Extremely low frequency electromagnetic fields (EMF) and brain cancer in adults and children: Review and comment

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Epidemiologic and experimental research on the potential carcinogenic effects of extremely low frequency electromagnetic fields (EMF) has now been conducted for over two decades. Cancer epidemiology studies in relation to EMF have focused primarily on brain cancer and leukemia, both from residential sources of exposure in children and adults and from occupational exposure in adult men. Because genotoxic effects of EMF have not been shown, most recent laboratory research has attempted to show biological effects that could be related to cancer promotion. In this report, we briefly review residential and occupational EMF studies on brain cancer. We also provide a general review of experimental studies as they relate both to the biological plausibility of an EMF-brain cancer relation and to the insufficiency of such research to help guide exposure assessment in epidemiologic studies. We conclude from our review that no recent research, either epidemiologic or experimental, has emerged to provide reasonable support for a causal role of EMF on brain cancer. *Neuro-Oncology 1, 212–220, 1999 (Posted to Neuro-Oncology [serial online], Doc. 99-11, June 3, 1999. URL <neuro-oncology.mc.duke.edu>)*

Because of the relatively poor survival probability, and the substantial risk of long-term morbidity among survivors, brain cancer is a particularly ominous disease. In the United States alone, an estimated 16,800 primary CNS malignancies will be diagnosed in 1999 (Landis et al., 1999). Since an estimated 45% of primary CNS tumors are of nonmalignant pathology (benign or uncertain pathologic behavior) (Davis et al., 1999), the total number of people diagnosed in the U.S. with malignant and nonmalignant CNS tumors in 1999 should exceed 30,000. Although the numbers are sobering, CNS malignancies represent only about 1.4% of the total burden of malignant neoplasms in the U.S. Proposed epidemiologic studies of CNS cancer have not, as a result, enjoyed the relatively high funding priority of lung, breast, prostate, colon, or several other common adult epithelial neoplasms. Additionally, since there is no comprehensive nationwide cancer registry, the relative rarity and the high degree of histologic heterogeneity of CNS tumors make epidemiologic studies inherently difficult to conduct. Etiologic studies of CNS cancer in human populations, therefore, have been quite limited.

From studies that have been conducted, no causal factor has been identified that explains even a modest proportion of CNS cancer occurrence (Davis and Preston-Martin, 1998; Kuijten and Bunin, 1993). The few known risk factors, most of which are related to genetic diseases that impart a CNS tumor susceptibility, likely account for not more than 10% of incident cases. Great interest, therefore, was generated when a ubiquitous environmental exposure, power frequency electromagnetic fields, was first reported in 1979 to be a possible cause of brain cancer (and leukemia) in children (Wertheimer and Leeper, 1979). A few years later, an occupational study found leukemia mortality to be associated with being an "electrical worker" (Milham, 1982). The stage was then set for many subsequent epidemiologic and laboratory studies and for major coverage by media and lay authors on potential adverse health effects of EMF,[2] including brain cancer. After 20 years of study, dialogue, and litigation, the issue of whether or not EMF causes cancer in humans is still unresolved and very controversial.

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[2]Abbreviations used are as follows: CI, confidence interval; EMF, extremely low frequency electromagnetic fields.

The purpose of this report is to briefly summarize results from published epidemiologic studies of EMF related to brain cancer and to provide an overview of results from experimental studies. We identified relevant studies from the MEDLINE® database, from other review articles on this topic, from references contained in articles identified from our review, and from the National Institute of Environmental Health Sciences' 1997 (NIEHS, 1997) and 1998 (Portier and Wolfe, 1998) reports on health effects from exposure to power frequency electric and magnetic fields. The literature on EMF health effects is very extensive. Although we evaluated all published epidemiologic studies for our assessment, we did not review all experimental studies. Rather, for experimental studies, we also relied on numerous other reviews to help guide our interpretations. Our report is not intended to represent a comprehensive critical review of the methodology of all studies that have been conducted. Instead, our goal is to provide the interested reader with a synopsis of results from relevant work and to provide our assessment of the current state of scientific knowledge regarding the EMF–brain cancer issue.

