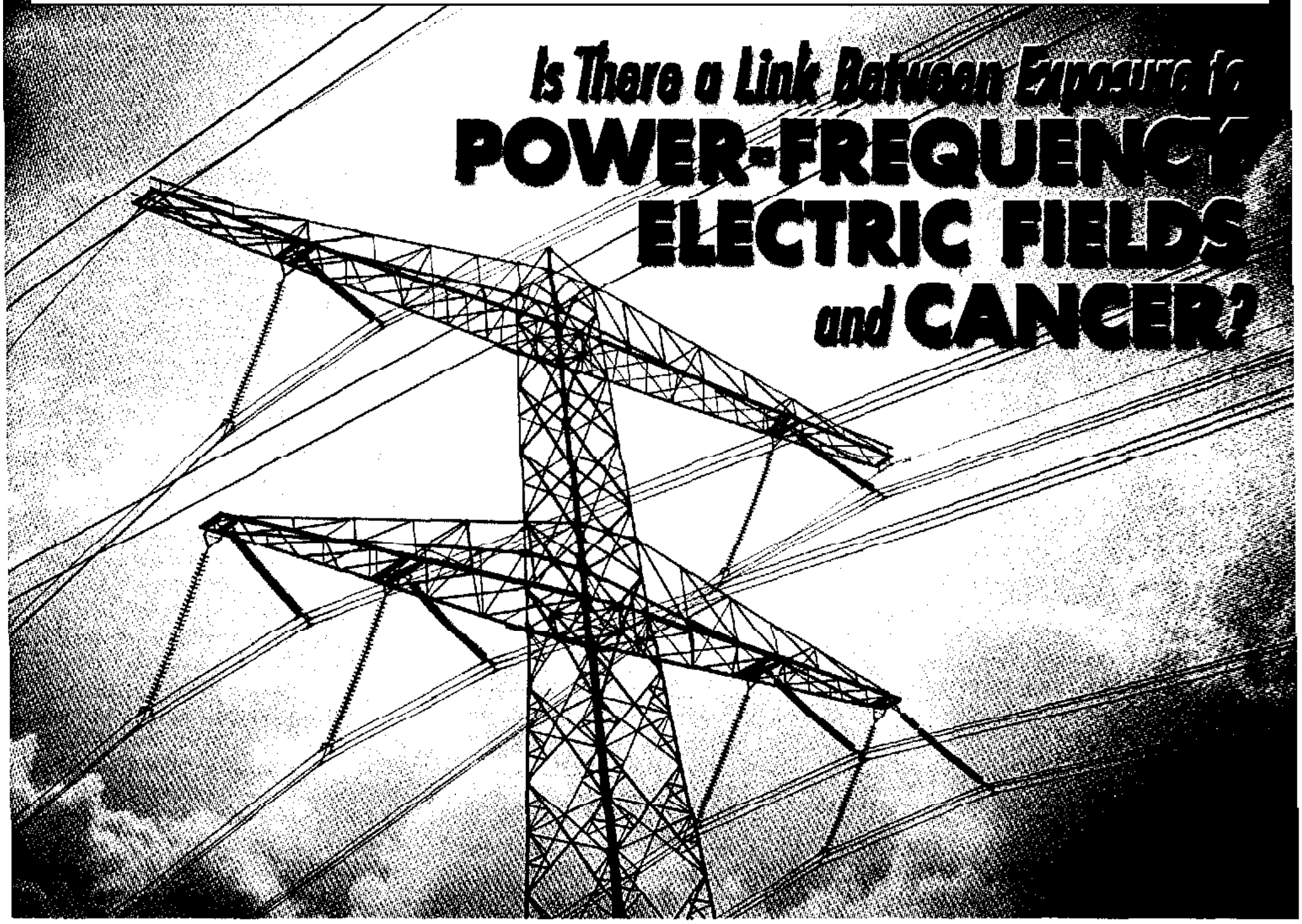
Is There a Link Between Exposure to POWER-FREQUENCY ELECTRIC FIELDS and CANCER?



