BIOLOGICAL EFFECTS OF EXTREMELY LOW-FREQUENCY ELECTROMAGNETIC FIELDS: *IN VIVO* STUDIES

Prepared by: Larry E. Anderson, Ph.D.
Bioelectromagnetics Program Manager
Battelle Pacific Northwest Laboratory
Richland, Washington

BIOLOGICAL EFFECTS OF EXTREMELY LOW-FREQUENCY ELECTROMAGNETIC FIELDS: *IN VIVO* STUDIES

INTRODUCTION

Until the last few decades, the natural background levels of atmospheric electric and magnetic fields were extremely low; however, they have since dramatically increased. The industrialization and the electrification of society have resulted in the exposure of people, animals and plants to a complex milieu of elevated electromagnetic (EM) fields that span all frequency ranges. One of the most significant contributions to this changing electrical environment has been the technological advances associated with the growth of electrical power generation and transmission systems. In addition, EM field-generating devices have proliferated in industrial plants, office buildings, public transportation systems, homes and elsewhere.

EM fields, which may extend far beyond their sources, are mostly imperceptible to people. In the past, there was considerable controversy as to whether fields in the extremely-low-frequency (ELF) portion of the electromagnetic spectrum could even cause significant biological effects, let alone pose a hazard to health. However, research and clinical experience have shown that biological effects from such fields are not precluded simply because they are not perceived. Recent data confirm some of the earlier reports that ELF fields do cause changes in certain biological systems. Thus, it is both reasonable and timely to evaluate the interactions between the modern EM environment and living organisms and to investigate whether such interactions are beneficial or detrimental, transient or permanent.

In the past two decades, research programs throughout the world have greatly expanded in scope and depth to address such issues. Significant progress has been achieved, both in defining the ways living organisms interact with ELF fields and in describing biological effects, both real and potential, from such fields. Much of this effort has been directed toward electric fields of power frequencies. However, frequencies other than 50 and 60 Hz have also been examined, and research has been expanded to include magnetic as well as electric fields. Although it is now clear that ELF EM fields do cause biological effects, the basis for those effects and the underlying mechanisms of interaction remain largely unknown, and the health implications for humans and animals have yet to be fully determined.

As in other areas of scientific investigation, the research being conducted on ELF bio-effects has been performed at several levels: human studies (primarily epidemiological), animal experiments, and cellular (mechanistic) studies.

Some of the earliest efforts to examine health-related issues of ELF fields were focused on the impacts of such fields in humans. Despite the obvious desirability of obtaining such data, they are the most complex and least complete. Additionally, often experimental questions cannot be investigated in humans. Therefore, many areas of biological investigation are more appropriately and efficiently conducted with animal models.

This paper specifically examines the biological effects of exposure to ELF EM fields observed in *in vivo* (animal) studies. An attempt is made to evaluate experimental results and, insofar as possible, interpret them with respect to potential health implications. An overview of current concepts and possible mechanisms is given, and possible future directions of research are discussed.

PHYSICAL CONSIDERATIONS FOR COMPARING EXTREMELY LOW-FREQUENCY EXPOSURE BETWEEN SPECIES

Physical Parameters of Exposure

ELF fields (less than 300 Hz) are quantified in terms of the electric field strength E (volts per meter) and the magnetic field strength H (amperes per meter) or the magnetic flux density B (tesla). Natural environmental ELF fields are normally very low, but with widespread and increasing use of electrical energy, the potential for exposure has increased considerably. Exposure from man-made sources generally ranges up to 100 V/m and from 0.1 μT to 30 μT; the higher exposures occur for short time durations. The highest occupational exposures may be on the order of tens of kilovolts per meter and tens of milliteslas. Typically, however, occupational exposures are 10 to 100 times lower than these high levels.

ELF fields are used in a variety of therapeutic and diagnostic applications, including healing of nonunion bone fractures, promotion of nerve regeneration, and acceleration of wound healing. These applications involve partial-body exposures in the range of 1 to 30 mT. Exposures to time-varying electric and magnetic fields also result from medical use of magnetic resonance devices.

Whole-body exposure to ELF electric fields may involve effects related to stimulation of sensory receptors at the body surface (hair vibration, or possible direct neural stimulation) and effects within the body caused by the flow of current. Magnetic fields would appear to interact predominantly by the induction of internal current flow.

Internal current flow is described in terms of current density in tissue J (amperes per meter squared). Ohm's law permits an equivalent expression of current density in terms of internal electric field strength E (volts per meter). It is not known whether J or E is the more useful and relevant physical quantity for an understanding of the mechanisms of biological effects. Internal current densities produced by exposure to external E or B fields at practical levels (up to approximately 100 kV/m and 1 mT) are far lower than the current densities produced by contact with electrical conductors that produce various electric shock effects.

Data on neuromuscular stimulation (including respiratory tetanus and cardiac fibrillation) indicate that current densities higher than about 0.1 A/m^2 can be dangerous. Current densities near 0.01 A/m^2, particularly with long-term exposures, may cause biological effects that are important to health. At lower levels a variety of biological effects may occur; however, the health implications of exposure at such levels are not clear.

The magnitude of the internal current density is in direct proportion to the frequency for sinusoidal external E and B fields. For pulsed or other wave forms the rate of change of the field is relevant. The duration of current flow is also important. It is practical to relate observed effects to internal current density and the inducing external fields. Accurate relationships of external field and internal current density are functions of frequency, orientation of the body in the field, body size and shape, and tissue composition. Thus, from these fundamentals of interactions, possible mechanisms can be proposed and defined in terms of external unperturbed E and B field strengths, frequencies, and durations.

Dosimetry of Field/Animal Interaction

Electric-field coupling to living organisms has been investigated, both from a theoretical and an experimental perspective. Theoretical treatments, which are addressed in other plenary papers, have been extensively reviewed (Kaune 1985; Kaune and Phillips 1985; Polk and Postow 1986) and will not be discussed here. Experimental modeling is briefly reviewed because it provides important scaling/dosimetric information for extrapolating data from animals to humans. A more detailed treatment of the subject can be found in reviews by Kaune and Forsythe (1985) and Tenforde and Kaune (1987).

In animals or models exposed to an electric field, an easily determined electrical parameter is the short-circuit current induced in the grounded subject. Although most of the data collected to date were obtained at only one frequency and body weight, currents at other frequencies (f) and body weights (W) can be determined using an $fW^{2/3}$ dependence (Kaune, 1981). The total short-circuit currents in humans and various animals have been compared during exposure to a constant vertical ELF electric field .

Table 1

Short Circuit Currents Induced in Grounded Humans and Animals by Vertical Extremely Low Frequency Electric Fields.*

Species	Short-Circuit Current $I \times 10^8/fw^{2/3}E_o$* (μA)
Human	15.0
Horse	8.5
Cow	8.6
Pig	7.7
Guinea Pig	4.2
Rat	4.0

* Taken from TS Tenforde and WT Kaune 1987

** I = current (A), f = frequency (Hz), W = weight (g), and E_0 = electric field intensity (V/m).

Another method of comparison, is a simple relationship described by Deno (1977), in which the external electric fields acting on the surface of a body are measured. Kaune and Phillips (1980) used such measures to compare surface electric fields and induced-current distributions in grounded models of rats and pigs. Current densities were estimated from the induced current data. By combining data derived from Deno's human measurements and Kaune's animal data, researchers have determined peak surface electric fields and current densities have been determined (Figure 1). All three models shown in this figure were exposed to an identical 60-Hz electric field of 10 kV/m. An evaluation of the data shows that, despite comparable exposure, the doses of electric fields received by the three models are quite different. If dose is represented by either the induced axial (along the long axis of the body) current density or the peak surface electric field, the values are considerably larger in the human than in the animal models. Therefore, if one wishes to extrapolate biological data from one species to another, adjustments must be made to scale the exposure parameters. Since exposures are usually given as unperturbed field levels (that is, fields with no bodies present), a scaling factor must be used to equalize differences between species. A complicating element is that the value of the scaling factor depends upon the internal or external quantity that is being scaled. For example, at the top of the body the surface fields (180, 67, and 37 kV/m for human, pig, and rat respectively) require scaling factors of approximately 1:3:5 for these respective species. If, on the other hand, axial current density in the neck is the desired comparison, the scaling factors are about 1:14:20 for the three species. These values