Biological Plausibility and Biological Studies

Wertheimer and Leeper (1979) conducted the first empirical research on residential EMF sources in relation to cancer. This seminal study compared the power distribution systems of residences among children who had died of brain and other cancers with those of similar children selected from birth certificate records who had not died of cancer. As discussed in more detail later, the homes were classified as high- or low-current configuration according to the characteristics and proximity of the power distribution system serving the home. The exposure measure, often called the "wire code," was based on theoretical capacity for carrying current and on empirical measurements of 60 Hz (power frequency) magnetic fields. Magnetic fields, rather than electric fields, were the focus of the study because they readily penetrate building materials and tissues (Alonso et al., 1993). Extremely low-frequency electric fields, in contrast, are easily shielded and have little ability to penetrate buildings or tissues. It was assumed, therefore, that any biologic effect from exposure to power frequency electromagnetic fields (60 Hz in the US, 50 Hz in Europe) must be due to the magnetic rather than the electric component of the field (Moulder and Foster, 1995). Epidemiologic field studies of EMF and cancer have thus been predicated on the assumption that magnetic fields pose the potential danger (Miller et al., 1997). One of the most important issues that continues to hamper the appropriate design of epidemiologic studies of EMF and cancer, however, is the lack of an identified biological mechanism for EMF carcinogenesis that can be translated into a relevant exposure assessment system (McCann, 1998; Patterson, 1992). Indeed, the plausibility of a causal role has been questioned by many because the energy levels of typical 50- and 60-Hz magnetic fields are so low that the internal currents they induce are many orders of magnitude smaller than the currents required to produce nerve and muscle stimulation or other endogenous biochemical processes (Portier and Wolfe, 1998), let alone cause direct mutagenic effects. A multitude of experimental studies, nevertheless, have reported biological effects of EMF. An EMF Science Review Symposium, sponsored by the EMF *RAPID* Program (NIEHS, 1997) was held in 1997 for experts to discuss and review theoretical mechanisms and in vitro research findings. Their break-out working groups reviewed study results and theoretical EMF bioeffects related to biophysical mechanisms; cellular growth, differentiation, and control of gene expression; and enzymes, intracellular pathways, and signal transduction. No clear conclusions were reached. The mechanisms by which EMF conceivably could cause adverse health effects (Adey, 1993; Anderson, 1993; Valberg et al., 1997; Wood, 1993), including those related to cancer (Hendee and Boteler, 1994; Kavet, 1996; Lacy-Hulbert et al., 1998; McCann et al., 1997; Moulder and Foster, 1995; Stevens, 1993; Wilson et al., 1990a) have been extensively reviewed and are beyond the scope of this paper. A brief discussion follows, however, on a few of the recurring themes that have been explored over the years and continue to be of interest.

Cancer Promotion

It is generally accepted that EMFs do not have sufficient energy to cause mutagenic damage to DNA and cannot cause the cellular damage usually associated with cancer initiation (Hester, 1992). Negative results from experimental studies on the potential genotoxicity of electric and magnetic fields provide strong support for this view (McCann et al., 1993; McCann et al., 1998). A general mechanism more plausible than a direct mutagenic effect is cocarcinogenicity, in which EMF exposure functions to increase the probability that cells with carcinogenic potential will proliferate and develop to neoplasticity after an initiating event (Anderson, 1993). Stuchly et al. (1992) examined the ability of 60-Hz magnetic fields to act as a tumor copromoter after an earlier study (McLean et al., 1991) indicated that magnetic fields did not promote the growth of tumors. Their experiment on SENCAR mice did not provide evidence of copromotion, although there was an indication that magnetic field exposure might have increased the rate of skin tumor development. McLean et al. (1997) recently confirmed their lack of success in demonstrating magnetic field tumor copromotion, although they argued that their experiments with SENCAR mice were not sensitive enough to detect weak responses. Goodman et al. (1989) observed increases in rates of both RNA transcription and translation in EMF experiments in a variety of cell and gene types. Their laboratory also reported altered mRNA and protein synthesis (Goodman and Henderson, 1990; Goodman et al., 1983). If transcription is affected, the probability of transformation may be increased by enhanced production of an oncogene product (Stevens et al., 1990). A study by Cridland et al. (1996), however, did not support the view that power frequency magnetic fields can increase the rate of DNA synthesis. In reviews of biological experiments related to EMF-induced effects, including whole-body and gene expression studies, the lack of independent

replication of positive experimental findings related to tumor promotion mechanisms is discussed (Lacy-Hulbert et al., 1998; NIEHS, 1997; Portier and Wolfe, 1998).