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The controversy over whether power-frequency (50/60-Hz) electromagnetic fields are a cause of cancer can be traced to a 1979 study by Wertheimer and Leeper [1] that reported an association between childhood cancer and the proximity of residences to certain types of power lines (particularly proximity to high-current distribution lines). Most of the resultant discussion has focused on power-frequency *magnetic* fields, which is how they framed the issue. However, after nearly two decades of further research, neither our own reviews [2-4] nor a definitive 1997 review by the National Academy of Sciences (NAS) [5] has concluded that there is credible evidence that power-frequency magnetic fields actually do cause or contribute to cancer.

Some authors [6-9] have recently suggested that power-frequency *electric* (rather than magnetic) fields might be linked to cancer; for the most part their conclusions are based on post-hoc re-interpretation of existing epidemiologic studies. In this article, we review the evidence bearing on the issue of whether power-frequency *electric* fields might cause or contribute to cancer. Unless otherwise stated in the discussion below, "fields" refer to 50/60-Hz electric fields.

Environmental Electric Fields and Biological Effects

Electric fields associated with the generation, transmission, distribution, and

John E. Moulder[1] and Kenneth R. Foster[2]
[1]Departments of Radiation Oncology and Pharmacology, Medical College of Wisconsin
[2]Department of Bioengineering, University of Pennsylvania

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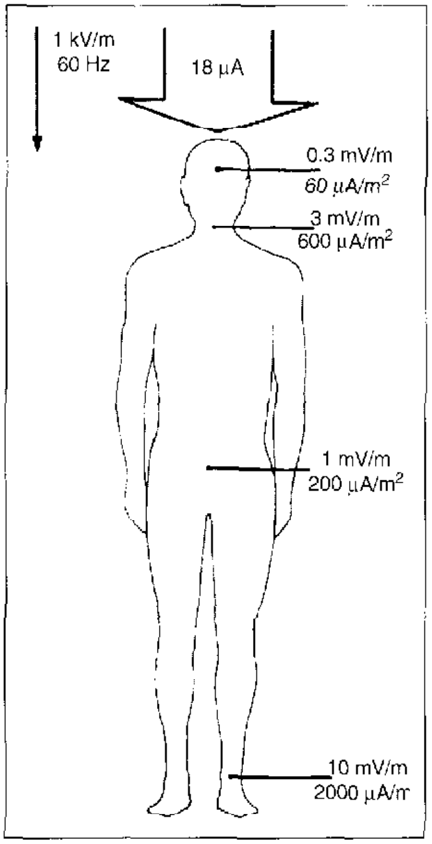

1. Induced electric fields in a human body exposed to an external 1 kV/m field (reproduced with permission from Carstensen [13]).

consumption of electric power are ubiquitous in modern society. At ground level beneath a 765-kV transmission line, electric field strength may reach 12 kV/m. However, these fields drop off roughly as the square of distance from the lines, beneath neighborhood distribution lines and in residences (the focus of most of the controversy about power-frequency fields and cancer) the electric fields are smaller and highly variable. In residences near power lines in Los Angeles, London, et al. [10], found that mean outdoor field strengths were 1.0-1.5 V/m, and mean indoor fields were 4-5 V/m. In contrast, Kaune, et al. [11], reported that the mean field strength in residences in Seattle was 33 V/m, and in residences along a 735-kV line, Levallois, et al., [12] found that mean indoor fields were 25 V/m. Field strength within 30 cm of some appliances (e.g., electric blankets) can reach 250 V/m, but field strength drops rapidly with distance. Thus, the exposure of people to electric fields is highly variable, but it is typically in the range of 1 to 30 V/m.