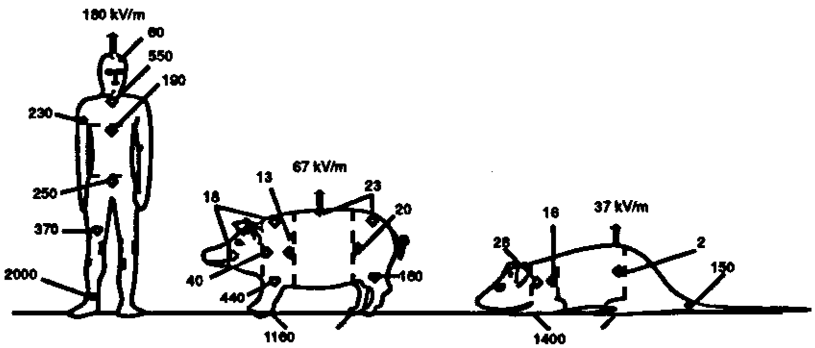

Figure 1. Electric field intensity (kV/m)comparisons are made for the highest point on the surface of a grounded man, pig, and rat exposed to a 10 kV/m, 60-Hz electric field. Estimated average axial current densities (nA/cm2) are also compared for the same species through the body sections as shown. Also given for man and pig are current densities calculated as being perpendicular to the body surface. Relative body sizes are not to scale (adapted from Kaune and Phillips 1980).

change to 1:12.5:125, respectively, for current densities through the lower abdomen. Although the general principle of scaling is applicable and necessary, precise, quantitative extrapolation of data across species requires additional knowledge about the specific site of action for a particular biological end point.

More precise current-density data have recently been obtained by measuring more than one component of the total internal current-density vector. Representative data for a human model exposed to a vertical, 10 kV/m electric field is shown in Figure 2 (Kaune and Forsythe 1985). Similar data have been obtained for animal models as well (Kaune and Forsythe 1988). Methods have also been developed to extrapolate data obtained with grounded subjects to the ungrounded condition (Kaune et al. 1987).

Coupling of humans or animals to ELF magnetic fields is different from the electric field coupling discussed previously. Although biological organisms do not perturb an incident ELF magnetic field, they serve as a conductive pathway in which eddy currents are induced. These circulating currents lie in planes perpendicular to the direction of the incident magnetic field (Tenforde 1986). The magnitude of an electric field induced by an external magnetic field depends mainly on the loop size of the induced current. Equivalent doses for subjects exposed to a magnetic field can be obtained by using a scaling factor based roughly on the size of the animal or human in question.

As described in a paper by Tenforde and Kaune (1987), if the relative magnitudes of the electric field induced in a human by electric (10 kV/m) and magnetic (30×10^{-4} T) fields (simulating the fields close to a high-voltage power transmission line) are compared, the internal fields induced by the electric field are roughly an order of magnitude larger than those induced by the magnetic field. That much of the ELF bio-effects research has been focused on electric field exposure can be partially explained by this large difference in induced internal electric fields.

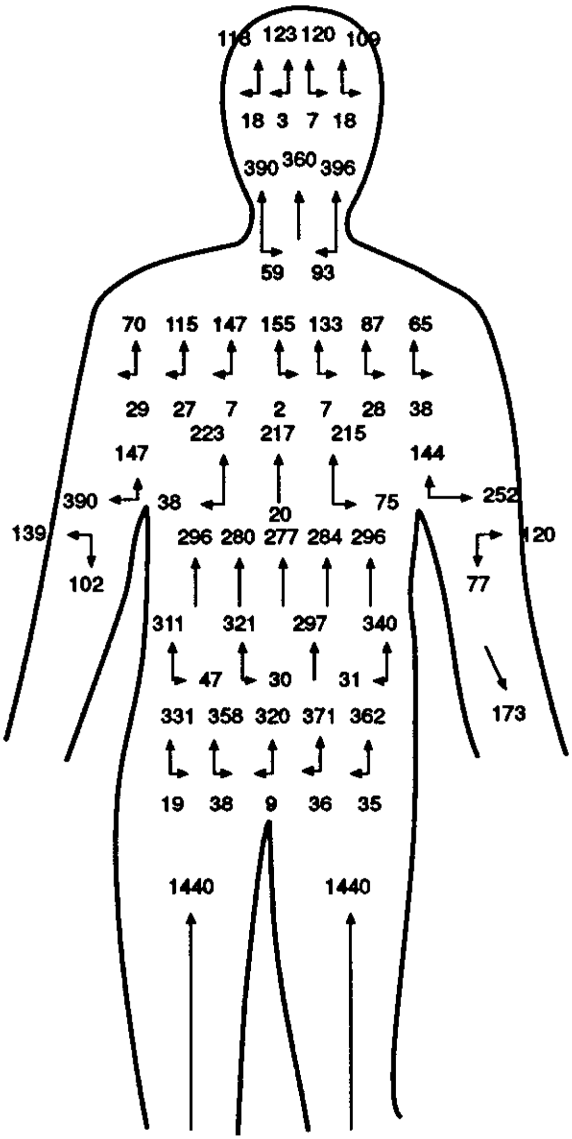

Figure 1. Induced current densities measured in a saline model of a man exposed to a 10 kV/m, 60-Hz electric field. Axial and radial components of the induced densities are represented by the vertical and horizontal arrows respectively with length of the arrows roughly comparable to the intensity value of the current (from Tenforde and Kaune 1987).

REVIEW OF ANIMAL STUDIES

Although the interaction of humans with electric and magnetic fields is of prime importance and concern, many areas of biological investigation are more efficiently and appropriately conducted using various other animal species. Animals provide an integrated system that can be used in prospective studies, in contrast to the retrospective studies usually done with humans. A major challenge of using data from animal studies is the question of extrapolation to human exposure conditions as discussed previously.

By far the largest body of information on biological effects of ELF fields has been obtained in experimental research on animals exposed to electric fields. Experiments have been performed primarily on rodents (rats and mice), but a wide variety of other subjects have also been used, including insects, birds, cats, dogs, swine, and nonhuman primates. A broad range of exposure levels has been employed and an equally large number of biological end points have been examined for evidence of possible electric and/or magnetic field effects. These multitudinous studies have been reviewed several times (Sheppard and Eisenbud, 1977; WHO, 1984; Anderson and Phillips, 1985; Graves, 1985). Summaries of the important findings are presented here, arranged according to the biological systems that appear to be principally involved: neural and neuroendocrine systems (including behavior), reproductive systems (including fertility, growth and development), and other functions (including cardiovascular and blood chemistry, bone growth and repair, and cellular and membrane properties). A separate section addresses the issue of carconogenesis and mutagenesis.

Biological research conducted at power-frequency electric fields of 50 to 60 Hz has produced the preponderance of experimental data. More limited work has been conducted at lower frequencies (15 to 35 Hz); very few studies have been performed at frequencies between 100 and 300 Hz. Only relatively recently have investigators begun to focus on the effects of ELF magnetic field exposures on biological systems.

Neural and Neuroendocrine Systems

Many of the biological effects observed in animals exposed to ELF fields appear to be directly or indirectly associated with the nervous system. This apparent relationship might be anticipated, since the nervous system is composed of tissues and processes that are unusually responsive to electrical signals. In addition, both the structure and function of this system are fundamentally involved in the interaction of an animal with its environment. The major features of this interaction; transmittal of sensory input from external stimuli, central processing of such information, and subsequent efferent innervation of tissues and organs, may provide the basis for explaining possible links between ELF exposure and observed biological consequences.

In early experimental studies, nervous system parameters were measured only occasionally, although many of the observed effects, primarily behavioral, were related to nervous system function. Before the late 1970s, studies on ELF exposure relating to nervous system function could generally be classified in three categories: assessments of activity or startle-response behavior, evaluations of stress-related hormones (such as corticosteroids), and general measurements of central nervous system responses (such as EEGs and interresponse times). Results were often contradictory, with claims of both effects and non-effects from ELF electric field exposure. However, because of the possible and suggested sensitivity of the nervous system to ELF fields, subsequent studies included a broader range of neurological assessments. Specific nervous system responses, in addition to behavior, began to be sought in experiments. This effort was mounted to determine the extent of ELF interaction with tissue and/or organ systems and also to investigate the mechanisms underlying the observed biological effects.

Behavior

Among the most sensitive measures of perturbations in a biological system are tests that determine modifications in the behavioral patterns of animals. This sensitivity is especially valuable in studying environmental agents of relatively low toxicity.