Calcium

Calcium has an important role in cell-to-cell communication and is a modulator or "second messenger" in the release of neurotransmitters. Calcium is also involved in cellular processes (signal transduction) leading to mitogenesis, and effects on calcium ion homeostasis from EMF exposure have been reported (Hendee and Boteler, 1994). The first effect of magnetic fields on calcium flux was reported by Bawin and Adey (1976), who observed a reduction in calcium efflux of 12–15% in chick brain tissue. Both frequency and amplitude sensitivities were observed, with maximum decreases at 6 and 16 Hz. By contrast, subsequent studies by Blackman et al. (1985; 1988) showed significant enhancement of calcium efflux in chick brain tissue at several frequencies, the lowest being 16 Hz. A window of effect that depends on frequency and amplitude seemed to determine whether electric and magnetic fields would influence calcium balance (Blackman, 1990). Data suggest that calcium could initiate signal transduction events in cells exposed to electromagnetic fields which could, in turn, be reflected in changes in transcript levels for inducible genes (Karabakhtsian et al., 1994). It has been proposed that deregulation of calcium could result in a number of phenomena, from activation of signaling mechanisms and alterations in cellular structure to alterations in gene expression, which could contribute to carcinogenesis (Trump and Berezesky, 1995). A carcinogenic role for EMF-induced calcium disruption, however, remains to be shown.

Melatonin

Electromagnetic fields are hypothesized to suppress pineal production of melatonin (Reiter, 1994; Stevens and Davis, 1996). Melatonin has been observed to inhibit cancer cell growth in certain human breast cancer cell lines, with additional in vivo effects on breast oncogenesis in various rat models (Webb and Puig-Domingo, 1995). Melatonin has a role in inhibiting DNA damage induced by free radicals, which may serve as a mechanism for inhibiting tumor growth. By scavenging highly toxic hydroxyl radicals, melatonin is potentially a potent cellular protector against cancer initiation. It also causes the metabolism of hydrogen peroxide, thereby reducing formation of hydroxyl radicals (Reiter, 1994). Consequently, reduction of circulating melatonin levels may increase the vulnerability of DNA to oxidative attack. However, the antioxidant effects of melatonin require concentrations that are much higher than peak nighttime serum concentrations (Brzezinski, 1997). Although data concerning the effect of exposure to EMF on human pineal function is limited (Stevens, 1993; Stevens and Davis, 1996), inhibition of melatonin production from magnetic field exposure has been reported (Burch et al., 1998; NIEHS, 1998; Pfluger and Minder, 1996; Wilson et al., 1990b). Several studies show effects for differing EMF exposure metrics, but there is no agreement across studies for the same metric (NIEHS, 1998). Other studies have not found EMF effective in altering nocturnal blood levels of melatonin in humans (Graham et al., 1996; 1997; Selmaoui et al., 1996).

Free Radicals

Free radicals are generated as intermediates in metabolism and may attack lipids, proteins, and DNA. Thus, any perturbation that causes an elevation in free radical production could increase the vulnerability of DNA to chemical damage. Scaiano et al. (1994), among others, proposed that 50- and 60-Hz magnetic fields may extend the lifetime of free radicals. In a review of the physics of several mechanisms by which electric and magnetic fields cause biological effects, however, Valberg et al. (1997) concluded that free radical effects of EMF have not been observed in biological systems or shown to occur at environmental field levels. In another review, it was concluded that consistent evidence does not exist to support the EMF–free radical mechanism of carcinogenesis (Lacy-Hulbert et al., 1998).

Summary

Many experimental studies have attempted to demonstrate biological effects of EMF, including those that could be associated with cancer (Portier and Wolfe, 1998). Most efforts have reflected general mechanisms; few were specific to brain cancer. The component of EMF that may be relevant to biological effects remains unknown (Portier and Wolfe, 1998; Valberg, 1996). Current results are extremely hard to compare or evaluate (Moulder and Foster, 1995) because investigators have employed a wide variety of biological systems, endpoints, and exposure conditions. Additionally, omission of many EMF exposure parameters causes considerable difficulty in interpreting, extrapolating, and replicating experiments (Valberg, 1995). Although reproducibility is crucial for the acceptance of positive results, very few replication attempts of positive studies have been published, and even fewer have been successful (Lacy-Hulbert et al., 1998). A number of pertinent replication studies, however, are currently in process (NIEHS, 1997; Portier and Wolfe, 1998). In short, despite the large number of experiments conducted, there is yet no consistent scientific evidence in support of a plausible neurocarcinogenic mechanism for 50- or 60-Hz EMF exposure.