Human thresholds for perception of power-frequency electric fields (associated with movement of hairs on the skin) have been variously reported to be at least 5 kV/m and possibly in excess of 20 kV/m [13]. Because of the high conductivity of body tissues, the inside of the human body is effectively shielded from external power-frequency electric fields. Thus, exposure to an initially unperturbed power-frequency field of 1 kV/m will induce fields of only about 0.001 V/m inside the body (see Fig. 1), which is a level that is far below those due to the EEG, EMG, and various other natural biological processes. Electric shock, an unequivocal hazard of electricity, requires contact with charged conductors and is beyond the scope of this article.

The biological effects of power-frequency electric fields have been studied for many years, and hundreds of papers have been published on the subject. However, the literature on electric fields is murky and contentious. Carstensen [13], in his 1987 review, listed 113 reported effects of 50/60-Hz electric fields in a variety of organisms; effects which were reported to occur at external field levels ranging from about 1 V/m to 500 kV/m. He considered 34 of these reports to be "confirmed" or "probable" because there was independent replication. He considered another 49 as "unconfirmed," and still another group of 30 effects as "negated" by unsuccessful attempts at independent confirmation. The "confirmed" effects were generally reported at high field strengths and involved obvious phenomena such as shock, whereas many of the "unconfirmed" or "negated" effects were reported at external field strengths of a few V/m and involved subtle phenomena that were at the edge of statistical detectability.

Identifying Human Carcinogens

The issue we are interested in, however, is not whether "effects" exist, but rather how strong the evidence is that such power-frequency electric fields cause or contribute to cancer under real-world exposure conditions. Identifying human carcinogens is a complex business, as there appears to be no simple "cause" of cancer, and thus there is no single definitive test for carcinogenic potential [14,15]. For a review of carcinogen risk assessment as it applies to electromagnetic fields, see Foster, et al. [3].

When evaluating possible human carcinogens, agencies such as the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (EPA) use a weight-of evidence approach that attempts to evaluate all relevant evidence. The range of relevant evidence includes epidemiology, standard-

Table 1. Cancer and Residential Exposure to Power-Frequency Electric Fields

Major studies:	Savitz, et al., '88 [17]; London, et al., '91 [10]; Coghill, et al., '96 [8]; Tynes and Haldorsen, '97 [18].
Major sites:	Childhood leukemia (4 studies), childhood brain cancer (2 studies); overall childhood cancer (1 study)
Results:	• Electrical fields measured in residences were associated with childhood leukemia in one study [8], but not in two others [10,17]. • Electrical fields measured in residences were not associated with childhood brain cancer [17]. • Calculated or measured electrical fields external to residences were not associated with childhood leukemia [10,18], childhood brain cancer [18], or overall childhood cancer [18]. • Proximity to high-voltage transmission lines was associated with childhood leukemia in one study [19], but not in three others [18, 20, 21]. • Proximity to high-voltage transmission lines was not associated with childhood brain cancer [18,19], overall childhood cancer [18,19,] or any type of adult cancer [20,22].
Exposure-response:	One study [8] shows evidence for an exposure-response relationship for childhood leukemia and measured fields in residences; otherwise, there is no evidence for an exposure-response relationship for any type of cancer and any measure of electric field exposure.

ized in vivo (animal) screening studies, and in vitro (cellular) studies related to mechanisms of carcinogenesis. In vivo and in vitro studies may examine endpoints related to different mechanisms of carcinogenesis: for example, genotoxicity (damage to DNA) or epigenetic mechanisms (e.g., promotion). Also examined is the pharmacology (in the case of chemicals), or the biophysics (in the case of physical effects), of the agent.

These different studies have different strengths and weaknesses. Epidemiology provides direct evidence about human health, but such studies are difficult to control (because of the heterogeneity of human populations) and are susceptible to many sources of bias that affect study validity. Thus, epidemiology is an inherently poor method for detecting weak carcinogens or for detecting carcinogens that affect small, but as yet unidentified, subpopulations. Animal screening studies can be well-controlled, but they typically require high exposure levels to produce measurable increases in cancer, and this (as well as biological differences between the animals and humans) complicates interpretation of results. Mechanistic (typically in vitro) studies can provide additional support for a causal connection between exposure and disease, but their relevance to human health is often difficult to determine.