Behavioral studies in several species provide evidence of field perception and of the possibility that EM fields may directly alter behavior. The threshold of detection reported by Stern et al. (1983) is between 4 and 10 kV/m in rats. Human volunteers were able to detect a 9 kV/m 60 Hz field in certain postures (Graham et al., 1987). Thresholds for perception of the field have been reported in the 25 to 35 kV/m range in other animal species, including mice (Moos, 1964; Rosenberg et al., 1983), pigs (Kaune et al., 1978), and pigeons and chickens (Graves et al., 1978 a,b). It appears that a change in other environmental factors, such as relative humidity has the potential to alter perception threshold values (Weigel and Lundstrom, 1987). Cutaneous sensory receptors that respond to a 60 Hz electric field have been identified in the cat paw (Weigel et al., 1987). Whether such receptors exist in human skin is unknown.

An evaluation of the preference/avoidance behavior of animals for remaining in or out of the E-field has been conducted at several field strengths for 60 Hz electric fields. At 100 V/m, no effect of exposure, either in preference behavior or temporal discrimination, was evident in monkeys (deLorge, 1974). At 25 kV/m, rats preferred to spend their inactive period in the field, whereas at 75-100 kV/m they avoided exposure (Hjeresen et al., 1980). Swine (Hjeresen et al., 1982) remained out of the field (30 kV/m) at night but demonstrated few other observable behavioral changes. Alterations in activity have also been reported in animals exposed to ELF fields, including a transitory, increased activity response on initial exposure of rats or mice at 25 to 35 kV/m (Hjeresen et al., 1980; Rosenberg et al., 1983).

Much of the behavioral work with nonhuman primates has been performed at very low field strengths (7 to 100 V/m), where essentially no effects of exposure were reported (summarized in NAS, 1977). Gavalas et al. (1970) and Gavalas-Medici and Day-Magdaleno (1976) observed changes in interresponse time of monkeys during exposure, but no other effects. At much higher field strengths (30 kV/m), Rogers et al. (1987) reported minor behavioral changes in exposed baboons that appear related to the animals' perception of the field. The observed effects do not seem to be permanent or deleterious.

In studies examining the effect of ELF magnetic fields on behavior, many of the investigations carried out at low field intensities have shown behavioral alterations, primarily activity changes (Persinger, 1969; Persinger and Foster, 1970; Smith and Justesen, 1977). In contrast, studies conducted at higher field intensities have shown no evidence of a field-associated effect on animal behavior (Creim et al., 1985; Davis et al., 1984).

In the experimental studies that have been conducted to determine whether ELF fields cause behavioral alterations, remarkably few robust effects have been demonstrated (Lovely, 1988). Effects that have been observed, usually arousal or activity responses, are probably due to the animal's detection and possible perception of the electric field.

Biological rhythms

Far from being static, living organisms exhibit marked dynamics in metabolism and function. Major elements of such dynamics are the endogenous rhythms of varying frequencies (such as ultradian, circadian, and infradian). These biological rhythms, which respond to exogenous environmental cues, are normally a complex mix of phase-locked rhythms and have significant impacts on the physiological and psychological well-being of the organism. Biochemical processes, cellular communications, and functional systems are all intimately associated with endogenous rhythms, as is overall systemic response to the environment. Dysfunctions in these underlying rhythms can profoundly affect the organism and lead to a variety of biological effects.

A number of investigations have been conducted to examine the effects of ELF electromagnetic fields on natural biological rhythms. Following Wever's significant findings (1971) on the influence of electromagnetic fields on humans, several studies have been performed. Dowse (1982) claimed that a 10 Hz, 150 V/m field affected the locomotor rhythm of individual fruit flies. Researchers in Ehret's laboratory (Duffy and Ehret, 1982; Rosenberg et al., 1983) used metabolic indicators to examine both circadian and ultradian rhythms in rats and mice exposed to 60 Hz electric fields. They observed no effects of exposure in rats, but they reported that the activity and rhythms of oxidative metabolism in male mice could be phase shifted by exposure.

Wilson et al. (1981, 1983) directly examined another aspect of circadian activity in rats by measuring the cyclical pineal production of indolamines and enzymes. A significant reduction in the normal nighttime rise of melatonin and biosynthetic enzymes in the pineal gland was observed in rats exposed to either 1.5 or 40 kV/m. Furthermore, the change in pineal indole response occurred only after at least 3 weeks of chronic exposure (Wilson et al., 1986). There was also a suggestion of phase-shifting in young rats exposed to 60 Hz fields (Reiter et al. 1988). In other studies, nocturnal pineal components in mice and rats have been shown to be sensitive to rotated magnetic fields (Welker et al., 1983; Kavaliers et al., 1984; Lerchl et al., 1990). Recent evidence suggests that retinal sensors may be involved in the pineal response to EM fields (Olcese et al., 1985; Reuss and Olcese, 1986).

Sulzman and Murrish (1987) investigated the effects of ELF fields on circadian function in squirrel monkeys. In an examination of exposure to a range of electric field intensities (2.6, 26, and 39 kV/m), accompanied by a 100 μT magnetic field, they reported apparent intensity-related effects. None of the monkeys exposed to 2.6 kV/m showed any change in activity or feeding after 2 weeks of exposure. However, 33% of the monkeys exposed to 26 kV/m and 75% of those exposed to 39 kV/m had significant changes in their circadian cycles.

Although firm conclusions cannot yet be made regarding potential health impacts from ELF effects on circadian or biological rhythms, it is apparent that EM fields can alter the circadian timing mechanisms in mammals. Much work remains to be accomplished before the observed effects and their biological consequences are clearly understood. It seems probable that ELF effects on rhythms, particularly those mediated by neuroendocrine systems, could play an important role in other areas of observed bio-effects, such as behavior and development.

Neurochemistry/Neurophysiology

The relationship between the neurotransmitters norepinephrine and epinephrine and the physiological responses of stress and arousal is well established. As researchers began to look for potential biological effects of ELF electric fields, measuring these transmitters became one of the assessments used to examine the nervous system for evidence of a stress response in animals. This approach, which benefited from the ease of measuring these chemicals in serum, urine, or brain tissue, specifically addressed reports that ELF fields act as mild stressors (Dumansky et al., 1977; Marino and Becker, 1977). Unfortunately, potential methodological problems raised serious questions about the validity of the results from early studies (Michaelson, 1979). Experimental design and methodology problems have also contributed to contradictory results in some of the more recent studies.

Groza et al. (1978) measured catecholamines in both urine and blood after exposure of rats to 100 kV/m, 60 Hz fields. They reported significant increases in epinephrine levels in both blood and urine after acute (6-hour to 3-day) exposures but no changes in norepinephrine or epinephrine with longer-term (12-day) exposures.

A report of increased norepinephrine in serum of rats exposed to 50 Hz (50 V/m and 5.3 kV/m) is found in the work of Mose (1978). A companion paper by Fischer et al. (1978) examined norepinephrine content in brain tissue of rats exposed to 5.3 kV/m for 21 days; after 15 minutes of exposure the levels increased rapidly. However, after 10 days of exposure, levels were significantly lower than in a control group. Portet and Cabanes (1988) reported no changes in adrenal epinephrine or norepinephrine in 2-month-old rats exposed to a 50 kV/M, 50 Hz field for 8 hours a day. In contrast, Wolpaw et al, (1987) reported decreases in cerebrospinal fluid concentrations of the major metabolites of dopamine and serotonin, homovanillic acid, and 5-hydroxindoleacetic acid in macaques exposed to electric and magnetic fields. In addition to possible species-specific response differences, some of the discrepancies between results of various laboratories may be explained in light of results described by Vasquez et al.

(1988). Because of circadian fluctuations in levels of neurotransmitters, the time of sampling may be critical in determining whether an ELF effect is observed. Vasquez et al. reported significant changes in diurnal patterns of several biogenic amines when rats were exposed to 60 Hz electric fields for 4 weeks.

Examining another neurochemical parameter, Kozyarin (1981) measured the acetylcholinesterase (AChE) enzyme levels in rats exposed to 50 Hz electric fields. He reported that serum AChE activity was approximately 25 times baseline levels in both young and old animals exposed to 15 kV/m for 60 days, 30 minutes a day. Brain levels of AChE decreased in exposed animals, although not by such large percentages. Further important measurements were made to estimate the course of recovery from the observed effects. All values had returned to normal 1 month after cessation of exposure. The author concluded that electric fields can cause changes in the functional condition of the central nervous system, although the changes appear to be temporary.

