be in the hundreds per year and comparable to the theoretical burden of ill health that has motivated other environmental regulation (di Bartolomeis, 1994). The annual California deaths from each of these conditions are shown in Table 20.1. The reader can apply 1% to these numbers to verify the assertion in the previous sentence.

TABLE 20.1 1998 YEARLY CALIFORNIA DEATHS (SOME FRACTION OF WHICH MIGHT BE AFFECTED BY EMFS) *

AGE GROUP	CHILD LEUK.	ADULT LEUK.	CHILD BRAIN	ADULT BRAIN	MALE BREAST	FEMALE BREAST	SPONT. ABORT.	ALS	ALZ-HEIMER	SUICIDE	ACUTE M.I.
0-19	99	0	79	0	0	0	11,000	0	0	171	2
29 Plus	0	1,888	0	1,294	30	4,095	49,000	434	320	3,044	17,236

* From http://www.ehdp.com/vn/ro/av/cau1/eg1/index.htm

20.2 POTENTIAL ADDED LIFETIME RISK FROM HIGH EXPOSURE

Since epidemiology is a blunt research instrument, the theoretical lifetime individual risk that derives from any agent that has an epidemiologically detectable effect will be automatically greater than the lifetime risk of 1/100,000 that triggers many regulatory processes. This means most of the epidemiological associations examined in this document could clearly be of regulatory concern if real.

That being said, with the exception of miscarriage, the theoretical lifetime risks from the highest EMF exposures are such that, depending on the disease and assuming relative risks ranging from 1.2 to 2.0, 93% to 99.9% of even highly exposed individuals would escape contracting the non-miscarriage health conditions studied.

These insights are illustrated in Table 20.2

TABLE 20.2 ADDED LIFETIME RISK IMPLIED BY RELATIVE RISKS OF 1.2 OR 2.0 FOR RARE AND COMMON DISEASES

ANNUAL INCIDENCE	DISEASES IN CATEGORY	ADDED ANNUAL RISK FROM: RR = 1.2; RR = 2.0	ADDED LIFETIME RISK FROM: RR = 1.2, RR = 2.0	LIFETIME CHANCE OF ESCAPING DISEASE AFTER EXPOSURE
1/100,000	ALS, Male Breast Cancer	0.2/100,000; 1/100,000	1.4/10,000; 7/10,000	99.99% ; 99.93%
5/100,000	Child Leukemia	1/100,000; 5/100,000	2/10,000 ; 10/10,000	99.98%; 99.9%
10/100,000	Suicide, Adult Brain & Leuk.	2/100,000; 10/100,000	14/10,000; 70/10,000	99.9%; 98.3%
100/100,000	Acute Myocardial Infarction	20/100,000; 100/100,000	1.4%; 6.8%	98.6%; 93.2%
1%	Alzheimer's	0.2%; 1%	NA (late onset)	NA
10%	Miscarriage	2%; 10%	NA (occurs during pregnancy)	NA

Two new epidemiology studies (Li et al., 2002), (Lee et al., 2002) suggest that a substantial proportion of miscarriages might be caused by EMFs. Miscarriages are common in any case (about 10 out of 100 pregnancies) and the theoretical added risk for an EMF-exposed pregnant woman may be an additional 10 out of 100 pregnancies according to these two studies. If true, this could clearly be of personal and regulatory concern. However, the type of EMF exposure implicated by the new epidemiological studies (short, very high exposures) probably come primarily from being very close to appliances and indoor wiring, and only rarely from power lines. Seventy-five percent of the women in the studies had at least one of these exposures during a day, and even one exposure a day, if typically experienced during pregnancy, seemed to increase the risk of miscarriage. Nonetheless, the vast majority of pregnant women with such exposures did NOT miscarry.

21.0 CONCLUSIONS

21.1 OVERALL CONCLUSIONS

Having examined and discussed each of the health endpoints mentioned above in a separate chapter in the main document, the three DHS reviewers each assigned their best judgment IARC classification and degree of certainty (as a number between 0 and 100). These determinations are summarized in Table 21.1. Column 1 displays the condition considered. Column 2 identifies the reviewer. Column 3 shows the IARC classification in which the number "1" denotes a definite hazard: "2a" a probable hazard, "2b" a possible hazard, and "3" evidence "inadequate" to make a classification. Column 4 displays the pre-agreed-upon phrases for describing zones of certainty. Column 5 shows the ratio of the reviewers imputed posterior odds to the reviewers imputed prior odds (more about this below). In column 6, the reviewers graphed their best-judgment degree of certainty as an "x" and indicated their uncertainty with a shaded bar on either side of that best judgment.

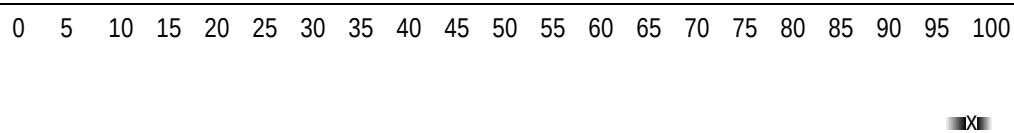
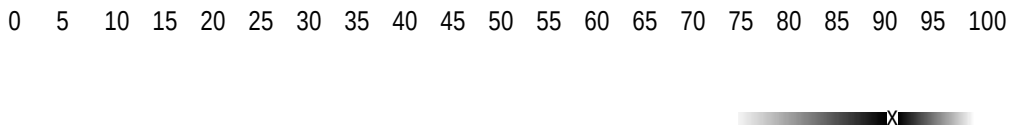
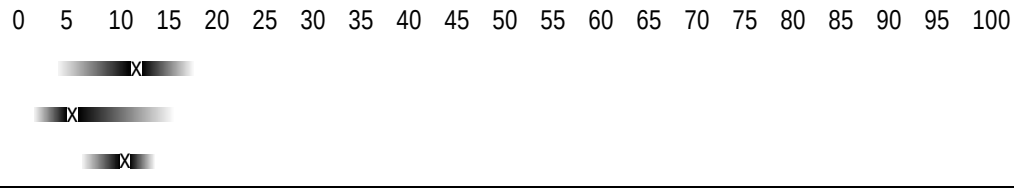
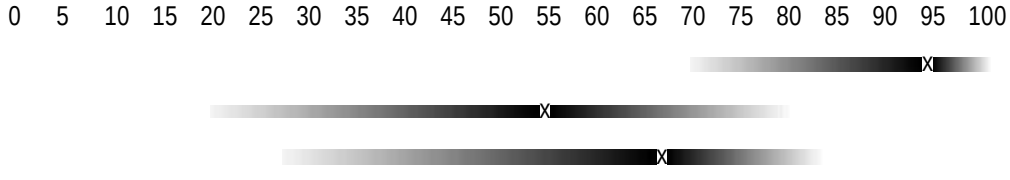
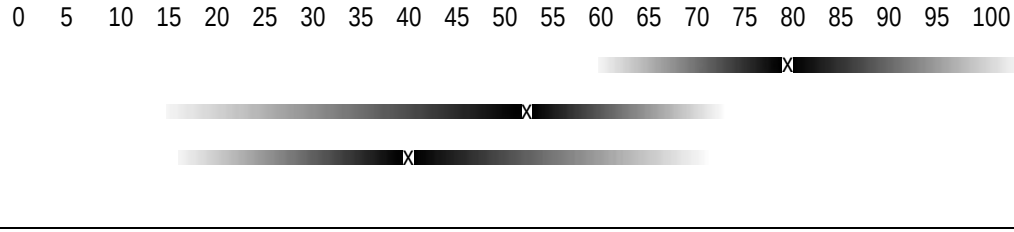
To provide an illustration, a method has been applied to two non-EMF examples in the first two rows. In row 1, Reviewer 2 has indicated that air pollution is a definite causal trigger of asthma attacks and that he is virtually certain of this. In row 2 he shows that he strongly believes that particulate air pollution causes excess deaths. There is relatively little uncertainty around either of these determinations.