Fears about power-frequency electric fields seem to be reappearing following the failure to demonstrate hazards from weak magnetic fields.

Evaluating the Evidence

Here we present a comprehensive review of data relevant to 50/60-Hz electric fields and carcinogenesis, using criteria modified from Hill [16] as a framework for analysis.

Epidemiology of Cancer and Exposure to 50/60-Hz Electric Fields

By now, more than a 100 epidemiology studies related to power-frequency electric or magnetic fields and cancer have been published. As indicated above, most have focused on magnetic field exposure. However, some scattered data exist that bear directly on the issue of electric fields (Tables 1 and 2).

As shown in Table 1, three of the four residential epidemiology studies that have assessed electric fields have found no associations between cancer and the strength of the electric field [10, 17, 18]. The exception is the 1996 study by Coghill, et al. [8], which measured electric and magnetic fields in bedrooms of 56 boys who had developed leukemia and an equal number of healthy controls. The investigators reported that the 24-hour mean electric fields in the bedrooms of the leukemic children was 13.5 (S.D. = 13.4) V/m, compared with 7.3 (S.D. = 12.9) V/m for the controls: a difference that the authors report to be statistically significant. Further analysis showed some indication of an exposure-response relationship.

The validity of the Coghill, et al. [8], study can be questioned on several grounds. First, the study had an unblinded design; that is, the workers doing the field measurements knew whether the homes were those of cases or controls. Second, the study recruited its subjects through media requests, and as in any case-control study, even a small tendency to select cases from high exposure groups will introduce serious errors. Because of the great media attention to the possible hazards of electromagnetic fields, it is quite possible that parents of children with cancer who lived near high voltage lines or other noticeable electrical equipment would have been more likely to volunteer for the study. Finally, the large standard deviations in the measured electric fields (which are larger than the difference between the mean fields of the cases and controls) is an indication of extreme variability in exposure.

Some residential epidemiology studies that did not measure electric fields have been interpreted by others (not necessarily the investigators themselves) as bearing on the issue of electric field exposure [5, 6]. For example, one might speculate that residences in close proximity to high-voltage transmission lines might have elevated electric fields. However, of the five studies that did use proximity to high-voltage transmission lines as a measure of exposure [18-22], only one [19] found any evidence for a statistically significant association; an association that was limited to a single type of cancer in children (Table 1). Several residential exposure studies (e.g., Wertheimer & Leeper [11]) used "wire codes" (essentially, the proximity of houses to different type of power lines) as a measure of exposure. Interpreting this "exposure metric" as evidence of ex-

Table 2. Cancer and Occupational Exposure to Power-Frequency Electric Fields

Major studies:	Tynes, et al., '94 [23][a]; Tynes, et al., '94 [24]; Miller, et al., '96 [9]; Baris, et al., '96 [25]; Guénel et al., '96 [26]; Kheifets, et al., '97 [27].
Major sites:	Leukemia (6), brain cancer (5), overall cancer (4)
Results:	• Leukemia was associated with electric field exposure in one study [9], but not in five others [23-27]. • Brain cancer was associated with electric field exposure in one study [26], but not in four others [9,23-25]. • Overall cancer was not associated with electric field exposure [9,24-26].
Exposure-response:	No evidence for significant exposure-response relationships for any type of cancer.

[a]Exposure was at 16.67 Hz

Epidemiology literature provides only the weakest evidence for an association between power-frequency electric fields and cancer.

posure to electric fields is highly speculative, as there is no evidence that "wire codes" have any direct relationship to the magnitude of electric field exposure [10, 11, 17]. Thus, very little of the residential epidemiology has any direct bearing on the issue of power-frequency electric fields and cancer, and most of the studies that do have a direct bearing show no significant association.