Exposure Measures in Epidemiologic Studies

Residential Exposure Measures of EMF

As mentioned previously, the first method developed to assess exposure to residential magnetic fields was the wire coding system developed by Wertheimer and Leeper (1979; 1982). Wire coding is a tool for roughly estimating ambient residential exposure to power frequency alternating current magnetic fields from the power distribution system near the home. The wire code meas-

ure is based on a few simple engineering assumptions (Wertheimer, 1991): Power lines that carry higher currents will generally produce higher magnetic fields; the field intensity will drop with distance from the source; neutral current return by alternate paths will often be a major source of magnetic fields; and currents in these alternate paths (including ground currents from metallic plumbing) will tend to be stronger where the current in associated power lines is large. A two-category wire code scheme was originally formed (high-current configuration and low-current configuration), but categorization of homes has since been expanded into five exposure levels: very high-current configuration, ordinary high-current configuration, ordinary low-current configuration, very low-current configuration, and buried lines. Wire codes have been shown to be moderately correlated with residential magnetic flux density, in that mean magnetic field levels tend to increase with increasing exposure category (EPRI, 1993; Kaune et al., 1987). There is a great deal of variability in the measure, however, and the probability of misclassification of exposure level is high.

In addition to external wire codes, efforts have been made to measure exposure to electric and magnetic fields within the home. For this purpose, spot measurements (Kaune et al., 1994; Kavet et al., 1992; Linet et al., 1997), fixed-site measurements (Dockerty et al., 1998; Kavet et al., 1992; Tarone et al., 1998), and personal monitoring (Friedman et al., 1996; Vistnes et al., 1997) have been considered. Spot measurements occur at specific locations over a short period of time (usually a few minutes), while fixed-site measurements take place in intervals of longer duration (usually a 24-hour period). For personal monitoring, study participants are asked to wear exposure meters for an extended period of time.

In several European countries, a system was developed to calculate theoretical cumulative estimates of ambient household magnetic field levels. The strength of magnetic fields produced by electric facilities depends in large part on the voltage, current, and geometry of the distribution system (Kaune, 1993). In the calculation of magnetic fields for this measure, variables such as current, typical spatial locations of phase conductors in power lines, the distance between the house and the power lines, the height of the towers, and currents on ground and neutral return pathways were used to predict exposure levels over time (Feychting and Ahlbom, 1994; Li et al., 1997; Verkasalo et al., 1996; Zaffanella et al., 1997).

Lastly, magnetic fields generated from electrical appliances are considerably stronger than those that emanate from residential power lines, although the strength of the fields drops off much faster with distance from the source (EPRI, 1993). Use of electrical appliances, including electric blankets and heated water beds, have been evaluated in relation to brain cancer occurrence in a few studies (Gurney et al., 1996; Preston-Martin et al., 1996a; Savitz et al., 1988).

Occupational Exposure Measures

Milham (1982) conducted the first study on occupational EMF surrogate exposure and mortality from leukemia. He stratified deaths by occupation and developed a classification of "electrical workers," such as electricians, linemen, power-station operators, and welders. A number of subsequent investigations on health risks of workers in electrical occupations have been performed using job titles abstracted from death certificates or from tumor registration data. Other examples of exposure surrogates used in occupational investigations include the longest job held during the career, the first job, or the last job.

Because of the lack of direct exposure measurements, the connection between electrical worker job titles and elevated exposures to electric and magnetic fields is considered speculative (Kaune, 1993). In the last decade, several studies have been specifically designed to perform field measurements, primarily personal monitoring, for exposure assessment in the electric utility work environment (Guénel et al., 1993; Lindh and Andersson, 1994; Loomis et al., 1994; Sahl et al., 1994; Semple and Cherrie, 1998). Job exposure matrices have been used to establish the connection between electrical worker occupational categories or job titles and elevated exposures to electric and magnetic fields. In its simplest form, a job exposure matrix is a cross-tabulation of a list of job titles or occupational categories with a list of agents to which workers carrying out the jobs may be exposed. Each cell of a job exposure matrix contains information on exposure to an agent within a category or job. All elements form a set of rules by which information on the job level can be converted to information on potential exposures. Grouping of workers with similar exposures is an important determinant of validity and has been used to obtain a statistically optimal job exposure matrix for linking health outcomes and occupational magnetic field exposures (Kromhout et al., 1995; 1997; Loomis et al., 1998). A worker's cumulative exposure can be determined by combining his or her work history with exposure levels in the job exposure matrix.