Row 3 displays the prior degree of certainty that there would be epidemiologically detectable effects when comparing disease rates among persons exposed to EMFs at or above the 95th percentile of US residential levels to rates at or below the 1st percentile residential exposure. These prior degrees of certainty range from 5 to 12 on a scale from 0 to 100.

Column 5 is labeled "IRL" for "imputed relative likelihood." If the degree of certainty is converted to a probability scale (0–1.0) and, in turn, if one converted the probability to odds (probability/1–probability) the imputed prior odds can be compared to analogously calculated imputed posterior odds. One would base these on the "best judgment" posterior degrees of certainty graphed in Table 21.1. The resulting "imputed relative likelihoods" provide some indication of how much the overall pattern of evidence in biophysics, mechanistic, animal pathology, and epidemiological streams of evidence have combined to move the reviewers from their respective starting degrees of certainty. For example, with regard to air pollution triggering asthma attacks, the existing evidence has caused Reviewer 2 to move 900-fold from his prior, while the childhood leukemia evidence has moved him 22-fold*. Royall (Royall, 1997) has suggested anchoring the interpretation of such relative likelihood numbers on the relative likelihoods derived by probability theory from the following hypothetical experiment: Suppose that a reviewer has two urns, one that contains only white balls, the other that contains half white balls and half black balls. He takes one of the two urns at random. To determine which urn he has ended up with, he begins repeatedly withdrawing a ball and then replacing it in the urn (after noting down its color) and mixing up the balls before pulling out yet another ball. If on only one draw he were to find a black ball, he would know that he was dealing with the urn containing 50% black balls. But what is the relatively likelihood conveyed by drawing one or more consecutive white balls? Royall demonstrates that drawing 5 white balls in a row conveys a relative likelihood of 32, while drawing 10 consecutive balls conveys a relative likelihood of 1,024. Reviewer 2 views the asthma/air pollution data as being almost as strong as the evidence conveyed by drawing 10 consecutive white balls during the urn experiment, while the childhood leukemia evidence is equivalent to drawing just shy of 5 consecutive white balls.

* Reviewer 2 had a prior of 0.05 and a posterior for childhood leukemia of 54. The prior odds are 0.05/0.95 = 0.0526. The posterior odds are 0.54/0.46 = 1.174. The imputed relative likelihood is 1.174/0.0526 = 22.3.

TABLE 21.1 SUMMARY OF CONCLUSIONS ON ALL THE END POINTS CONSIDERED

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Air Pollution Triggered Asthma Attacks (Example: Not EMF-Related)	2	Human Risk	Virtually certain	931	
Particulate Air Pollution Triggered Deaths (Example: Not EMF-Related)	2	Prob. Risk	Strongly believe	171	
Prior Confidence that EMFs Could Cause Epidemiologically-Detectable Disease	1		Prone not to believe	1	
	2		Strongly believe not	1	
	3		Strongly believe not	1	
Childhood Leukemia	1	1	Strongly believe	140	
	2	2B	Close to dividing line	22	
	3	2A	Prone to believe	17	
Adult Leukemia	1	1	Prone to believe	29	
	2	2B	Close to dividing line	21	
	3	2B	Close to dividing line	6	

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Adult Brain Cancer					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Prone to believe	29	
	2	2B	Close to dividing line	20	
	3	2B	Close to dividing line	13	
Childhood Brain Cancer					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line		
	2	3	Prone not to believe		
	3	3	Prone not to believe		
Breast Cancer, Female					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	7	
	2	3	Prone not to believe	3	
	3	3	Prone not to believe	2	
Breast Cancer, Male					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	6	
	2	3	Prone not to believe	12	
	3	3	Prone not to believe	2	
EMF Universal Carcinogen?					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Strongly believe not	0.4	
	2	3	Strongly believe not	0.5	
	3	3	Strongly believe not	0.2	

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Miscarriage					0 5 10 1 5 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	9	
	2	2B	Close to dividing line	20	
	3	2B	Close to dividing line	11	
Other Reproductive					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Strongly believe not	0.4	
	2	3	Strongly believe not	0.8	
	3	3	Strongly believe not	0.2	
ALS (Lou Gehrig's Disease)					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	2B	Close to dividing line	9	
	2	2B	Close to dividing line	21	
	3	2B	Close to dividing line	11	
Alzheimer's					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	5	
	2	3	Prone not to believe	4	
	3	3	Prone not to believe	2	
Suicide					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	6	
	2	3	Close to dividing line	15	
	3	3	Close to dividing line	7	

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	IRL	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Heart Disease					0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	6	
	2	3	Prone not to believe	8	
	3	3	Prone not to believe	3	

21.2 How Different Is This Evaluation From The NIEHS, NRPB and IARC Findings?

As outlined in Table 21.2 below, there are both common points and significant differences between the EMF Program's evaluation and those carried out at about the same time by the NIEHS Working Group for the Federal EMF-RAPID Program (Portier & Wolfe, 1998), (IARC, 2001), and the NRPB (NRPB, 2001a), (NRPB, 2001b) (Note: The NRPB did not use the IARC classification system but expressed their conclusion using common language expressions).

The following table compares these evaluations:

Table 21.2 A Comparison of DHS Reviewers' Degree of Certainty with That of Other Agencies

HEALTH OUTCOME	NIEHS WORKING GROUP	IARC	NRPB	DHS
Childhood leukemia	2B*	2B	Possible	2B to 1
Adult leukemia	2B (lymphocytic)	Inadequate	Inadequate	2B to 1
Adult brain cancer	Inadequate	Inadequate	Inadequate	2B
Miscarriage	Inadequate	Not Considered	Not considered	2B
ALS	Inadequate	Not Considered	Possible but perhaps due to shocks	2B
Childhood brain cancer, breast cancers, other reproductive, Alzheimer's, suicide, sudden cardiac death, sensitivity	Inadequate	Inadequate or Not Considered	No for Parkinson's disease, inadequate for Alzheimer's, other endpoints not yet considered	Inadequate

* Although the majority of scientists assembled to prepare the NIEHS Working Group Report voted for a "possible 2B" classification for these cancers, the lay person's summary submitted by the Director of NIEHS to Congress stated: "ELF-EMF exposure cannot be recognized as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard." (Final Report NIH Publication 99-4493, May 1999)

It is clear from Table 21.2 that, when applying the IARC guidelines, the DHS reviewers agreed with IARC and NIEHS reviewers that in many cases (e.g., childhood brain cancer and male and female breast cancer), the evidence would be classified by IARC as inadequate to reach a conclusion. One of the DHS reviewers agreed with the IARC and NIEHS on childhood leukemia. Two of the reviewers agree with NIEHS, but not with IARC, on adult leukemia. All three reviewers agreed with NRPB that EMF was a "possible" cause of ALS. Otherwise, the DHS reviewers regard the EMFs association more likely to be causal than NRPB, IARC, or NIEHS did.

It should be noted that all of the review panels thought that the childhood leukemia epidemiology warranted the classification of EMF as a "possible" carcinogen and thus did not agree with the biophysical arguments that EMF physiological effects (and therefore pathological effects) were "impossible."

There is a wide range of opinions in the scientific community as to the probability that EMFs cause health problems. The DHS reviewers provided numerical values for their degrees of confidence that risk of various diseases could be increased to some degree by EMF exposure. Other researchers have rarely packaged their judgments in this way, so it is hard to make comparisons. Judging by one such exercise that the DHS reviewers conducted (Neutra, 2001), reasonable scientists can have different ways of interpreting the data resulting in different degrees of certainty.