There have also been numerous epidemiological studies of occupational exposure to 50/60-Hz electric fields (Table 2). Some workers are unequivocally exposed to large electric and magnetic fields (e.g., utility linemen). However, in most occupations, exposure to power-frequency electric and magnetic fields are poorly correlated [28], so that evaluation of electric fields as a causal agent requires examination of studies that have looked at electric field exposure separate from magnetic field exposure. Miller, et al. [9], reported an increased risk of leukemia (but not overall cancer, brain cancer, or any other of 13 cancer types) for occupational exposure to power-frequency electric fields. Guénel, et al. [26], on the other hand, reported an increased risk of brain cancer, but not leukemia, for similar occupational exposure to electric fields. Other studies of occupational exposure to power-frequency electric fields have found no significant associations with either leukemia [23 27], brain cancer [9, 23-25], lymphoma [9, 24-26], or overall cancer [9, 24-26].

These occupational exposure studies have not consistently identified a group of workers who are both highly exposed to electric fields and who have a significant increase in any one form of cancer. For the comparatively few carcinogens that were first identified by epidemiology, the situation was quite different (e.g., a large, consistent, and exposure-related increase in bladder cancer reported in dye-factory workers and, equally striking, consistent and exposure-related increase in mesothelioma in asbestos workers). In contrast, the occupational epidemiology of electric (and magnetic) fields consists of a scattering of weak positive findings in a background of generally negative results.

Thus, the epidemiology literature provides only the weakest evidence for an association between power-frequency electric fields and cancer. The studies that do show statistical evidence for an association (e.g., Coghill, et al. [8], Miller, et al. [9]), are technically weak, show only very weak associations, show little or no evidence for an exposure response relationship, and/or are contradicted by similar studies done by other groups.

As with the studies involving cancer and exposure to magnetic fields, uncertainties in electric field exposure assessment also may result in significant misclassification errors (i.e., misclassifying subjects into high or low exposure groups). Such errors would dilute the magnitude of any observed effect. Thus, if the studies such as those of Coghill, et al. [8], and Miller, et al. [9], have identified a real effect of electric fields, the effect would have to be considerably stronger than indicated by the studies. Other kinds of evidence, which we now consider be-

Table 3. Experimental Assessment of the Carcinogenic Potential of Power-Frequency Electric Fields

Endpoint	Outcome
Mutation	• No increase in mutation in fruit flies exposed to 700-2500 kV/m[a] [43].
	• No increase in mutation in mice exposed to 15 [42], 20 [45], or 50 kV/m[a] [42].
	• No increase in mutation in mammalian cells at 0 0001-0.011 kV/m[b] [46].
	• No increase in mutation in bacteria exposed to 11 kV/m[a] [47].
Chromosome abnormalities	• No increase in chromosome abnormalities in mice exposed to 15 [42], 50 [42], or 100 kV/m[a] [48].
	• Increase in chromosome abnormalities in mice exposed to 170-290 kV/m[a] [48].
	• No increase in chromosome abnormalities in plants at 0.01 kV/m[b] [44].
	• No increase in chromosome abnormalities in human cells exposed at 0.03 [49,50] or 1.0 mA/cm-sq[b] [29].
	• No increase in chromosome abnormalities in human cells exposed to 0.5-10 kV/m[a] [57].
	• Increase in chromosome abnormalities in mammalian cells exposed at 0.002-1.0 mA/cm-sq[b] [51].
	• Increase in chromosome abnormalities in human cells exposed to spark discharges in one experiment [29], but not in an independent replication [52].
DNA strand breaks	• No increase in DNA strand breaks in mammalian cells at 0.001-0.038 kV/m[b] [53].
	• No increase in DNA strand breaks in human cells [54], yeast [55], or bacteria [56] exposed to 20 kV/m[a].
Epigenetic activity	• No inhibition of repair of DNA damage in mammalian cells exposed to 0.2-30 kV/m[a] [58-60].
	• No inhibition of repair of DNA damage in human cells at 0.001-0.02 kV/m[b] [61].
	• No enhancement of chemical genotoxicity in human cells exposed to 0.5-1.0 kV/m[a] [57].

[a]The fields to which the organisms or culture vessels were exposed.