Results from Epidemiological Studies of EMF and Brain Cancer

Residential Studies of Childhood Brain Cancer

For the Wertheimer and Leeper (1979) study of childhood cancer mortality, homes in the Denver area were compared according to wire code classification. A case-control study design was used. Relative to children in low-current configuration homes, children living in a high-current configuration home had a risk of death from brain cancer that was 2.4-fold (95% CI 1.0–5.4) higher. In 1988, Savitz et al. published results of a similar wire code study in the Denver area, although they considered cases of incidence rather than death, and improved on many methodological deficiencies that were present in the earlier Denver study. In their case-control study, Savitz et al. (1988) reported a 2.0-fold higher risk (95% CI 1.1–3.8) for children living in a high-current configuration versus low-current configuration homes. In the 1990s, considerably larger case-control studies on wire codes and childhood brain cancer incidence were conducted in Los Angeles by Preston-Martin et al. (1996b) and in Seattle by Gurney et al. (1996); neither

study found an association between wire code configuration and brain tumor occurrence. Similarly, epidemiologic studies using measures of exposure based on calculated cumulative or average residential magnetic field exposure (Feychting and Ahlbom, 1993; Olsen et al., 1993; Tynes and Haldorsen, 1997; Verkasalo et al., 1993), in-home magnetic field measurements (Preston-Martin et al., 1996b; Savitz et al., 1988), electrical appliance use (Gurney et al., 1996), and electric blanket use (Preston-Martin et al., 1996a) found little if any evidence to support an EMF–brain cancer relation in children.

Residential Studies of Adult Brain Cancer

Eight studies have addressed the possible relation of residential EMF exposure to brain cancer in adults (Feychting and Ahlbom, 1994; 1997; Li et al., 1997; Schreiber et al., 1993; Verkasalo et al., 1996; Wertheimer and Leeper, 1982; 1987; Wrensch et al., 1999). Wertheimer and Leeper (1982; 1987) reported from their case-control study that CNS cancer was strongly associated with high-current configuration residential power-line exposure. Six subsequent studies did not find comparable results. In a Dutch retrospective cohort study (Schreiber et al., 1993), study subjects who lived in a residence within 100 meters of high voltage electricity transmission equipment did not have higher mortality from brain cancer than expected from population estimates. (For men the relative risk estimate was 0.65, 95% CI 0.1–3.59; for women it was 1.75, 95% CI 0.20–6.33.) As reflected in the CIs, however, the size of their study was very small. Feychting and Ahlbom (1994) conducted a case-control study of people who had lived in Sweden within 300 meters of a power line. Exposure was estimated by calculating the magnetic field exposure closest in time to diagnosis, calculating cumulative exposure during the 15 years preceding diagnosis, determining magnetic field strength from spot measurements, and measuring the distance from the power line. They observed a relative risk estimate for CNS cancer that was close to unity for all exposure estimates. Again, results were based on a small number of cases. As with all of the residential measures, their exposure assessment ignored sources of magnetic fields other than power lines (occupational exposures, for example), which inevitably results in some degree of exposure misclassification. To try to account for this, Feychting et al. (1997) used the same study base to examine the effects of residential magnetic field exposure in combination with occupational exposure. Their results were almost the same as in the original study, yielding a relative risk estimate of 1.3 (95% CI 0.3–4.8) in the highest exposure category, relative to the lowest. Verkasalo et al. (1996) conducted a nationwide cohort study of cancer in Finnish adults who lived within 500 meters of overhead power lines of 110–400 kV. Exposure assessment took into account historical exposures over a period of 20 years. They did not find an increase in risk of CNS tumors associated with high magnetic fields. Relative risk estimates were 0.94 (95% CI 0.72–1.22) for men and 0.98 (95% CI 0.81–1.20) for women. A case-control study from Taiwan also did not show an increased risk of brain tumors with elevated residential exposure levels (Li et al., 1997). Relative risk estimates by distance from transmission lines, as well as by calculated magnetic field exposure in the year of diagnosis, were close to unity. Most recently, Wrensch et al. (1999) conducted a case-control study on residential EMF exposure and adult glioma in the San Francisco area. Exposure was assessed with wire codes, and with spot measurements at the front door of subjects. The relative risk estimate for longest held residence, coded as high configuration compared with low configuration, was 0.9 (95% CI 0.7–1.3). The risk estimates corresponding to spot measurements of 1 to 2 mG, 2 to 3 mG, or higher than 3 mG, relative to ≤1 mG, were 1.0 (95% CI 0.7–1.4), 0.6 (95% CI 0.3–1.1), and 1.7 (95% CI 0.8–3.6), respectively.