The three DHS reviewers have been active in the EMF field for more than a decade and are familiar with the opinions and arguments used by the scientists in scientific meetings. Since Reviewer 1 was part of the IARC-EMF review panel and all three reviewers had some participation in the earlier parts of the NIEHS process, they also have some understanding of the process by which selected panels of these individuals arrived at a group determination about EMFs. The reviewers think there are at least two relevant differences between their process and the usual procedures followed by the other groups.

First, the DHS Guidelines require that they consider the inherent tendency of the several streams of evidence to either miss a true effect, or falsely "indict" a putative causal agent. The weight given to those streams of evidence was influenced by this consideration. The standard guidelines involve discussions of whether the adjectives "limited" or "sufficient" best fit the pattern observed in a stream of evidence, and depending on the decision one makes, simple guidelines of how combinations of "limited" and "sufficient" streams of evidence influence whether a "possible," "probable," or "definite" causal status is assigned. While the DHS Guidelines allow null results of animal pathology studies using one ingredient of a mixture to get little weight, the IARC rules involve a simple combination of binary judgments about the animal and epidemiological evidence. The way the DHS reviewers used the Guidelines meant that they did not let the primarily null results from the mechanistic and animal pathology streams of evidence decrease their certainty as much as seems to be the case for reviewers in other panels. The reasons for this have been explained above. Having been less deterred by the null mechanistic and animal pathology, they were also less prone to invoke unspecified confounders and bias as an explanation for the persistent, if not homogeneous, epidemiological findings for certain health endpoints.

The other reason for the discrepancies in the DHS reviewers' IARC classification choices can be traced to differences in the procedures for combining the scientists' judgments. They found several striking differences between the IARC and this evaluation processes:

- The Panel's Composition. The EMF Program's review was carried out by the EMF Program's scientific staff and not by a large panel of experts outside the agency. An outside panel, however, evaluated the document. One could criticize the DHS panel as being too small and not diverse enough, but this is standard procedure for California government agencies. The IARC followed its usual practice of convening outside experts to write drafts, discuss the drafts, and turn these over to staff to finalize. Given the spread of the scientific opinions on the EMF issue, it is safe to say that the outcome of any review is a strong function of the working group members' belief before the review takes place. (The DHS reviewers have striven to make this transparent through the elicitation of the prior beliefs and the "pro and con" discussion.) Two unbiased ways to assemble a working group would be by random selection out of a pool of "qualified" individuals or through a conscious effort to include balanced numbers of individuals known to have opposite points of view. In the first case, the definition of "qualified" could influence the verdict of any sample, and sampling variability could yield a mix of opinions that would vary from sample to sample so that different working groups could reach different conclusions. The second procedure could be an excellent solution, if the evaluation were carried out through extensive debates and discussions, with a shared desire to come to a consensus opinion irrespective of its potential social and economic consequences. This was the original approach used by IARC (Tomatis, private communication). However, the pressure to conclude the evaluation within a short period of time led to

abandoning the discussion format in favor of the voting system. This leads to the next important difference.

- The Time Element: The meeting to draft the IARC-EMF monograph (June 2001) lasted five-and-a-half days. The vast majority of the plenary session time was dedicated to reviewing the draft chapters prepared ahead of time by designated committee members with maybe 10% of the time allowed for discussion of the rationale for reaching conclusions. Whenever a paragraph precipitated a controversial discussion, a common way out was to propose the deletion of the offending paragraph, a proposal that the time-pressured working group members were usually glad to adopt. In contrast to this process, the DHS reviewers spent innumerable hours and days, over a period of years and in consultation with independent consultants, to explain their inferences and resolve or clarify their differences.
- The Format of the Conclusion: IARC aims for a consensus conclusion. Members with more extreme views are strongly encouraged to converge on a middle of the road conclusion. In the California evaluation, if consensus could not be reached (as was the case for some endpoints), each member was allowed to express his or her personal belief. Although two of the DHS reviewers were subordinate to the third, substantial differences remained for some endpoints and are openly revealed in this evaluation.
- IARC's Voting System: The members of the working group were asked to vote separately on animal and human evidence. Although a sizable minority of the working group believed that there was limited animal evidence indicating a possible cancer risk, their opinion was not carried past that point of the process. Since the majority regarded the animal evidence as "inadequate," when the final vote on the overall evaluation was taken, the options posed to the working group's members were the majority positions, that is, that animal evidence was inadequate and epidemiological evidence for childhood leukemia was limited. According to the guidelines, these two majority positions resulted automatically in a Group 2B classification and Class 2A or Class 1 were not even considered as options to vote on, even if individual reviewers, such as Reviewer 1, might have so voted. The published monograph does not document that the minority view had in fact a higher degree of certainty of the EMF risk than the majority view.

Somewhat similar considerations apply to the NIEHS evaluation. Although the whole process lasted eighteen months, the decision was reached over the course of a week-long meeting, followed by a vote. This meeting was preceded by a series of workshops including discussions and presentations, but not all members of the working group participated in the workshops, and most of the workshop participants were not members of the working group. Therefore, the final conclusion was still the result of a few days intensive meeting, during which much of the time was devoted to revising and finalizing the wording of the final report rather than to writing about points of controversy. The working group report did document the vote count.

Apart from procedural differences, there are also philosophical differences between the various review panels. For example, with regard to adult leukemia, the IARC's evaluation differs from the NIEHS and the California evaluation because of the way epidemiological evidence was considered. Almost all the evidence on adult leukemia comes from occupational studies. The Epidemiology subgroup at the IARC meeting regarded most of these studies as being of poor quality, with within- and between-study inconsistencies. Most of the evaluation centered on the most recent large studies (Sahl et al., 1993), (Savitz & Loomis, 1995), and (Theriault et al., 1994), which contradicted each other. The DHS reviewers' evaluation considered the whole body of studies, residential and occupational. While they acknowledge that many of the studies have limitations, neither they, nor the IARC reviewers, have identified fatal flaws. For example, there is no evidence to suggest that the use of crude exposure assessment surrogates, while virtually certain to influence the quantitative estimate of risk and to frustrate any attempt to explore the dose-response relationship, introduced an upward bias in the reported association. On the contrary, the limitations of the studies may well be responsible for the inconsistencies between them. And while these inconsistencies do exist, they are not as common as the IARC evaluation may suggest. The Kheifets (Kheifets,1997) meta-analysis concludes that the body of epidemiological evidence shows a slight but statistically significant increase in risk. From a binary outcome standpoint, the studies with an RR estimate >1 are more than twice as numerous as those with an RR # 1.

Nonetheless, where the DHS and other reviewer panels agreed to assign a "possible" carcinogen label to an EMF/disease association, it is not easy to infer if there would be agreement on a degree of certainty. According to Dr. Rice, Chief of IARC's Carcinogen Identification and Evaluation Unit (personal communication to DelPizzo), "If IARC were to say that an exposure is in Group 2A, probably carcinogenic to humans, that would mean that the evidence is just a little short of certainty that the exposure in question has actually caused human cancer . . . Group 2B is the lowest level of identifiable carcinogenic hazard in the IARC system."