[b]The field strength in the nutrient medium.

low, would be required to support such a conclusion.

Cytogenetic Studies of "Electrical Workers"

In studies that blur the boundary between epidemiology and laboratory science, lymphocytes from workers with occupational exposure to power-frequency electric fields have been examined for genotoxic injuries [29-33]. The interpretation of these studies is complex, as they have all of the problems of exposure assessment, confounding, and bias that characterize epidemiological studies. A major statistical issue that must be considered is that all of these studies examine multiple endpoints and subgroups. When examining the results of so many comparisons, it is impossible to determine which "statistically significant" differences are real effects and which are merely statistical noise—the so-called multiple comparison problem [4].

Even with the multiple comparison problems, several patterns emerge. First, the positive reports are predominantly from workers exposed to "spark discharges." An ungrounded person standing in a strong electric field who touches a grounded and conductive object will get a shock, called a spark discharge. If the electric field is strong enough, and the capacitance of the grounded object is high enough, the peak value of the body current at the point of a spark discharge can reach several amperes, and the discharge time can be several microseconds [29]. This kind of physical stimulus is clearly quite different from exposure to electric fields in the absence of spark discharges. Second, the reported effects are seen predominantly in smokers and former smokers, among whom an excess in chromosomal abnormalities is expected. Finally, the reported increases are largely limited to increased chromosomal aberrations, with no effects on sister chromatid exchanges (SCEs). This latter observation is somewhat surprising, as the SCE assay is generally considered to be at least as sensitive an assay for genotoxic agents as the chromosome aberration assay.

In summary, cytogenetic studies of workers exposed to strong power-frequency electric fields provides little convincing evidence that these fields are genotoxic. The reports of genotoxic effects in such workers are unreplicated and largely confined to current and former smokers who were exposed to spark discharges.

Long-Term Animal Studies with Power-Frequency Electric Fields

There have been no standardized cancer screening studies using power-frequency electric fields alone, but several studies have been published that bear on the issue of whether power-frequency electric fields have carcinogenic potential. These studies would have been able to detect pronounced carcinogenic or cancer promoting effects of strong electric fields, had any existed. The absence of detectable carcinogenic effects at high exposure levels gives support for the absence of hazard at much lower exposure levels, as well.

The most extensive screening studies were conducted at Battelle Pacific Northwest Laboratories. These studies involved multigeneration exposures of rats [34-37] and swine [38] at high field levels (up to 150 kV/m), with evaluation of numerous physiological and behavioral endpoints. The studies showed clear effects (e.g., rats try to avoid fields of 100 kV/m and show behavioral changes at similar field strengths), but the results showed no indication that the fields had carcinogenic potential or that they produced other pronounced toxic effects.

Other studies involving long-term exposure to strong (> 10 kV/m) fields were reported by Fam [39] and Seto, et al. [40]. These studies involved fewer endpoints than the Battelle studies, and, like those studies, they reported some biological effects, but no clear indications of toxic activity or carcinogenic potential.

The overall impression of these studies [34-40] is that rodent behavior is affected by electric fields of 100 kV/m and above, but that weaker fields (tens of kV/m) have either very subtle effects or no effects at all. These results contrast with a study by Marino, et al. [41], which reported increased infant mortality (but no enhanced adult mortality) in mice raised for several generations in 3.7 kV/m fields. This study has been criticized because of the possibility that the animals received shocks from their drinking water bottles, reducing their water intake. The results of that study have not been replicated and, in the light of the larger and more elaborate Battelle studies [34-38], should be regarded with skepticism. The lack of clear toxicity from exposure to strong electric fields [34-40] is significant because most

Laboratory studies of animals and cells exposed to strong electrical fields show no indication that these fields can cause or contribute to cancer.

known human carcinogens (e.g. tobacco smoke, benzene, x-rays) are toxic, and to produce measurable carcinogenicity in laboratory animals generally requires exposure levels close to those producing other indications of toxicity.