Measurements of corticosteroids in animals exposed to electric fields have resulted in a somewhat confusing picture, perhaps because of the quick response to stimuli of these adrenal steroids (Michaelson, 1979). Studies at Pennsylvania State University examined the hypothesis that 60 Hz electric fields act as a biological stressor (Hackman and Graves, 1981). In that study an acute, transient increase in plasma corticosterone levels occurred in mice exposed to 25 or 50 kV/m. Serum levels of the steroid returned to normal within 1 day. In some studies conducted in the Soviet Union, Dumansky et al. (1976) showed an increase in corticosteroids in rats exposed for 1, 3, or 4 months at 5 kV/m.

In a study conducted by Marino et al. (1977), serum corticosteriod levels were decreased in animals exposed to 15 kV/m for 30 days. This study, however, used pooled, grouped samples of serum. It also had several other technical problems: cages varied, and in four experiments exposed rats were individually housed, whereas control rats were housed in groups.

Results that appear to contradict Marino's and Dumansky's data have been described by Free et al. (1981) and Portet and Cabanes (1988), who exposed rats or rabbits to 100 and 50 kV/m, respectively, for 30 days or 120 days. No differences in corticosterone levels were observed between exposed and control animals. Providing additional support for these data was a study by Gann (1976) in which dogs exposed to 15 kV/m showed no effects of E-field exposure on corticosterone secretion. Quinlan et al. (1985) collected blood samples from rats via carotid artery cannulas during exposure or sham exposure to an 80 kV/m, 60 Hz electric field. No statistically significant differences in corticosterone levels were noted.

In general, neurochemical data provide relatively weak evidence that exposure to electric fields in the power-frequency range may cause slight changes in nervous system function. The number of experiments is not large, and there are significant questions about the validity of several of the studies. Nevertheless, the findings support the hypothesis that ELF exposure alters internal rhythms, increases arousal in animals, and is transient in its effect.

Several laboratories have examined the morphology of brain tissue from animals exposed to ELF electric fields. Carter and Graves (1975) and Bankoske et al. (1976) exposed chicks to 40 kV/m E fields and saw no effects on central nervous system morphology. This finding was supported by those of Phillips et al. (1978), who examined rats exposed to 100 kV/m for 30 days. Again, no morphological evidence of an electric field effect was observed. In a study in Sweden (Hansson 1981a,b), dramatic changes in cell structure were reported in the cerebella of rabbits exposed to a 14 kV/m E field. Exposed animals showed disintegration of Nissl bodies and the three-dimensional endoplasmic reticulum structure, as well as the abnormal presence of many lamellar bodies, particularly in the Purkinje cells of the cerebellum. Reduced numbers of mitochondria, reduced arborization of the dendritic branches, and an absence of hypolemmal cisterns were also evident in these cells. However, these reported changes must be interpreted with caution. The animals were exposed outdoors and showed evidence of significant health deficits (whether resulting from the electric field, other environmental conditions, or some combinations of these factors is not clear). Furthermore, results from these studies are in conflict with experiments conducted by Portet and Cabanes (1988), in which no ultra-structural changes occurred in the cerebella of young rabbits exposed to 50 kV/m. These questions concerning neuroanatomical changes have yet to be resolved. However, the lack of obvious, significant functional deficits in the central nervous systems of thousands of animals exposed to date suggests that the dramatic morphological alterations in exposed rabbits may result from conditions unrelated to electric field exposure. The possibility of synergistic effects from the E field and a stressful environment cannot be ruled out.

Because the nervous system is by nature electrically sensitive, it has been assumed to be particularly sensitive to influence by external ELF fields. To some degree this assumption has been borne out by experimental results, although in the area of neurophysiology a confusing array of studies have claimed both effects and no effects of ELF field exposure. A case in point is the commonly used measure of general central nervous system activity, the EEG. When chicks were exposed for 3 weeks to 60 Hz E fields of up to 80 kV/m, Graves et al, (1978b) noted no changes in EEGs recorded via electrodes implanted after exposure. Similarly, no effects were observed in the EEGs of cats exposed to 80 kV/m at 50 Hz (Silney, 1981). Earlier, Blanchi et al. (1973) reported significant changes in EEG activity when guinea pigs were exposed for 1/2 hour to a 100 kV/m, 50 Hz field. Takashima et al, (1979) examined EEGs from rabbits exposed to 1 to 10 MHz, modulated at 15 Hz. Before exposure, these animals had silver electrodes implanted in their skulls for recording the EEG. After 2 to 3 weeks of exposure, abnormal responses were observed in the EEGs, although it was subsequently determined that the EEG returned to normal when the electrodes were removed during exposure. The investigators thus concluded that the effect on the EEG was due to the local fields created by the presence of the electrodes in the cranial cavity. Gavalas et al. (1970) noted that 7 and 10 Hz E fields of only 7 V/m affected EEGs recorded from monkeys via implanted electrodes. The significance of these results is unclear, since they may be due to an artifact caused by the implanted electrodes as noted previously.

EEGs from cats exposed to 50 Hz magnetic fields (8 hours a day at 20 mT) showed short-term decreases in power density spectra (Silney, 1979). This response was observed only for a short time after the magnetic field was switched on.

In an assessment of a more specific electric "fingerprint" of the brain, the visual evoked response (VER), no effects of exposure were observed in adult or developing rats. Jaffe et al. (1983) assessed the VER in 114 rats exposed *in utero* through 20 days post partum. The dams, fetuses, and subsequent pups were exposed to a 65 kV/m, 60 Hz electric field. No consistent, statistically significant effects of exposure were observed. Wolpaw and associates (1987) examined evoked potentials in pig-tailed macaques exposed to combined electric and magnetic fields. As in Jaffe's studies, the VER and the auditory evoked potential showed no changes caused by exposure. However, an attenuation of the late components of the somatosensory evoked potentials was demonstrated in exposed animals. The authors suggest that these abnormalities may have been due to a particularly large number of stimuli giving rise to a change in the mechanisms of attention.

Two other neurophysiological studies have had clear, replicable results. Jaffe et al. (1980) examined synaptic junctions from chronically exposed rats (60 Hz and 100 kV/m for 30 days). In these studies, presynaptic fibers were stimulated with a pair of above-threshold pulses. The height ratio of the resultant action potentials, observed as a function of the interspike interval, demonstrated an enhanced neuronal excitability in nerves from exposed animals. However, many other parameters tested in these nerves showed no changes in exposed animals. In a second experiment Jaffe et al. (1981) examined a wide range of physiological parameters of the peripheral nervous system and neuromuscular function. The only effect observed was slightly faster recovery from fatigue after chronic stimulation in one class of muscle; the soleus, slow-twitch muscle.

In summary, numerous studies have been initiated to determine how greatly an electrical environment containing electric or magnetic fields of ELF affects the nervous system. Many of the experiments have not confirmed any neuropathological effects, even after prolonged exposures to high-strength (100 kV/m) electric fields and high-intensity (5 mT) magnetic fields (Tenforde, 1985). As discussed previously, nervous system effects that have been observed include altered neuronal excitability, altered circadian levels of pineal hormones, and behavioral aversion to or preference for the field. In addition, in several instances where unconfirmed or controversial data exist, observed effects may or may not be real. Examples are changes in serum catecholamines or corticosteroids, morphology of brain tissue, and EEG wave forms. Possibly these and other putative effects are due to a direct interaction of the electric field with tissue or to an indirect interaction, such as a physiological response owing to detection or stimulation of sensory receptors by the field. The nature of the physical mechanisms involved in field-induced effects is obscure, and elucidating them is one of the urgent goals of current research.

The behavioral tests that most frequently showed an effect of exposure were those relating to detection of the field or to activity responses. Most other behaviors did not change with ELF field exposure. It should also be noted that influences of the nervous system on other biological systems are often mediated indirectly through neuroendocrine or endocrine responses.

Reproduction and Development

Developing organisms, including prenatal and postnatal mammals, are generally considered more sensitive to physical or chemical agents than are adult animals (Mahlum et al., 1978). This greater sensitivity, when it occurs, is thought to originate in subtle effects on the increased number and activity of processes and controls that guide the developing cellular interactions. A number of studies have examined the effects of ELF exposure on reproduction and development of both mammalian and non-mammalian species. These studies have been assessed in detail by other reviewers (Chernoff, 1985; Sikov, 1985) and are briefly summarized here.

Most of the non-mammalian studies have been performed on chickens or pigeons. Many studies have indicated that electric field exposure of chicks at several field strengths, before and after hatching, did not significantly affect viability, morphology, behavior, or growth (Krueger et al., 1972; Reed and Graves 1984; Veicsteinas et al., 1987). However, in one series of experiments chicks exposed to 40 or 80 kV/m on days 1 to 22 after hatching showed significantly less motor activity during the week after removal from the field (Graves et al., 1978b).