Finally, it must be remembered that in DHS's EMF Program, policy recommendations were addressed separately from the risk evaluation. In some other cases evaluations are part and parcel of a policy recommendation (they may include regulatory recommendations in the conclusion). This may make them more conservative, as it seems to be the case with IARC:" ... the IARC Monographs system of carcinogenic hazard evaluations is deliberately a very conservative one. There are many carcinogenic hazards in the human environment that are very real indeed, and control of exposures to those hazards is extremely important for public health. To accomplish this, it is necessary that carcinogenic hazards be correctly identified. We must avoid misdirecting public attention to any exposure of any kind that may be perceived as a hazard, but in fact is a misplaced concern." (Dr. Jerry Rice in a letter to Vincent DelPizzo, Aug 10, 2001.) The cover letter to the NIEHS report to congress concluded with a recommendation for only "passive regulatory action" (NIEHS, 1999). The DHS three reviewers have packaged their differing degrees of confidence about causality in a way that can be used in the decision analytic models prepared for the program. It has pointed out that the policy implications of this range of confidences depends on the policy framework of the decision maker: non-interventionist, utilitarian, virtual-certainty-required, or social justice. The public regulatory process will determine which one or which mixture of these frameworks will apply to govern policy. Thus the DHS risk evaluation is packaged to facilitate decision making but separates risk assessment from risk management. The fact that a reviewer may feel very certain that EMF is a risk factor for a particular disease does not imply that he or she advocates exposure mitigation.

In summary, the differences between the DHS reviewers' judgments and those of other reviewers are partly due to differences in procedure and terminology and partly due to the way those three reviewers weighed the several streams of evidence.

21.3 Differences Between DHS Reviewers

As noted above, the three DHS reviewers were not able to reach a consensus on all health endpoints. In this section, they explain the reasons behind their respective judgments.

21.3.1 Reviewer 1 (DelPizzo)

In almost all cases, Reviewer 1's posterior degree of certainty is higher than that of the other two reviewers. There are several reasons for this difference.

c) Different priors—the reviewer is generally more suspicious of man-made environmental pollutants, which have no place in the evolution process.

d) Reliance on the sign test—this reviewer has put much weight in the sign test, a simple, dichotomous test, which measures the probability of several studies erroneously reporting the existence of a risk while no risk truly exists. In many cases the test finds that this probability is extremely small, that is, the results are **unlikely** to be erroneous. In the reviewer's opinion, this test is particularly suitable to answer the simple question, is there a risk or not? rather than asking what the relative risk is. The results of this test are not changed if the outcome of one or more studies are **partly** due to bias. Some worst-case scenarios, assuming extraordinary coincidences of chance and bias acting simultaneously in the same direction, do weaken the evidence, but when a condition has been studied by many different investigators, these scenarios do not reduce Reviewer 1's belief by much.

c) Weight given to empirical results—Reviewer 1's prior was limited by the intuitive belief that the energy associated with environmental EMFs is so small that, even if these fields are potentially disruptive, the amount of disruption is insufficient to cause a biological effect. Once Reviewer 1 examined the results of *in vivo* and *in vitro* research on EMF exposure, however, he became convinced that biological EFFECTS (as distinct from PATHOLOGY) can result from exposure to levels below those which conventional knowledge considers necessary. That is, if one equates "energy" to "dose," exposure to environmental fields may be regarded as a non-negligible dose. Thus, the argument that kept Reviewer 1's prior low disappears and the possibility of a hazard, when repeatedly reported by independent epidemiological studies, becomes more credible.

21.3.2 Reviewer 2 (Neutra)

The fact that EMFs are the only agent that this reviewer has encountered for which there are theoretical arguments that no physiological, much less pathological, effect could be possible, did decrease Reviewer 2's prior somewhat. But physics applied to simplified models of biology were not convincing enough to make this prior credibility vanishingly small. This reviewer noted biological effects in mechanistic experiments in the thousands of mG but accepted the arguments that these were probably not relevant to effects below 100 mG. The few experiments that claimed to show an effect below 100 mG (the chicken embryo studies and the confirmatory studies of Liburdy's melatonin studies) were considered highly worthy of further study, but not robust enough or free enough of alternative explanations at this point

to cancel out the modest initial doubts about the energetic feasibility of residential EMFs to produce biological effects. The animal pathology studies have convinced Reviewer 2 that very high intensity pure 60 Hz or 50 Hz sinusoidal magnetic fields do not have a strong enough effect to produce consistent pathological effects in small numbers of the species and strains of animals selected for study. If these species of animals were to respond as humans are described to have done in the epidemiology, this was a predictable result even if pure sinusoidal 60 Hz fields were the active ingredient of the EMF mixture. Humans exposed to hundreds of mG, when compared to persons with 24-hour average exposures around 1 mG like electric train engineers, do not show relative risks consistently above 1.00, much less very high relative risks. Why would animals be expected to do so? Moreover, pure sinusoidal fields may not be a bioactive ingredient of the mixture, and the animal species chosen may not be appropriate models for humans. Reviewer 2 believes that the animal bioassay stream of evidence in this case is thus triply vulnerable to missing a true effect, and the null results do not reduce his confidence in an EMF effect much. The fact that there are epidemiological associations with several different cancer types and with other diseases that have different known risk factors does increase confidence somewhat but, without mechanistic reasons, not a great deal. Any changes from the prior were due to epidemiological evidence. Large studies likely to be free of selection bias carried a lot of weight. Many studies of different design and in different locations showing similar results also carried substantial weight, although Reviewer 2 only interpreted the sign test to indicate whether a meta-analytic or pooled association came from just a few large studies, or from a rather consistent pattern of result from many studies. Reviewer 2 did not think that any of the specific candidate confounders or biases that had been proposed to date for explaining away the epidemiology had convincing evidence to support it. The fact that most of the associations are not much above the resolving power of epidemiological studies left open the possibility of unspecified combinations of bias, confounding, and chance having produced these associations. This kept Reviewer 2 from having an updated degree of certainty above the certainty zone of "close to the dividing line between believing and not believing" that EMFs increase the risk to some degree.

21.3.3 REVIEWER 3 (LEE)

Reviewer 3 mainly used the human epidemiological evidence to form a posterior degree of certainty. The large number of studies showing consistent results across different study designs, study populations, and exposure assessments, as well as large, well-conducted studies with adequate power to address confounding, bias, dose response, and effects among subgroups contributed strongly in updating the prior degree of certainty. The association of EMFs with several types of disease and experimental and animal evidence were minor contributions to the updating process. Specificity, visibility, analogy, and, in general, temporality did not contribute much to the posterior degree of certainty.

21.4 HOW THE DEGREES OF CONFIDENCE AND RANGE OF UNCERTAINTY COULD BE USED IN POLICY ANALYSES

Community and stakeholder policy decisions usually are made from one or more of the following ethical perspectives: "non-interference," which emphasizes individual choice and rights free from the infringement of others and of government; "social justice," which emphasizes the protection of the weak, and rights and duties; "virtual-certainty-required," where protective action is only taken when the vast majority of scientists are virtually certain that there is a problem; and the "utilitarian perspective," which emphasizes results and the most good for the most people at the least cost. Each perspective would have somewhat different requirements for the degree of certainty of causality before initiating action.

The "non-interference" perspective seeks to avoid regulatory impingement and taxes and tends to favor "right-to-know" warnings and voluntary solutions to problems, regardless of the degree of certainty. The "virtual-certainty-required" framework would tend to require a high degree of certainty with narrow uncertainty bounds on the part of most scientists and a high probability of harm from exposure before acting on an environmental hazard. Indeed, this perspective would favor risk-assessment methods having few false positives, even at the cost of false negatives.

The "social justice" perspective seeks to avoid even the possibility of risk, particularly if the risk and the benefit are imposed on different parties. This perspective would tend to advocate protective action at lower degrees of confidence, wider uncertainties, and lower absolute probabilities of harm given exposure. It would favor risk-assessment approaches with few false negatives, even in the face of false positives. It would focus on the added lifetime risk to the most highly exposed.