Occupational Studies of EMF and Brain Cancer

Lin et al. (1985) conducted the first study on brain cancer that categorized occupation according to assumed degree of EMF exposure. Men working in electricity-related occupations, such as electricians, electric or electronic engineers, and utility company servicemen, had a significantly higher proportion of brain tumors than did those in nonelectrical occupations, including a positive trend with increasing likelihood of exposure. Many subsequent studies have used job titles or occupational categories as crude measures of exposure to address the potential relation between brain cancer and occupational EMF. A meta-analysis of 29 such studies (Kheifets et al., 1995) and several review articles have been published on these results (Bates, 1991; Miller et al., 1997; Savitz, 1993; Stevens, 1996). The meta-analysis suggested a small (10–20%) overall increase in brain tumor risk associated with electrical occupations (Kheifets et al., 1995), although no consistent dose-response trend was observed. Two additional cohort studies that used job titles did not find support for the brain cancer–EMF hypothesis (Kelsh and Sahl, 1997; Tynes et al., 1994).

A number of studies have conducted field measurements to determine actual exposure levels related to electrical occupations. Sahl et al. (1993) evaluated brain cancer mortality in a cohort of about 36,000 workers. A variety of exposure scores based on measured magnetic fields were used in their nested case-control studies, yielding odds ratios near or below unity. Floderus et al. (1993) conducted a case-control study in Sweden to evaluate different indices of average daily magnetic fields based on the job held longest during the 10 years before diagnosis. Relative to the lowest quartile of exposure, risk estimates for brain cancer associated with increasing exposure quartiles were 1.0 (95% CI 0.7–1.6), 1.5 (95% CI 1.0–2.2), and 1.4 (95% CI 0.9–2.1). A risk estimate of 1.9 (95% CI 1.2–3.1) was observed for those in the 90th percentile relative to those in the lowest quartile. Savitz and Loomis (1995) published the results of a cohort study in almost 140,000 workers at five electric utility companies in the United States. Exposure was estimated by linking individual work histories of at least 6 months' duration to data from work-shift magnetic field measurements. Brain cancer mortality was modestly elevated in relation to duration of work in exposed jobs, and more strongly elevated in relation to exposure indices. Relative to workers unex-

posed to occupational magnetic fields, a risk estimate of 2.6 (95% CI 1.4–4.9) was observed for those in the highest exposure (80th percentile) category. Even after accounting for different exposure categorization models, increasing cumulative magnetic field exposure was associated with increasing brain cancer mortality (Loomis et al., 1998). Thériault et al. (1994) conducted a nested case-control study within three cohorts of electric utility workers in Ontario and Quebec, Canada, and in France. They observed a risk estimate of 1.95 (95% CI 0.76-5.00) for brain cancer incidence in men for whom cumulative magnetic field exposure was above the 90th percentile, compared with a reference group of men with less than the median level of exposure. Kheifets et al. (1995) pooled the results of the studies by Floderus et al. (1993), Savitz and Loomis (1995), and Thériault et al. (1994) into four exposure categories (<50% as the reference category, 50–70%, 75–90%, >90%) and reported relative risk estimates of 1.33, 1.41, and 1.42, respectively. Four additional studies (Armstrong et al., 1994; Baris et al., 1996; Guénel et al., 1996; Miller et al., 1996) have been conducted using the three cohorts of electric utility workers that were assembled by Thériault et al. (1994). Overall, these studies provided weak evidence for an association of electric and magnetic fields with brain tumors. Elevated risk estimates were noted in all five studies, although they were not statistically significant in four of them. Other recent occupational studies by Floderus et al. (1994), Feychting et al. (1997), Harrington et al. (1997) and Johansen and Olsen (1998) found no EMF–brain cancer association.