Few studies have examined the effects of ELF magnetic fields on growth and development of birds. Krueger et al. (1972) exposed chicks from hatching through 28 days of age to a nonuniform, 45 Hz, 1.4×10^{-4} T field. Growth rates were depressed, but no other parameters were affected. Great interest has been shown in the reports of Delgado et al, (1982), who observed a marked increase in malformation rate in chick eggs exposed to low levels of pulsed magnetic fields (0.12 or 12×10^{-6} T). It was subsequently reported that an important determinant of the results was the wave shape of the pulse (Ubeda et al., 1983). Several research groups have cooperated in a multi-laboratory replication of the Delgado experiments. Results described in a combined report (Berman et al., 1990) indicated that significant malformation increases were suggested in 5 of 6 laboratories with statistically significant differences observed in two of the laboratories.

Unreplicated studies have given some indications that exposure of prenatal mammals to electric fields produces deleterious effects on postnatal growth and survival (Knikerbocker et al., 1967; Marino et al., 1976, 1980; Hansson, 1981b; Sikov et al., 1987). These results are countered by others in which rats, rabbits, or mice were exposed to 20, 50, 100, 200, or 240 kV/m and no effects on reproduction, survival, or growth and development were demonstrated (Cerretelli et al., 1979; Fam, 1980; Sikov et al., 1984; Pafkova, 1985; Rommereim et al., 1987; Portet and Cabanes, 1988).

In an evaluation of reproductive and developmental toxicology in swine, Sikov et al. (1987) observed no increased terata in progeny from the first breeding of swing exposed during preganancy to a 60 Hz electric field. After 18 months of continued exposure the dams were rebred and their litters were examined at 100 days of gestation. At that time, malformation incidence in litters of exposed animals was significantly greater than in comparable sham-exposed litters. Similar results were obtained in litters of second generation gilts that were born in the field and bred after 18 months of exposure.

This study was followed by one of similar design (but much greater statistical power) in which rats were the experimental model. No significant differences in growth and development were observed in litters of rats exposed to 10, 65, and 130 kV/m when compared with sham-exposed controls (Rommereim et al., 1988). In similar experiments using 60-Hz magnetic fields, no significant changes were demonstrated in exposed animals (Rommereim et al., 1990; Brinkman et al., 1988).

In other studies a rotating magnetic field (0.5 to 15 x 10^{-4}T) was used to expose pregnant rats during various stages of gestation. Some differences were noted between exposed and sham-exposed offspring, including increased thyroid and testis weights in exposed pups. Also, the exposed offspring were more responsive when tested in a suppressed response paradigm (Ossenkopp et al., 1972; Persinger and Pear, 1972). As indicated previously, conflict remains over results of studies investigating the potential for ELF electric or magnetic field exposure to affect reproduction and development. This confusion over results indicates the need for carefully designed, statistically sound experiments that will help clarify this important area of investigation.

Other Biological Functions

Bone growth and repair

One report of animals exposed to 60 Hz electric fields (McClanahan and Phillips, 1983) indicated that bone growth per se was not affected by exposure to 100 kV/m. However, this study, as well as an additional report (Marino et al., 1979), suggested that bone fracture repair was retarded in rats and mice exposed to 5 or 100 kV/m, 60 Hz fields but not to very low (1 kV/m) field strengths. McClanahan and Phillips (1983) suggest that exposure affects the rate of healing but not the strength of the healed bone.

In contrast to the experiments with sinusoidal 60 Hz fields, research studies and clinical trials (discussed previously) have been performed in which magnetic fields were used to treat bone fractures and arthroses in humans. The weak electrical currents induced in bone tissue by magnetic field pulses may enhance fracture repair by altering intracellular concentrations of calcium ions, thus modifying cellular metabolism and stimulating growth of the osteoblasts and chondrocytes (Luben et al., 1982; Bassett, 1978). Why 60 Hz sinusoidal electric fields cause a retardation of fracture repair, whereas pulsed magnetic fields facilitate repair, is unclear.

Cardiovascular system

Cardiovascular function has been assessed by measuring blood pressure and heart rate and performing electrocardiographic measurements. Early studies indicated as possible effects a decrease in heart rate and cardiac output in dogs exposed to 15 kV/m (Gann, 1976) and increased heart rates in chickens exposed to 80 kV/m (Carter and Graves, 1975). A more recent and comprehensive study in rats exposed to 100 kV/m showed no such effects of exposure, even when the animals were subjected to cold stress (Hilton and Phillips, 1980). Cerretelli and Malaguti (1976) reported transient increases in blood pressure in dogs exposed to 50 Hz E fields greater than 10 kV/m. Hilton and Phillips (1980) were unable to confirm a report by Blanchi et al. (1973) of electrocardiographic changes in animals exposed to 100 kV/m.

Magnetic field exposure of dogs (50 Hz, 2 T) caused a stimulation of the heart in the diastolic phase, with salvos of ectopic beats appearing in the recordings (Sliney, 1985). Humans exposed to combined electric and magnetic fields (9 kV/m, 20 μT) have demonstrated a longer cardiac interbeat interval than sham-exposed subjects (Graham et al., 1987).

Serum chemistry appears to be relatively unaffected by exposure to either ELF electric or magnetic fields (Marino and Becker, 1977; Mathewson et al., 1977; Ragan et al., 1979, 1983). Hematological data, however, present a more confusing picture. With electric field exposure, white blood cell count was often elevated in populations of mice and rats (Graves et al., 1979; Ragan et al., 1983). With the exception of one report by Tarakhovsky et al. (1971), all the published studies on hematological effects of magnetic field exposure have shown no field-associated effects (Beischer et al., 1973; de Lorge, 1974; Fam, 1981; Sander et al., 1982). The occasional positive or negative effects on the hematopoietic system must be carefully evaluated. Apparent sporadic effects may not be biologically or statistically significant; particularly when appropriate multi-variate analyses are used to evaluate the wide range of hematological and serum chemistry parameters.

Immunology

There is some indication that exposure of animals to electric fields does not markedly affect the immune system. In a comprehensive investigation of the humoral and cellular aspects of the immune system, Morris et al. (1979, 1982, 1983) observed no effects of exposure at very low field strengths (150 to 250 V/m) in mice or rats. In subsequent experiments at higher field exposures (100 kV/m), no effects were seen in immune system response. However, Lyle et al. (1983) reported significant decrements in the cytolytic capacity of lymphocytes exposed to radio frequency fields modulated at 60 Hz. Further work with 60 Hz electric fields alone also resulted in a suppression of T-lymphocyte cytotoxicity (Lyle et al., 1988). A significant difference between the work reported from these two laboratories is that Morris measured lymphocyte responses from exposed animals, whereas Lyle exposed lymphocytes in culture.

In contrast to the apparent lack of strong or consistent electric field influences on the immune system, immunoresponse to mitogens and antigens appears to be significantly susceptible to ELF magnetic fields (Odintsov, 1965; Mizushima et al., 1975; Conti et al., 1983).

Carcinogenesis and Mutagenesis

No effects suggesting a direct effect of electric field exposure on mutagenesis or carcinogenesis have been observed (Mittler, 1972; Frazier et al., 1987). However, there is considerable research interest on this question due to an increasing number of epidemiological studies that suggest a possible association between ELF magnetic field exposure and cancer. As yet, only a few published laboratory studies, conducted in animals, bear directly on this question and there is an urgent need for such studies.

No studies to date have been reported in which spontaneous tumor development was followed in normal animals exposed to ELF fields. Another possible approach would be a cocarcinogenesis system in which EM exposure is used as a promoter following an initiating event (chemical or ionizing radiation).

In a preliminary report, Leung et al., (1988) describes an experiment wherein animals were exposed to 60 Hz electric fields for extended periods (approximately 180 days). The exposed and sham-exposed animals were treated with a single dose of the potent mammary tumor initiator dimethylbenz(a)- anthracene at 55 days of age. No increases were reported in the number of rats developing tumors. However, they did observed an increase in the number of tumors per tumor-bearing animal.

Tumor growth was inhibited in a few experimental animal models when pulsed magnetic fields were used to expose the animals (Bellossi et al., 1986). However, sinusoidal 60 Hz fields, did not exhibit growth altering action (Thomson et al., 1988).

ACKNOWLEDGMENT

Portions of this chapter were previously published in "Biological Effects and Applications of Electromagnetic Energy" Om Gandhi, Editor. Work supported in part by US Department of Energy under Contract DE-AC06-76RLO-1830.