The "utilitarian cost/benefit" perspective would evaluate the policy implications of the best estimate of the degree of certainty but would explore the consequences of the lower and upper bounds of the confidence that a hazard exists. It would focus on the burden of societal disease that could be avoided by EMF mitigation. Depending on the relative prevalence of stakeholders who suffer, respectively, from false positives and false negatives, the utilitarian perspective would develop a preference for risk-assessment methodologies. The reviewers would propose that the policy integration

document discuss the implications for policy arising from the range of best-estimates among the three reviewers and the range of uncertainties expressed. It should also discuss where the three DHS reviewers' degrees of confidence lie in the spectrum of scientific opinion.

21.5 Evidence of Risk Relevant for Policymakers Mindful of Environmental Justice Issues

It is sometimes alleged that lower SES subjects are more likely to live in areas with stronger environmental EMFs. Salzberg et al. (Salzberg et al., 1992) first explored this hypothesis and found only weak support for it. Bracken et al. (Bracken et al., 1998) reported a strong correlation between some SES indicators (women's occupations, house values) and the very high-current configuration (VHCC) wire code configuration. Two very large data sets collected in the San Francisco Bay Area as part of the study by Lee et al (Lee et al., 2002) found no evidence of an association between family income and measured EMF exposure. However, there was a weak association between low SES and wire code (Hristova et al., 1997). In a geographic information system (GIS) study as part of the power grid policy project, English et al. (http://www.dhs.ca.gov/ehib/ emf/ pdf/ AppendixG-GIS.PDF) examined the ethnic and income characteristics of census blocks within 500 feet of transmission lines. The proportion of black and Hispanic residents in these corridors was lower than the state average proportion. Zafanella (Zaffanella & Hooper, 2000) found somewhat higher magnetic fields in schools of lower socioeconomic status. In summary, the evidence to support the contention that the EMF exposure, if real, disproportionately affects low SES subjects is not very strong, but there is some suggestive data that decision-makers may consider when evaluating policy options.

21.6 The EMF Mixture

A variety of electrical phenomena are present in the vicinity of power lines, in-home wiring, plumbing, and appliances. These include EMFs with a variety of frequencies and orientations, stray currents from contact with grounded plumbing, and air pollution particles charged by electric fields. The epidemiological studies primarily implicate the magnetic fields or something closely correlated with them. Some researchers think that associated high- or low- frequency stray contact currents or charged air pollution particles are the true explanation rather than magnetic fields. The actions one would take to eliminate the fields are not always the same as one would take to eliminate the currents or the charged particles. There are some situations where different costly measures would be required to address the above-mentioned three possible explanations. There are other situations where one or more inexpensive avoidance actions will address all three. This additional uncertainty about what aspect of the mixture might need to be mitigated will thus provide a challenge for policymakers. The California EMF program funded policy projects to explore options that could be pursued in the face of these uncertainties (see www.dhs.ca.gov/ehib/emf). These are available to guide CPUC and other state agencies in policy formation. DHS is making no recommendations at this time.

21.7 Policy Relevant Areas for further Research

One of the major impediments to evaluating the potential bioactivity of a complex mixture is identifying the bioactive components of that mixture. This usually requires finding some kind of bioassay with which to assess the mixture and then successive fractions of it. While some epidemiologists have attempted to evaluate the effects of different aspects of the EMF mixture and some exposure analysts have attempted to characterize the occurrence and intercorrelation of its aspects, important policy-relevant questions still remain.

Experimentalists have rarely used the mixture as it occurs in real life and have focused instead on one or the other aspect of the mixture, usually pure sinusoidal 60 Hz fields at intensities far above those found in residential or blue collar occupational environments. Deeply ingrained experimental research styles and an orientation to explaining mechanisms rather than describing phenomena has meant that investigator-initiated research and even programs which attempted to guide research have rarely been characterized by progressively refined descriptions of dose response relationships to produce stronger bioeffects.

This has been compounded by the expectation of a quick resolution of the question by those who fund research, as was the case with the New York State program of the mid-1980s, the current California Program, and the recent five year federal EMF–RAPID program. As was discovered after President Nixon's "War on Cancer" in the early 1970s, research progresses slowly and in successive multi-year research cycles, with the results of each cycle governing the direction of the next. It would not be surprising if it took four more five-year research cycles to clarify the EMF issue.

This means that if one were serious about clarifying this issue there would need to be a long-term commitment to steady research funding and funding for intermittent assessments of the state of the science and research directions. Most research peer review groups would favor research where a clear bioeffect was present and credible alternative mechanisms were being explored. Those situations tend to have a high yield of early definitive results, and such results lead to continued research

funding, publications, and research career advancement. The EMF area does not fit this description, and from this perspective would receive a low priority for funding from the usual peer review study sections. Indeed, prominent researchers who doubt that there are any bioeffects, much less epidemiological effects, from the residential and occupational EMF mixture, feel there is nothing to find and have recommended that no more funding for this area be provided (Park, 1992).

Clearly the three DHS reviewers disagree with the assessment of the evidence to date and see a number of research areas which are worth pursuing that could influence and focus exposure avoidance strategies, if any. The cost effectiveness of further research has been a topic of the program's policy analysis and will be discussed at greater length in our policy integration document. The cost/benefit analysis of EMF research suggests that there is so much at stake in choosing between "expensive," "inexpensive," and "no mitigation," that more research funding can be easily justified. (http://www.dhs.ca.gov/ehib/emf/pdf/Chapter09-ValueofInformation.pdf)

The highest initial priorities for the reviewers would be to carry out exposure studies in residential settings and the workplace to see if purported aspects of the EMF mixture that would require different mitigation strategies are correlated with magnetic field exposure and could therefore explain their apparent effect. Such aspects include sudden exposures to the 60 Hz fields, such as micro-shocks, stray ground currents, and charged air pollutants. Such exposure studies would make it possible to reanalyze some of the existing worker cohorts to determine if these aspects are associated with diseases.

Rather than further pursuing new studies of rare diseases with long incubation periods, further studies of the more common conditions in which EMFs might have shorter induction periods, such as spontaneous abortion, acute myocardial infarction, and suicide should be given priority. These would be more relevant to a utilitarian policymaker.

On the experimental front, the reviewers suggest giving priority to finding reliable bioeffects below 100 mG and to carefully exploring dose response relationships and then mechanisms. The balance between investigator-initiated and programmed research, as well as the guidelines that will be used for interpreting results, need to be carefully considered.

SAFETY AND HEALTH TOPICS

Extremely Low Frequency (ELF) Radiation

Contents

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Highlights

- Welcome to the California Electric and Magnetic Fields (EMF) Program. California Electric and Magnetic Fields (EMF) Program. Contains fact sheets in English and Spanish concerning EMF hazards and solutions in homes and schools. Also, provides a link to a video that describes how improperly connected electrical wiring could pose hazards in schools, as well as a school design guidelines checklist which discusses practical, "no- and low-cost" techniques for minimizing exposure to magnetic fields in new and remodeled school buildings.

Introduction

Extremely low frequency (ELF) fields includes alternating current (AC) fields and other electromagnetic, non-ionizing radiation from 1 Hz to 300 Hz. ELF fields at 60 Hz are produced by power lines, electrical wiring, and electrical equipment. Some epidemiological studies have suggested increased cancer risk associated with magnetic field exposures near electric power lines.

There are currently no specific OSHA standards that address extremely low frequency (ELF) fields.

Standards

There are national consensus standards and standards from the United Kingdom (UK) which OSHA could consider referencing in a general duty clause citation. This section highlights those standards.

OSHA

Note: Twenty-five states, Puerto Rico and the Virgin Islands have OSHA-approved State Plans and have adopted their own standards and enforcement policies. For the most part, these States adopt standards that are identical to Federal OSHA. However, some States have adopted different standards applicable to this topic or may have different enforcement policies.

National Consensus

Note: These are NOT OSHA regulations. However, they do provide guidance from their originating organizations related to worker protection.