Also noteworthy is the series of studies conducted in the early 1970s with the support of the New York Power Lines Project. The Project supported several studies involving long-term exposure of animals to strong electric fields, some involving cancer-related endpoints. For example, Benz, et al. [42], exposed large numbers of mice to 60-Hz fields (up to 1 mT and 50 kV/m) for three generations. The investigators reported no increase in the mutation rate (indicating no genotoxic potential), no reduction in life span, and no increase in cancer mortality. Although this study was not a standard carcinogen assay, its design was such that it would have been able to detect a pronounced increase in cancer incidence from these (comparatively very strong) electric and magnetic fields.

Experimental Studies of the Carcinogenic Potential of Electric Fields

Despite rather intensive studies [29,42-57], power-frequency electric fields show no replicated evidence of genotoxicity (Table 3). Nordenson, et al. [29], reported that exposure of human lymphocytes to spark discharges caused chromosome aberrations, but Paile, et al. [52], found no evidence for this effect in a replication study. El Nahas and Oraby [48] reported an enhanced incidence of micronuclei in mice exposed to 170-290 kV/m fields, but found no effect in mice exposed at 100 kV/m. Finally, d'Ambrosio, et al. [51], found excess chromosome aberrations, but no excess SCEs, in mammalian lymphocytes exposed to 50-Hz electric fields. The reports of El Nahas and Oraby [48] and d'Ambrosio, et al. [51], have not been replicated or confirmed.

Similarly, the studies of power-frequency electric fields show no evidence of *epigenetic activity* (Table 3). Whitson, et al. [58], Frazier, et al. [61], and Cantoni, et al. [59,60], found no evidence that power-frequency electric fields could inhibit repair of DNA damage induced by ionizing radiation or UV light. Scarfi, et al. [57], found that power-frequency electric fields did not enhance genotoxic injury caused by chemical genotoxins. Power-frequency electric fields also showed no consistent effects on immune function [62-65] or on cell growth [54,58,64].

In summary, laboratory studies of animals and cells exposed to strong electrical fields (typically 1000 or more times higher than environmental levels) show no indication that these fields have the potential to cause or contribute to cancer.

Biophysical and Biological Plausibility of Carcinogenesis by Power-Frequency Electric Fields

Biological effects in humans from power-frequency *magnetic* fields of the magnitude encountered in residential and most occupational settings (< 100 μT) are implausible because of the lack of biologically plausible mechanisms of interaction [4, 66, 67]. However, as reviewed in detail by Valberg, et al. [66], biological effects in humans from 50/60-Hz *electric* fields of amplitudes below 1 kV/m (outside the body) are equally implausible. Fields at typical ambient levels (1-30 V/m) induce electric fields in the body of only a few μV/m, a level that is several orders of magnitude below naturally occurring fields from the ECG, EEG, and various other biological processes.

An additional implausibility problem is posed by the fact that there is extensive laboratory evidence that strong power-frequency magnetic fields do not have the potential to either cause or contribute to cancer [2-5]. Some of these unsupportive laboratory studies have used very high magnetic field strengths (> 100 μT and often > 1000 μT at 50/60 Hz). Such high-amplitude magnetic fields induce electric fields within the body that far exceed those induced by the external electric fields normally encountered in the environment (< 1 kV/m). Thus, if environmental electric fields are carcinogenic, it would appear that their interaction mechanism cannot involve induced electrical fields or induced currents within the body; and no interaction mechanisms have been seriously proposed that would not involve such induced fields or currents.

Conclusion

With a body of evidence as large and complex as this, one can always pick and choose evidence in support of almost any hypothesis. Lay-oriented articles commonly point to the many reported "effects" of power-frequency fields and suggest that there thus might be some health problem. With selective reporting and skillful writing, a scary story can be put together [68].

But the issue of current interest is not whether biological "effects" are produced by power-frequency electric fields, or whether post-hoc subgroup analysis of epidemiological studies suggests that electric fields might be associated with cancer. The issue is how strong the overall evidence is that power-frequency electric fields cause or contribute to cancer. Table 4 summarizes the results of applying Hill's [16] criteria to the relevant published studies.