REFERENCES

Anderson, L.E., and Phillips, R.D. (1985). Biological effects of electric fields: an overview. In: Grandolfo, M., Michaelson, S.M., and Rindi, A. (eds.). Biological effects and dosimetry of static and ELF electromagnetic fields. New York, Plenum Publishing Corp., pp. 345-378.

Bankoske, J.W., McKee, G.W., and Graves, H.B. (1976). Ecological influence of electric fields. Interim Report 2, EPRI Research Project 129, EPRI Report No. EX-178. Palo Alto, CA, Electric Power Research Institute.

Bassett, C.A.L. (1978). Pulsing electromagnetic fields: a new approach to surgical problems. In: Buchwald, H., and Varco, R.L., (eds.). Metabolic surgery. New York, Grune & Stratton, pp. 255-306.

Beischer, D.E., Grissett, J.D., and Mitchell, R.R. (1973). Exposure of man to magnetic fields alternating at extremely low frequency, USN Report No. NAMRL-1180. Pensacola, FL, Naval Aerospace Medical Research Laboratory.

Bellossi, A., Desplaces, A., and Morin, R. (1986). Effect of Low Frequency Pulsed Magnetic Fields on Tumoral C3H Mice - Preliminary Results. Abstracts of the Bioelectromagnetics Society, 8th Annual Meeting, June 1-5, 1986, Madison, WI., p. 51b.

Berman, E., Chacon, L., House, D., Koch, B.A., Koch, W.E., Leal, J., Lovtrup, S., Mantiply, E., Martin, A.H., Martucci, G.I., Mild, K.H., Monahan, J.C., Sanstrom, M., Shamsaifar, K., Tell, R., Trillo, M.A., Ubeda, A., and Wagner, P. (1990). Development of Chicken Embryos in a Pulsed Magnetic Field. Bioelectromagnetics *11*:169-187.

Blanchi, C., Cedrini, L., Ceria, F., Meda, E., and Re, G. (1973). Exposure of mammalians to strong 50-Hz electric fields: effect on heart's and brain's electrical activity. Arch. Fisiol. *70*:33-34.

Brinkman, K., Buntenkotter, S., Zittlau, E., Zwingelberg, R., Reinhard, H.J. (1988). A teratological study on rats exposed to 50-Hz magnetic fields. Abstracts of the Bioelectromagnetics Society, 10th Annual Meeting, June 19-24, 1988. Stamford, CT., p. 38.

Carter, J.H., and Graves, H.B. (1975). Effects of high intensity AC electric fields on the electroencephalogram and electrocardiogram of domestic chicks: literature review and experimental results. University Park, Pennsylvania State University.

Cerretelli, P., and Malaguti, C., (1976). Research carried on in Italy by ENEL on the effects of high voltage electric fields. Rev. Gen. Elect. (spec. iss.): 65-74.

Cerretelli, P., Veicsteinas, A., Margonato, V., et al. (1979). 1000-kV project: research on the biological effects of 50-Hz electric fields in Italy. In: Phillips, R.D., et al. (eds.). Biological effects of extremely-low-frequency electromagnetic fields, Proceedings of the 18th Annual Hanford Life Sciences Symposium, CONF-781016, Springfield, VA., National Technical Information Service, pp. 241-257.

Chernoff, N. (1985). Reproductive and developmental effects in mammalian and avian species from exposure to ELF fields. In: Biological and human health effects of extremely low frequency electromagnetic fields. Arlington, VA., American Institute of Biological Sciences, pp. 227-240.

Conti, P., Gigante, G.E., Cifone, M.G., et al. (1983). Reduced mitogenic stimulation of human lymphocytes by extremely low frequency electromagnetic fields. FEBS Lett. *162*:156-160

Creim, J.A., Lovely, R.H. Kaune, W.T., Miller, M.C., and Anderson, L.E. (1985). 60-Hz magnetic fields: do rats avoid exposure? In: 7th Annual Meeting abstracts, Bioelectromagnetics Society, June 16-20, 1985, San Francisco. Gaithersburg, MD., Bioelectromagnetics Society, p.58.

Davis, H.P., Mizumori, S.J.Y., Allen, H., Rosenzweig, M.R., Bennett, E.L., and Tenforde, T.S. (1984). Behavioral studies with mice exposed to DC and 60-Hz magnetic fields. Bioelectromagnetics *5*:147-164.

Delgado, J.M.R., Leal, J., Monteagudo, J.L., and Gracia, M.G. (1982). Embryological changes induced by weak, extremely low frequency electromagnetic fields. J. Anat. *134*:533-551.

De Lorge, J. (1974). A psychobiological study of rhesus monkeys exposed to extremely low-frequency low-intensity magnetic fields. USN Report NAMRL-1203. NTIS No. AD A000078, Springfield, VA., NTIS.

Deno, D.W. (1977). Currents induced in the human body by high voltage transmission line electric field - measurement and calculation of distribution and dose. IEEE Trans. Power Appar. Syst. *96*:1517-1527.

Dowse, H.B. (1982). The effects of phase shifts in a 10 Hz electric field cycle on locomotor activity rhythm of Drosophila melanogaster. J. Interdiscip. Cycle Res. *13*:257-264.

Duffy, P.M. and Ehret, C.F. (1982). Effects of intermittent 60-Hz electric field exposure: circadian phase shifts, splitting, torpor, and arousal responses in mice. In: Abstracts, 4th Annual Scientific Session, Biolectro-magnetics Society, June 28-July 2, Los Angeles, Gaithersburg, MD., Bioelectromagnetics Society, p. 610.

Dumansky, Y.D., Popovich, V.M., and Kozyarin, I.P. (1977). Effects of low-frequency (50 Hz) electromagnetic field on functional state of the human body. Gig. Sanit. *12*:32-35.

Dumansky, Y.D., Popovich, V.M., and Prokhvatilo, Y.V. (1976). Hygiene assessment of an electromagnetic field generated by high-voltage power transmission lines. Gig. Sanit. *8*:19-23.

Fam, W.Z. (1980). Long-term biological effects on very intense 60-Hz electric fields on mice. IEEE Trans. Biomed. Eng. *27*:376-381.

Fam. W.Z. (1981). Biological effects of 60-Hz magnetic field on mice. IEEE Trans. Magnet. *17*:1510-1513.

Fischer, G., Udermann, H. and Knapp, E. (1978). Ubt das netzfrequente wechsel-feld zentral wirkungen aus? [Does a 50-cycle alternating field cause central nervous effects?] Zentralbl. Bakteriol. Mikrobiol. Hyg. [B] *166*:381-385.

Frazier, M.E., Samuel, J.E., and Kaune, W.T. (1987). Viabilities and mutation frequencies of CHO-K1 cells following exposure to 60-Hz electric fields. In: Anderson, L.W., Weigel, R.J., and Kelman, B.J. (eds.). Interaction of biological systems with static and ELF electric and magnetic fields. Proceedings of the 23rd Annual Hanford Life Sciences Symposium. DOE Symposium Series CONF 841041, Springfield, VA., National Technical Information Service, pp. 255-268.

Free, M.M., Kaune, W.T., Phillips, R.D., and Cheng, H.-C. (1981). Endocrinological effects of strong 60-Hz electric fields on rats. Bioelectromagnetics *2*:105-121.

Gann, D.W. (1976). Biological effects of exposure to high voltage electric fields: final report. Electric Power Research Institute, RP98-02. Palo Alto, CA.

Gavalas, R.J., Walter, D.O., Hammer, J., and Adey, W.R. (1970). Effect of low-level, low-frequency electric fields on EEG and behavior in Macaca nemestrina. Brain Res. *18*:491-501.

Gavalas-Medici, R., and Day-Magdaleno, S.R. (1976). Extremely low frequency, weak electric fields affect schedule-controlled behavior of monkeys. Nature *261*:256-259.

Graham, C., Cohen, H.D., Cook, M.R., Phelps, J., Gerkovich, M. and Fotopoulos, S.S. (1987). A double-blind evaluation of 60-Hz field effects on human performance, physiology, and subjective state. In: Anderson, L.E., Weigel, R.J., Kelman, B.J. (eds.). Interaction of biological systems with static and ELF electric and magnetic fields. Proceedings of the 23rd Annual Hanford Life Sciences Symposium. DOE Symposium Series CONF 841041, Springfield, VA., National Technical Information Service, pp. 471-486.

Graves, H.B. (ed.) (1985). Biological and human health effects of extremely low frequency electromagnetic fields. Arlington, VA., American Institute of Biological Sciences.