American National Standards Institute (ANSI)

American National Standards Institute (ANSI). Publishes consensus standards on radio frequency (RF) exposures and measurements. The Institute of Electrical and Electronics Engineers (IEEE), Standards Coordinating Committee 28 is the secretariat for ANSI for developing radio frequency (RF) standards. It is also the parent organization for the IEEE Committee on Man and Radiation (COMAR) that publishes position papers on human exposure to electromagnetic fields.

- *C95.6-2002*, Safety Levels with Respect to Human Exposure to Electromagnetic Fields, 0-3 kHz. Defines exposure levels to protect against adverse effects in humans from exposure to electric and magnetic fields at frequencies from 0 to 3 kHz.
- *EPRI Comments on the IEEE Standard for Safety Levels with Respect to Human Exposure to Electromagnetic Fields, 0 to 3 kHz.* Electric Power Research Institute (EPRI), (2003, January). EPRI comments that the IEEE Standard represents a clear advancement in the development and documentation of exposure guidelines in the designated frequency range.

American Conference of Industrial Hygienists (ACGIH)

- *Documentation of the Threshold Limit Values for Physical Agents, 7th Ed.* Provides consensus exposure limits from the Organization of Governmental Industrial Hygienists for Sub-Radiofrequency (30kHz and below) and Static Electric and Magnetic Fields.

International Commission on Non-Ionizing Radiation Protection (ICNIRP) Guidelines

- Guidelines for Limiting Exposure to Time-Varying Electric, Magnetic, and Electromagnetic Fields (up to 300 GHz) [611 KB PDF, 29 pages]. (1998). Establishes guidelines for limiting EMF exposure that will provide protection against known adverse health effects. The ICNIRP is an affiliate of the World Health Organization (WHO).

United Kingdom (UK)

Note: These are NOT OSHA regulations. However, they do provide guidance from their originating organizations related to worker protection.

- Radiation. Health Protection Agency - Radiation Protection Division (HPA/RPD). Provides standards of protection for exposure to radiation, which includes electric and magnetic fields. Information sheets are available, including:
  - Application of ICNIRP Exposure Guidelines for 50 Hz Power Frequency Fields. (2005, April). Provides clarification and advice on exposure guidelines for 5-Hz electric and magnetic fields (EMFs) and practical approaches to demonstrating compliance with the 2004 ICNIRP limits.

Health Effects

The issue of extremely low frequency (ELF) biological effects is very controversial. Research has focused on possible carcinogenic, reproductive, and neurological effects. Other suggested health effects include cardiovascular, brain and behavior, hormonal and immune system changes.

General Health Effects Reviews

- Health Effects and Exposure Guidelines Related to Extremely Low Frequency Electric and Magnetic Fields - An Overview. BC Centre for Disease Control, (2005, January). Provides links to health effects literature published by the Federal-Provincial-Territorial Radiation Protection Committee (FPTRPC).
- Review of the Scientific Evidence for Limiting Exposure to Electromagnetic Fields (0–300 GHz) [1 MB PDF, 233 pages]. Health Protection Agency (HPA), Documents of the National Radiation Protection Board (NRPB): Volume 15, No. 3, (2004, April 30). Reflects the understanding and evaluation of the current scientific evidence.
- Electromagnetic Fields. World Health Organization (WHO). Links to studies and publications.
  - Electromagnetic Fields and Human Health: Static and Extremely Low Frequency (ELF) Fields. (1998, November). Reviews sources of electric magnetic field (EMF) exposure, transients, dosimetry, static electric fields, ELF electric and magnetic fields, principles, models, laboratory studies, epidemiological studies, and human studies.
- Electric & Magnetic Fields. National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).
  - 1999 NIEHS Report on Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields [751 KB PDF, 80 pages]. Publication No. 99-4493.
- AIHA White Paper on Extremely Low Frequency (ELF) Fields [69 KB PDF, 10 pages]. American Industrial Hygiene Association (AIHA), (1993, June 15). Summarizes the biological and health effects associated with exposure to ELF fields and present exposure guidelines.
- Review of the Epidemiologic Literature on EMF and Health [235 KB PDF, 23 pages]. International Commission for Non-Ionizing Radiation Protection (ICNIRP) Standing Committee on Epidemiology, (2001, December).
- An Evaluation of the Possible Risks From Electric and Magnetic Fields (EMFs) From Power Lines, Internal Wiring, Electrical Occupations and Appliances. California Electric and Magnetic Fields (EMF) Program, (2002, June). Provides an evaluation of the animal, laboratory, and human evidence that shows how exposure to 50/60 Hz magnetic fields may or may not increase human health risks.

Leukemia and Other Cancers

- 1999 NIEHS Report on Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields [751 KB PDF, 80 pages]. National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH) Publication No. 99-4493. States that the strongest evidence for health effects comes from associations observed in human populations with two forms of cancer: childhood leukemia and chronic lymphocytic leukemia in occupationally exposed adults.
- *ELF Electromagnetic Fields and the Risk of Cancer: Report of an Advisory Group on Non-ionising Radiation*. Health Protection Agency (HPA), National Radiological Protection Board (NRPB) Documents, Volume 12, No.1. Reviews the evidence on cancer risks from residential and occupational extremely low frequency (ELF)-electric magnetic field (EMF) exposures, which has been published since an earlier NRPB report (1992).
- Assessment of Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields [3 MB PDF, 523 pages]. National Institute of Environmental Health Sciences (NIEHS) Working Group Report. By a vote of 19 to 9, a panel of experts convened by the NIEHS concluded that the electric and magnetic fields like those surrounding electric power lines should be regarded as a "possible human carcinogen." This conclusion was based largely on human epidemiological evidence in the face of animal and other laboratory studies that the panel agreed did not support or refute the population studies.

Cellular, Physiological, and Behavioral Changes

- Largest study finds evidence of association between EMFs and exposed worker suicide. The University of North Carolina at Chapel Hill, News Release No. 147, (2000, March 15). Provides a press release from a large and detailed positive study of the possible link between exposure to low frequency electromagnetic fields (EMFs) and suicide among electric utility workers.

Static Fields

Note: Although static fields are not part of the radio frequency (RF) spectrum, static is most closely associated with extremely low frequency (ELF), and so it is included here. At this time, there is no Static Fields Safety and Health Topics page.

- Electromagnetic Fields and Human Health: Static and Extremely Low Frequency (ELF) Fields. World Health Organization (WHO), (1998, November). Reviews sources of electric magnetic field (EMF) exposure, transients, dosimetry, static electric fields, ELF electric and magnetic fields, principles, models, laboratory studies, epidemiological studies, and human studies.

Hazard Locations and Solutions

Although extremely low frequency (ELF) exposures occur everywhere, potentially hazardous exposure depends on the strength of the ELF fields at the source, the distance from the source, and possibly the duration of exposure. The following references describe where significant exposures may occur and may be useful in identifying significant exposures and possible solutions.