Summary

The two Denver studies on childhood brain cancer reported moderately elevated risks associated with living in close proximity to a residential power distribution system of high current configuration. Subsequent studies on childhood brain cancer that used wire codes or calculated historical measures found no such association. The evidence on adult brain cancer and exposure to magnetic fields follows a similar pattern. The initial findings of Wertheimer and Leeper (1987) with respect to residential exposure were not confirmed in the six subsequent studies. The weight of evidence from early occupational studies suggests a positive brain cancer association with surrogate exposures such as job title or occupation. Recent studies with more advanced methods of exposure assessment and better control for confounding exposures (for example, solvents, PCBs, or pesticides) have been inconsistent. Of 11 studies involving exposure assessment using field measurements, only three provided some support for a positive association (Floderus et al., 1993; Guénel et al., 1996; Savitz and Loomis, 1995), and a dose-response trend was apparent in only one (Savitz and Loomis, 1995).

Discussion

In observational (nonexperimental) human studies, drawing causal inferences from study results must be made very cautiously. Many problems in design or conduct—most notably, inappropriate comparison populations, misclassified measures of exposure, or measures of effect that are confounded by extraneous factors—can result in biased estimates of the exposure-disease relation (Rothman and Greenland, 1998). It is well understood in epidemiology that statistical associations do not necessarily equate to causation (Petitti, 1991). As such, a number of guidelines are used to evaluate results across studies to help judge whether associations should be considered causally related. These guidelines for evaluation include the strength and validity of the exposure-disease risk estimates; a coherent temporal sequence of exposure in relation to disease onset; the consistency of findings across studies; and the biological coherence of the exposure-disease relation. Admittedly, understanding the probable causal mechanism is not required for causality to be reasonably established. Cigarette smoking as a cause of lung cancer, for instance, is an example for which the epidemiologic evidence was virtually irrefutable long before specific biological mechanisms were established.

The lack of a coherent biologic understanding of how magnetic field exposure is likely to be involved in the carcinogenic process, however, is more than an academic inconvenience. As discussed above, no guidance has emerged from experimental studies to identify characteristics of magnetic field exposure (if any) which would translate into a biologically effective dose that should be targeted for exposure assessment. Should we be concerned with transients or harmonics? What level of field intensity is important? What duration of exposure is necessary? Are there acute or chronic threshold effects of magnetic fields that need to be crossed before damage can occur? None of these answers are known, and until they are, the current EMF exposure assessment techniques—such as wire codes, ambient levels in the home, personal dosimetry, calculated household exposure from historical information, job classifications, or work site measurements—can only be considered crude measures. It is inevitable that exposure assessment will be inaccurate if we do not know what to measure, and the validity of the methods used for both residential and occupational exposure assessment have long been of concern (Savitz et al., 1989). As with many areas of environmental and occupational epidemiology, this is the principle challenge facing future EMF research in human populations.

Exposure assessment issues not withstanding, if one assembles the evidence of 20 years of observational and experimental research on the potential role of EMF on brain cancer occurrence, it seems reasonable to judge that the case for causation has not been made. A substantial majority of the observational residential studies have not found elevated brain cancer risks in relation to a variety of exposure surrogates. The occupational studies are less consistent in their results, with many studies based on job classification showing weak to moderate effects, and many others showing no effect. The majority of the occupation studies that used more direct measures of EMF exposure found little to no evidence for an elevated brain cancer risk in relation to high exposure; and the experimental studies have not provided consistent or compelling evidence in support of the EMF–brain cancer relation.

The National Institute of Environmental Health Sciences Working Group on Health Effects of EMF care-

fully reviewed and debated the body of evidence related to EMF exposure and cancer. While the majority (20 of 26) of those in the working group concluded that EMF is "possibly carcinogenic to humans," they also found that there was inadequate evidence for carcinogenic effects with respect to CNS cancer. Limitations in study design and exposure assessment, inconsistencies in findings across studies, and/or a lack of association were noted in describing the inadequacy of the epidemiologic evidence (Portier and Wolfe, 1998; pp. 396–397). In 1991, Poole and Tricholpoulos made the distinction between biological conceivability and plausibility in their paper on EMF and cancer (Poole and Trichoupolos, 1991). They wrote that "a biological finding is one that is based on solid biomedical grounds, whereas an association can be thought of as biologically conceivable when it is not impossible or absurd." The experimental evidence at that time led them to conclude that it may be conceivable, but not plausible, that EMF could be a cause of cancer. At least in regard to brain cancer, our view is that no evidence, either experimental or observational, has recently emerged to refute this conclusion.

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