Graves, H.B., Carter, J.H. Jenkins, T., Kellmel, D., and Poznaniak, D.T. (1978a). Responses of domestic chicks to 60-Hz electrostatic fields. In: Mahlum, D.D., Sikov, M.R., Hackett, P.L., and Andrew, F.D. (eds.). Develop-mental toxicology of energy-related pollutants. CONF. 771017, Springfield, VA., National Technical Information Service, pp. 317-329.

Graves, H.B., Carter, J.H., Kellmel, D., Cooper, L., Poznaniak, D.T., and Bankoske, J.W. (1978b). Perceptibility and electro-physiological responses of small birds to intense 60-Hz electric fields. IEEE Trans. Power Appar. Syst. *97:*1070-1073.

Graves, H.B., Long, P.D., and Poznaniak, D.T. (1979) Biological effects of 60-Hz alternating-current fields: a Cheshire cat phenomenon? In: Phillips, R.D. (ed.). Biological effects of extremely-low-frequency electromagnetic fields. Proceedings of the 18th Annual Hanford Life Sciences Symposium. CONF-781016, Springfield, VA., NTIS, pp. 184-197.

Groza, P., Carmacia, R., and Bubuiann, E., (1978). Blood and urinary catecholamine variations under the action of a high voltage electric field. Physiologie *15:*139-144.

Hackman, R.M., and Graves, H.G., (1981). Corticosterone levels in mice exposed to high intensity electric fields. Behav. Neural Biol. *32:*201-213.

Hansson, H.-A. (1981a). Lamellar bodies in Purkinje nerve cells experimentally induced by electric field. Exp. Brain Res. *216:*187-191.

Hansson, H.-A. (1981b). Purkinje nerve cell changes caused by electric fields: Ultrastructural studies on long term effects on rabbits. Med. Biol. *59:*103-110.

Hilton, D.I., and Phillips, R.D. (1980). Cardiovascular response of rats exposed to 60-Hz electric fields. Bioelectromagnetics *1*:55-64.

Hjeresen, D.L., Kaune, W.T., Decker, J.R., and Phillips, R.D. (1980) Effects of 60-Hz electric fields on avoidance behavior and activity of rats. Bioelectromagnetics *1*:299-312.

Hjeresen, D.L., Miller, M.C., Kaune, W.T., and Phillips, R.D. (1982). A behavioral response of swine to 60-Hz electric field. Bioelectromagnetics *2*:443-451.

Jaffe, R.A., Laszewski, B.L., and Carr, D.B. (1981). Chronic exposure to a 60-Hz electric field: effects on neuromuscular function in the rat. Bioelectromagnetics *2*:277-239.

Jaffe, R.A., Laszewski, B.L., Carr, D.B., and Phillips, R.D. (1980). Chronic exposure to 60-Hz electric field: effects on synaptic transmission and the peripheral nerve function in the rat. Bioelectromagnetics *1*:131-147.

Jaffe, R.A., Lopresti, C.A., Carr, D.B., and Phillips, R.D. (1983). Perinatal exposure to 60-Hz electric fields: effects on the development of visual-evoked response in the rat. Bioelectromagnetics *4*: 327-339.

Kaune, W.T. (1981). Power-frequency electric fields averaged over the body surfaces of grounded humans and animals. Bioelectromagnetics *2*:403-406.

Kaune, W.T. (1985). Coupling of living organisms to ELF electric and magnetic fields. In: Biological and human health effects of extremely low frequency electromagnetic fields. Arlington, VA., American Institute of Biological Sciences, pp. 25-60.

Kaune, W.T., and Forsythe, W.C. (1985). Current densities measured in human models exposed to 60-Hz electric fields. Biolectromagnetics *6:*13-32.Kaune, W.T., and Forsythe, W.C. (1988). Current densities induced in swine and rat models by power-frequency electric fields. Bioelectromagnetics *9:*1-24.

Kaune, W.T., Kistler, L.M., and Miller, M.C. (1987). Comparison of the coupling of grounded and ungrounded humans to vertical 60-Hz electric fields. In: Anderson, L.E., Weigel, R.J., and Kelman, B.J. (eds.). Interaction of biological systems with static and ELF electric and magnetic fields. Proceedings of the 23rd Annual Hanford Life Sciences Symposium. DOE Symposium Series CONF 841041, Springfield, VA., National Technical Information Service, pp. 185-196.

Kaune, W.T., and Forsythe, W.C. (1988). Current densities induced in swine and rat models by power-frequency electric fields. Bioelectromagnetics 9:1-24.

Kaune, W.T., and Phillips, R.D. (1980). Comparison of the coupling of grounded humans, swine and rats to vertical, 60-Hz electric fields. Bioelectromagnetics *1:*117-129.

Kaune, W.T., and Phillips, R.D., (1985). Dosimetry for extremely low frequency electric fields. In: Grandolfo, M., Michaelson, S.M., and Rindi, A. (eds.). Biological effects and dosimetry of non-ionizing radiation: static and ELF electromagnetic fields. New York, Plenum Publishing Corp., pp. 145-165.

Kaune, W.T., Phillips, R.D., Hjeresen, D.L., Richardson, R.L., and Beamer, J.L. (1978). A method for the exposure of miniature swine to vertical 60-Hz electric fields. IEEE Trans. Biomed. Eng. *25:*276-283.

Kavaliers, M., Ossenkopp, K.-P., and Hirst, M. (1984). Magnetic fields abolish the enhanced nocturnal analgesic response to morphine in mice. Physiol. Behav. *32:*261-264.

Knickerbocker, G.G., Kouwenhoven, W., and Barnes, H. (1967). Exposure of mice to strong AC electric field - an experimental study. IEEE Trans. Power Appar. Syst. *86:*498-505.

Kozyarin, I.P. (1981). Effects of low frequency (50-Hz) electric fields on animals of different ages. Gig. Sanit. *8:*18-19.

Krueger, W.F., Bradley, J.W., Giarola, A.J., and Daruvalla, S.R. (1972). Influence of low-level electric and magnetic fields on the growth of young chickens. Biomed. Sci. Instrum. *9:*183-186.

Lerchl, A., Nonaka, K.O., Stokkan, K-A., and Reiter, R.J. (1990). Marked rapid alterations in nocturnal pineal serotonin metabolism in mice and rats exposed to weak intermittent magnetic fields. Biochem Biophys Res Commun 169(1):102-106.

Leung, F.C., Rommereim, D.N., Stevens, R.G., Wilson, B.W., Buschbom, R.L., and Anderson, L.E. (1988). Effects of electric fields on rat mammary tumor development induced by 7,12-dimethylbenz(a)anthracene. In: 10th Annual Meeting abstracts, Bioelectromagnetics Society, June 19-23, 1988, Stamford, CT., Gaithersburg, MD., Bioelectromagnetics Society, p. 2.

Lovely, R.H. (1988). Recent studies in the behavioral toxicology of ELF electric and magnetic fields. In: O'Connor, M.E., and Lovely, R.H. (eds.). Electromagnetic fields and neurobehavioral function. New York, A.R. Liss, Inc., p. 2.

Luben, R.A., Cain, D.D., Chen, M.C.-y., Rosen, D.M., and Adey, W.R. (1982). Effects of electromagnetic stimuli on bone and bone cells *in vitro*: inhibition of responses to parathyroid hormone by low-energy low-frequency fields. Proc. Natl. Acad. Sci. USA *79:*4180-4184.

Lyle, D.B., Ayotte, R.D., Sheppard, A.R., and Adey, W.R. (1988). Suppression of T-lymphocyte cytotoxicity following exposure to 60-Hz sinusiodal electric fields. Bioelectromagnetics *9*:303-313.

Lyle, D.B., Schechter, P., Adey, W.R., and Lundak, R.L. (1983). Suppression of T-lymphocyte cytotoxicity following exposure to sinusoidally amplitude-modulated fields. Bioelectromagnetics *4*:281-292.

Mahlum, D.D., Sikov, M.R., Hackett, P.L., and Andrew, F.D. (1978). Developmental toxicology of energy-related pollutants. CONF 771017, Springfield, VA., NTIS.

Marino, A.A., and Becker, R.O. (1977). Biological effects of extremely low-frequency electric and magnetic fields: a review. Physiol. Chem. Phys. *9*:131-147.

Marino, A.A., Becker, R.O., and Ullrich, B. (1976). The effects of continuous exposure to low frequency electric fields on three generations of mice: a pilot study. Experientia *32*:565-566.

Marino, A.A., Berger, T.J., Austin, B.P., Becher, R.O., and Hart, F.X. (1977). *In vivo* bioelectrochemical changes associated with exposure to extremely low frequency electric fields. Physiol. Chem. Phys. *9*:433-441.