- EMF (Electric and Magnetic Fields). National Institute for Occupational Safety and Health (NIOSH) Safety and Health Topic.
- NIOSH Fact Sheet: EMFs in the Workplace. US Department of Health and Human Services (DHHS), National Institute for Occupational Safety and Health (NIOSH) Publication No. 96-129. A Spanish version is also available. Answers frequently-asked questions about extremely low frequency (ELF)- electric magnetic fields (EMFs) in the workplace and helps identify EMF sources at work and suggests simple steps for reducing exposures.
- Electric & Magnetic Fields. US Department of Health and Human Services (DHHS), National Institute for Occupational Safety and Health (NIOSH), National Institute of Environmental Health Sciences (NIEHS), and Oak Ridge National Laboratory. Provides links to EMF health effects, results of EMF research and EMF Questions and Answers.
- Electromagnetic Fields. World Health Organization (WHO). Links to studies and publications.
- Understanding Radiation in Our World [3 MB PDF, 100 pages]. National Safety Council (NSC), (2005). Provides an overview of radiation.
- *EMF in your Environment: Magnetic Field Measurements Of Everyday Electrical Devices*. National Center for Environmental Publications and Information (NCEPI), P.O. Box 42419 Cincinnati, OH 45242-2419, Fax Number: (301) 604-3408.
- General Information. California Electric and Magnetic Fields (EMF) Program. Contains fact sheets in English and Spanish concerning EMF hazards and solutions in homes and schools. Also, provides a link to a video that describes how improperly connected electrical wiring could pose hazards in schools, as well as a school design guidelines checklist which discusses practical, "no- and low-cost" techniques for minimizing exposure to magnetic fields in new and remodeled school buildings.
  - Building Checklist: General Information. Discusses conventional "no and low cost" techniques and provides practical ways to minimize exposure to magnetic fields in the building of new schools. It proceeds step-by-step from initial planning and site selection through construction, furnishing and occupancy.
  - EMF Checklist Appendices. Provides information about remodeling, conducting EMF surveys, and types of EMF shielding.

Evaluating ELF Exposure

Public and employee concerns about extremely low frequency (ELF) exposure has grown as a result of increased media coverage over the last few years. The issue of ELF radiation is very controversial. Exposure to electric and magnetic fields (EMFs) depends on the strength of the ELF fields at the source, the distance from the source, and the duration of exposure. The 50 to 60 Hz range is of particular interest because it is associated with electrical power distribution, and equipment utilizing alternating current. The American Conference of Governmental Industrial Hygienists (ACGIH) has established occupational exposure guidelines for ELF radiation.

- Electromagnetic Radiation: Field Memo. OSHA Cincinnati Technical Center (CTC), (1990, May 20). Provides OSHA compliance officers with basic principles of electromagnetic (EM) radiation, discusses the effects of radio frequency interference (RFI) on the operation of industrial hygiene instruments, explains why special isotropic probes are used for making non-ionizing radiation surveys, and emphasizes the need for special attention in measuring radio frequency fields.
- Manual for Measuring Occupational Electric and Magnetic Field Exposures [903 KB PDF, 150 pages]. US Department of Health and Human Services (DHHS), National Institute for Occupational Safety and Health (NIOSH) Publication No. 98-154, (1998, October). Assists investigators in developing methods for occupational exposure assessments for electric and magnetic fields (EMFs).
- EMF Electric and Magnetic Fields Associated with the Use of Electric Power [11 MB PDF, 65 pages]. US Department of Energy (DOE), National Institute for Occupational Safety and Health (NIOSH), National Institute of Environmental Health Sciences (NIEHS), and Oak Ridge National Laboratory, (2002, June). Provides information on exposures to extremely low frequency (ELF)- electric magnetic fields (EMFs).
- *EMF in your Environment: Magnetic Field Measurements Of Everyday Electrical Devices*. National Center for Environmental Publications and Information (NCEPI), P.O. Box 42419 Cincinnati, OH 45242-2419, Fax Number: (513) 489-8695.

ELF Safety Programs

Extremely low frequency (ELF) radiation safety programs are often a part of a larger radiation or non-ionizing radiation safety program.

- Expanded Position Statement on Extremely Low Frequency and Magnetic Fields [17 KB PDF, 2 pages]. American Industrial Hygiene Association (AIHA), (2002, August 4).
- For additional information on radiofrequency (RF) safety programs, see OSHA's Radiofrequency and Microwave Radiation Safety and Health Topics Page.

Additional Information

Training

- Non-Ionizing Radiation Presentations. OSHA. Links to the latest OSHA presentations on safety and health topics including:
  - Non-Ionizing Radiation: Standards and Regulations [10 MB PPT*, 93 slides]. Slide Presentation, (2002, October).
- Fields and Waves, HS4370-W, UCRL-MI-126382. Lawrence Livermore National Laboratory (LLNL). Includes a training course on electric and magnetic fields (EMFs).

Other Resources

- American Industrial Hygiene Association (AIHA). OSHA Alliance Page.
- Environews by Topic: EMFs. National Institute of Environmental Health Sciences (NIEHS). Provides links to articles in *Environmental Health Perspectives*, the NIEHS online journal, on the topic of EMFs.
- EMF-Link. Information Ventures, Inc. A biomedical Science and Engineering Clearinghouse on Electric and Magnetic Fields (EMF). Provides substantive information on biological and health effects of electric and magnetic fields (EMFs) from common sources such as power lines, electrical wiring, appliances, medical equipment, communications facilities, cellular phones, and computers.
- Information in Health Physics Specialties and Related Fields: Non-Ionizing Radiation. The University of Michigan (UM), Health Physics Society. Links to other sources containing information on non-ionizing radiation.

Accessibility Assistance: Contact the OSHA Directorate of Technical Support and Emergency Management at (202) 693-2300 for assistance accessing PDF and PPT materials.

***These files are provided for downloading.**

Encroachment Permits

What is an Encroachment Permit?

An encroachment permit is required whenever work is proposed within the public rights-of-way or easement. Typical examples of work include:

- Trenching across public right-of-way for installation of water, sewer, storm drain, cable, and other underground utilities
- Construction of curb, gutter, sidewalk, driveway, and roadway pavement
- Water monitoring and extraction wells, soil sample borings

What do I need to provide to obtain an Encroachment Permit?

Download the Application for Encroachment Permit and submit it to the Flood Control District office. Read the list below to find out what else is required.

1. Completed Check List with all applicable items addressed
2. Completed and signed Application Form
3. Two sets of approved and signed plans for the proposed work
4. One copy of the District as-built drawing(s) clearly showing the proposed work to be done under the requested encroachment permit. As-built drawings can be purchased from the District's Reproduction Section (951.955.1221).
5. A check or money order written for the appropriate fee amount to be deposited. Fees will be placed in an individual account and all District costs will be tracked as work is performed. If the balance in the account drops under 25% of the original deposit and the General Manager-Chief Engineer determines that the remaining amount is insufficient to complete the processing of the application (including environmental review, inspection and finalization of the project), the applicant will be required to submit an additional depositprior to continuing to work on the application or proceeding with any further work on the project. Further inspections will not be scheduled until the additional deposit is submitted. Once a project is completed and accepted by the District, all unused funds will be refunded to the applicant within 60 days. All applicants, including public entities, must submit the required fee.
6. A copy of the approved and filed California Environmental Quality Act (CEQA) document (e.g., Notice of Exemption, Negative Declaration, Mitigated Negative Declaration/Initial Study, Environmental Impact Report and Statement of Overriding Consideration) as prepared by the Lead Agency for the proposed project shall be submitted to the District. The CEQA document is usually available from the City or County Planning Department that originally approved the proposed project. The District, as a CEQA Responsible Agency, must prepare the appropriate CEQA document for the proposed project prior to issuance of the requested encroachment permit.
7. Proof of prior compliance with the approved Western Riverside County Multiple Species Habitat Conservation Plan (MSHCP) must be submitted to the District for proposed projects with the boundaries of the MSHCP. For projects previously approved by the County or Cities, this proof may consist of written documentation from the applicable jurisdiction confirming compliance with the MSHCP. Documentation concerning payment of the MSHCP Mitigation Fee alone is not sufficient. The District must receive written documentation specifically confirming compliance with Sections 6.1.2, 6.1.3, 6.1.4 and 6.3 of the MSHCP as well as the Criteria if the project is located within the Criteria Area/Cell. Encroachment Permits associated with a project not previously reviewed by the County or a City for MSHCP compliance or Encroachment Permits not associated with any project that are located within the boundaries of the MSHCP will need to be reviewed for compliance with the requirements of the MSHCP by the District prior to issuance of the requested Encroachment Permit. The issuance of an Encroachment Permit by the District is a discretionary action subject to compliance with the MSHCP.
8. NPDES REQUIREMENTS: Encroachment permit applications associated with new or redevelopment projects proposing to discharge stormwater or non-stormwater into District facilities must identify the structural and non-structural best management practices (BMPs) to mitigate water quality impacts from the proposed project.
    a. ENCROACHMENT PERMITS WITHIN THE SANTA ANA OR SANTA MARGARITA WATERSHEDS: Projects within the Santa Margarita and Santa Ana watershed regions of Riverside County must meet the requirements of Section 6 of the Riverside County Drainage Area Management Plan (DAMP) for the Santa Margarita and Santa Ana watershed regions of Riverside County (SA/SM DAMP). Encroachment permit applications for projects that meet the definition of new development or significant redevelopment per Section 6 of the SA/SM DAMP may demonstrate compliance by providing proof of completion of a project-specific Water Quality Management Plan (WQMP). Projects that do not meet the definition of new development or significant redevelopment per Section 6 of the SA/SM DAMP must demonstrate compliance with the structural and non-structural BMPs requirements specified for other development projects per the requirements of Section 6.4.4 of the SA/SM DAMP. Submittal of plans identifying the locations of post-construction BMPs can be used to demonstrate compliance with this requirement.
    b. Projects within the Whitewater Region of Riverside County must demonstrate compliance with Supplement A to the Riverside County DAMP for the Whitewater Region (WW DAMP). This may be accomplished by submitting plans demonstrating the location of approved postconstruction BMPs, or by submitting conditions of approval requiring compliance with Supplement A.
    c. Encroachment permit applicants not associated with new or redevelopment projects who discharge stormwater or non-stormwater to District facilities must identify the necessary structural and nonstructural BMPs to mitigate water