There is a certain symmetry in the history of this controversy. Before the appearance of the Wertheimer and Leeper study in 1979 [1], the public concern about the safety of electromagnetic fields was directed almost entirely at the strong electric fields beneath high-voltage power lines. Following this study, public concern gradually shifted to the relatively weak magnetic fields in homes due to neighborhood distribution systems and from electrical appliances. Fears about power-frequency electric fields seem to be reappearing following the failure of science to demonstrate hazards from weak magnetic fields. But the overall case that power-frequency *electric* fields are causally linked to human cancer is even weaker than that for *magnetic* fields and can reasonably be called nonexistent (Table 4).

Table 4. Hill's Criteria [16] Applied to Power-Frequency Electric Fields and Cancer

Criterion	Strength of Evidence
How strong is the epidemiologic association between power-frequency electric fields and cancer?	Very weak or no association
Is the epidemiologic evidence for an association between power-frequency electric fields and cancer internally and externally consistent?	Very inconsistent
Does the incidence of cancer increase with increased exposure to power-frequency electric fields (i.e., are there exposure-response trends)?	No consistent evidence for exposure-response trends
Are there mechanisms for carcinogenesis that are consistent with cancer biology and with the biophysics of power-frequency electric fields?	No plausible mechanisms
Is there experimental evidence that power-frequency electric fields are genotoxic?	No replicated evidence for genotoxicity
Is there experimental evidence that power-frequency electric fields have epigenetic activity?	No evidence for epigenetic activity
How strong is the overall evidence for a causal relationship between power-frequency electric fields and cancer?	Nonexistent

Governments and electrical utilities in several countries have funded research investigations of the reported links between power-line fields and cancer, despite the questionable credibility of such claims. We believe that fears about possible links to cancer have been adequately addressed, and see no reason to recommend further studies on this subject. Needless to say, our society has many urgent health problems, but to all appearances, cancer from power-line fields is not one of them.

John E. Moulder received the B. S. degree in chemistry and biology from Carleton College, Northfield, MN, in 1967 and the Ph.D. degree in biology from Yale University, New Haven, CT, in 1972. His primary research interest is the biological basis for cancer and cancer therapy. He has served on the Experimental Therapeutics and Radiation initial review groups for the National Institutes of Health (NIH) and has been a member of many of the NIH panels that reviewed grant proposals on nonionizing radiation biology. He has lectured on power-frequency fields and human health to biologists, physicists, physicians, policy makers and industry groups around the world. He also served as a consultant and expert witness in several cases involving the alleged health effects of exposure to power-frequency fields. He also maintains the Electromagnetic Fields and Human Health site on the World Wide Web.

Dr. Moulder is a member of the Radiation Research Society, the American Society of Therapeutic Radiation Oncology, the Environmental Mutagen Society, the Bioelectromagnetics Society, and the IEEE. He is an Associate Editor of *Radiation Research*, and he is a member of the IEEE Committee on Man and Radiation (COMAR) and the IEEE Medical Technology Policy Committee.

Kenneth R. Foster is Associate Professor of Bioengineering at the University of Pennsylvania. Since receipt of the Ph.D. in 1971, Dr. Foster has been engaged in studies on the interaction of nonionizing radiation and biological systems, including studies on mechanisms of interaction and biomedical applications of radio frequency and microwave energy. In addition he has written widely about scientific issues related to possible health effects of electromagnetic fields. He has published approximately 90 technical papers in peer-reviewed journals, numerous other articles, and is the author of two books related to technological risk. His latest book, *Judging Science*, was published by MIT Press in April 1997. He is a Fellow of the IEEE, Chair of the IEEE EMBS Committee of Man and Radiation, and President of the IEEE Society on Social Implications of Technology.

Address for Correspondence: John Moulder, Radiation Oncology Department, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, U.S.A. Tel: 414-456-4672. Fax: 414-456-6553. E-mail: jmoulder@its.mcw.edu

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