NIEHS REPORT on

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

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

NIEHS

National Institute of Environmental Health Sciences
National Institutes of Health

Supported by the NIEHS/DOE

EMF RAPID

NIH Publication No. 99-4493

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

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

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

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

Animal Cancer Data

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Non-Cancer Health Effects in Experimental Animals

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

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

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

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

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

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

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

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

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

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

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

Studies of Cellular Effects of ELF-EMF

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