quality impacts from the proposed project. The applicant must complete the Application for Third-Party Discharge to the District Facilities. The application form is available on-line from the NPDES/Municipal Stormwater Management Program page. It may be advisable to contact the NPDES representative listed on the form to determine what, if any, water quality sampling data may be needed to process the application.

9. STORM DRAIN CONNECTIONS, BRIDGES AND CULVERT CROSSINGS: Hydrology and hydraulic calculations prepared and signed by a Registered Civil Engineer must be submitted with all applications for storm drain connections, bridges and culvert crossings. The maximum confluence angle at the junction of a lateral storm drain and mainline channel shall be 45 degrees. A hydraulic junction analysis must be done if the lateral flowrate is greater than 25% of the mainline flowrate. The hydraulic grade line, flow rate, and velocity shall be shown on the storm drain profile drawing. Only reinforced concrete pipe (RCP minimum 1500D) will be approved within District right of way.
10. EXCESS MATERIAL REMOVAL: Excess material removal shall be approved by the District's Chief of Operations and Maintenance, prior to submitting the encroachment permit application. An inspection fee for a minimum of $0.35 per cubic yard will take effect when the permit is issued and is payable to the District monthly or as specified in the encroachment permit. proposed project.
    a. Applicants requesting encroachment permits for the removal of excess material from District facilities must also submit a Storm Water Pollution Prevention Plan (SWPPP) per the requirements of the appropriate Regional Water Control Board. A copy of the SWPPP shall be provided and approved by the District prior to receiving the requested encroachment permit. A SWPPP template and guidance on the preparation of a SWPPP can be downloaded from the California Association of Stormwater Quality Agencies (CASQA) website at http://www.cabmphandbooks.com/Construction.asp.
    b. Applicants requesting encroachment permits for the removal of excess material from District facilities must also submit a fugitive dust control plan (DCP) per the requirements of the Air Quality Management District or local ordinances, as required. A copy of the DCP shall be provided and approved by the District prior to receiving the requested encroachment permit. DCP Handbooks for the Coachella Valley region can be downloaded from the Coachella Valley Association of Governments at http://www.cvag.org/depts/hcr.htm.
11. The applicant shall accept full responsibility for obtaining and complying with all applicable provisions of the appropriate regulatory permits. If the requested encroachment permit is for facilities that will be ultimately maintained by the District, the regulatory permits shall address both the construction and maintenance activities of these facilities in compliance with all applicable Federal, State and local regulations. These regulatory permits include, but are not limited to: a Section 404 Permit issued by the U.S. Army Corps of Engineers in compliance with Section 404 of the Clean Water Act, a California State Department of Fish and Game Streambed Alteration Agreement in compliance with the Fish and Game Code Sections 1600 et seq., and a 401 Water Quality Certification or a Report of Waste Discharge Requirements in compliance with Section 401 of the Clean Water Act or State Porter-Cologne Water Quality Act, respectively, from the appropriate Regional Water Quality Control Board. The applicant shall also be responsible for complying with all mitigation measures as required under CEQA and all Federal, State, and local environmental rules and regulations. A copy of the above mentioned permits shall be submitted to the District for review and approval for all facilities that will ultimately be maintained by the District prior to District issuance of the requested encroachment permit. For projects that will not be maintained by the District a copy of the above mentioned permits shall be submitted to the District for the encroachment permit file. Mitigation measures may not be placed within District rights of way without prior approval from the General Manager–Chief Engineer.
12. ADDITIONAL DEPOSIT - If the District determines that survey monuments are located in the area of work, an additional deposit will be required to cover the cost of replacing any survey monuments that may be disturbed. District survey crews will replace monuments. A map will be provided to the applicant showing locations of survey monuments involved.

Requirements Due Prior to the Issuance of the Encroachment Permit

Prior to the issuance of the encroachment permit, the applicant or the contractor performing the work shall furnish a certificate of insurance specifying comprehensive liability limits of $2,000,000 per occurrence and $2,000,000 general aggregate. The applicant, the District, the County of Riverside, and any municipal corporation within which the work is to be performed, shall each be named as an additional insured. Alternatively, comprehensive liability limits shall be $1,000,000 per occurrence, with $2,000,000 general aggregate and a minimum of $2,000,000 excess liability. This insurance shall remain in effect for the duration of the work. Please reference the encroachment permit number (shown on your receipt for the initial deposit) on the certificate of insurance.

Additional Information

1. Please contact the District's Permit Engineer at 951.955.1266 if you have any questions or need any additional information.
2. Processing time for a typical encroachment permit (if all required information is submitted with the initial application) is approximately 30 working days.

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Lakeview Substation - Preliminary Permit List[1]

No.	PERMIT/LICENSE	AGENCY	LEVEL	JURISDICTION/PURPOSE
1	Permit to Construct (PTC)	CPUC	State	Overall project approval and CEQA review
2	Letter of Inclusion for Regional Conservation Authority	Regional Conservation Authority	Local/Reg Agency	Implements the Multiple Species Habitat Conservation Plan
3	NPDES Permit	RWQCB	Local/Reg Agency	For Stormwater runoff associated with construction & operation activity
4	Crossing Permit	Riverside County Flood Control District.	Local/Reg Agency	For Flood Control Crossing
5	Encroachment Permit	Riverside County Transportation Dept.	Local/Reg Agency	For construction, operation and maintenance within, under or over county road ROW or easement
6	After Hours Permit or Variance	City Agency	City	For after hours work per individual city standards
7	Landscape Permit	Riverside County Public Works Dept.	Local/Reg Agency	For landscaping plan
8	Overload Permit	CA Dept of Transportation State & Local Project Development	State	For vehicles exceeding the legal weight
9	Grading Permit	Riverside County Public Works Dept.	Local/Reg Agency	For construction grading
10	Lane Closure Permit	Dept of Public Works	City	For traffic control

1 - As further engineering and review is conducted SCE will update this preliminary list as appropriate