Marino, A.A., Cullen, J.M., Reichmanis, M., and Becker, R.O. (1979). Fracture healing in rats exposed to extremely low-frequency electric fields. Clin. Orthop. *145*:239-244.

Marino, A.A., Reichmanis, M., Becker, R.O., Ullrich, B., and Cullen, J.M. (1980). Power frequency electric field induces biological changes in successive generations of mice. Experientia *36*:309-311.

Mathewson, N.S., Oosta, G.M., Levin, S.G., Diamond, S.S. , and Ekstrom, M.E. (1977). Extremely low frequency (ELF) vertical electric field exposure of rats: a search for growth, food consumption and blood metabolite alterations. Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, Bethesda, MD., ADA 035954, Springfield, VA., NTIS.

McClanahan, B.J., and Phillips, R.D. (1983). The influence of electric field exposure on bone growth and fracture repair in rats. Bioelectromagnetics *4*:11-20.

Michaelson, S.M. (1979). Analysis of studies related to biologic effects and health implications of exposure to power frequencies. Environ. Prof. *1*:217-232.

Mittler, S. (1972). Low frequency electromagnetic radiation and genetic aberrations, Final Report, Northern Illinois University, AD-749959, Springfield, VA., NTIS.

Mizushima, Y., Akaoka, I., and Nishida, Y. (1975). Effects of magnetic field on inflammation. Experientia *21*:1411-1421.

Moos, W.S., (1964). A preliminary report on the effects of electric fields on mice. Aerospace Med. *35*:374-377.

Morris, J.E., and Phillips, R.D. (1982). Effects of 60-Hz electric fields on specific humoral and cellular components of the immune system. Bioelectromagnetics *3*:341-348.

Morris, J.E., and Phillips, R.D. (1983). (Erratum) Effects of 60-Hz electric fields on specific humoral and cellular components of the immune system. Bioelectromagnetics *4*:294.

Morris, J.E., and Ragan, H.A. (1979). Immunological studies with 60-Hz electric fields. In: Phillips, R.D., et al. (eds.). Biological effects of extremely-low-frequency electromagnetic fields. Proceedings of the 18th Annual Hanford Life Sciences Symposium. CONF 781016, National Technical Information Service, Springfield, VA.

Mose, J.R. (1978). Problems of housing quality. Zentralbl. Bakteriol. Mikrobiol. [B] *166*:292-304.

National Academy of Sciences (1977). Biologic effects of electric and magnetic fields associated with proposed Project Seafarer, report of the Committee on Biosphere Effects of Extremely-Low-Frequency Radiation. Washington, DC., National Research Council.

Odintsov, Y.N. (1965). The effect of a magnetic field on the natural resistance of white mice to Listeria infection. Tomsk Voprosy Epidemiol. Mikrobiol. Immunol. *16*:234-238.

Olcese, J., Reuss, S., and Vollrath L. (1985). Evidence for the involvement of the visual system in mediating magnetic field effects on pineal melatonin synthesis in the rat. Brain Res. *333*:382-384.

Ossenkopp, K-P., Kolteck, W.T., and Persinger, M.A. (1972). Prenatal exposure to an extremely low frequency-low intensity rotating magnetic field and increases in thyroid and testicle weight in rat. Dev. Psychobiol. *5*:275-285.

Pafkova, H. (1985). Possible embryotropic effect of the electric and magnetic component of the field of industrial frequency. Pracov. Lek. *37*:153-158.

Persinger, M.A., (1969). Open-field behavior in rats exposed prenatally to a low intensity-low frequency, rotating magnetic field. Dev. Psychobiol. *2*:168-171.

Persinger, M.A., and Foster, IV, W.S. (1970). ELF rotating magnetic fields: prenatal exposures and adult behavior. Arch. Meteorol. Geophys. Biol. Ser. B *18*:363-369.

Persinger, M.A. and Pear, J.J. (1972). Prenatal exposure to an ELF-rotating magnetic field and subsequent increase in conditional suppression. Dev. Psychobiol *5*(3):269-274.

Phillips, R.D., Chandon, J.J., Free, J.J., et al. (1978). Biological effects of 60-Hz electric fields on small laboratory animals. Annual Report, DOE Report No. HCP/T1830-3. Washington, DC., Department of Energy.

Polk, C., and Postow, E., (1986). Handbook of Biological effects of electromagnetic fields. Boca Raton, FL., CRC Press.

Portet, R.T., and Cabanes, J. (1988). Development of young rats and rabbits exposed to a strong electric field. Bioelectromagnetics *9*:95-104.

Quinlan, W.J., Petrondas, D., Lebda, N., Pettit, S., and Michaelson, S.M. (1985). Neuroendocrine parameters in the rat exposed to 60-Hz electric fields. Bioelectromagnetics *6*:381-389.

Ragan, H.A., Buschbom, R.L., Pipes, M.J., Phillips, R.D., and Kaune, W.T. (1983). Hematologic and serum chemistry studies in rats and mice exposed to 60-Hz electric fields. Bioelectromagnetics *4*:79-90.

Ragan, H.A., Pipes, M.J., Kaune, W.T., and Phillips, R.D. (1979). Clinical pathologic evaluations in rats and mice chronically exposed to 60-Hz electric fields. In: Phillips, R.D., et al.

(eds.). Biological effects of extremely-low-frequency electromagnetic fields. Proceedings of the 18th Annual Hanford Life Sciences Symposium. CONF-781016, Springfield, VA., National Technical Information Service, pp. 297-325.

Reed, T.J., and Graves, H.B. (1984). Effects of 60-Hz electric fields on embryo and chick development, growth, and behavior, Vol. 1. Final Report, EPRI Project 1064-1. Palo Alto, CA., Electric Power Research Institute.

Reiter, R.J., Anderson, L.E., Buschbom, R.L., and Wilson, B.W. (1988). Reduction of the nocturnal rise in pineal melatonin levels in rats exposed to 60-Hz electric fields in utero and for 23 days after birth. Life Sci. *42*:2203-2206.

Reuss, S., and Olcese, J. (1986). Magnetic field effects on the rat pineal gland: role of retinal activation by light. Neurosci. Lett. *64*:97-101.

Rogers, W.R., Feldstone, C.S., Gibson, E.G., Polonis, J.J., Smith, H.D., and Cory, W.E. (1987). Effects of high-intensity, 60-Hz electric fields on operant and social behavior of nonhuman primates. In: Anderson, L.E., Weigel, R.J., and Kelman, B.J. (eds.). Interaction of biological systems with static and ELF electric and magnetic fields. Proceedings of the 23rd Annual Hanford Life Sciences Symposium. DOE Symposium Series, CONF 841041, Springfield, VA., National Technical Information Service, pp. 365-378.

Rommereim, D.N., Kaune, W.T., Buschbom, R.L., Phillips, R.D., and Sikov, M.R. (1987). Reproduction and development in rats chronologically exposed to 60-Hz electric fields. Bioelectromagnetics *8*:243-258.Rommereim, D.N., Rommereim, R.L., Buschbom, R.L., and Anderson, L.E.

(1990). Developmental toxicity study in rats exposed to 60-Hz horizontal magnetic fields. p. 20. In: Abstracts, Twelfth Annual Meeting of the Bioelectro-magnetics Society, June 10-14, 1990, San Antonio, TX.

Rommerein, D.N., Rommereim, R.L., Anderson, L.E., and Sikov, M.R. (1988). Reproduction and teratologic evaluation in rats chronically exposed at multiple strengths of 60-Hz electric fields. In: 10th Annual Meeting abstracts, June 19-23, 1988, Stamford, CT., Gaithersburg, MD., Bioelectromagnetics Society, p. 37.

Rosenberg, R.S., Duffy, P.H., Sacher, G.A., and Ehret, C.F. (1983). Relationship between field strength and arousal response in mice exposed to 60-Hz electric fields. Bioelectromagnetics *4*:181-191.

Sander, R., Brinkmann, J., and Kuhne, B. (1982). Laboratory studies on animals and human beings exposed to 50-Hz electric and magnetic fields. In: International Conference on Large High Voltage Electrical Systems (abstracts), No. 36-01. Paris, CIGRE.

Sheppard, A.R., and Eisenbud, M. (1977). Biologic effects of electric and magnetic fields of extremely low frequency. New York, New York Unviersity Press.

Sikov, M.R. (1985). Reproductive and developmental alterations associated with exposure of mammals to ELF (1-300 Hz) electromagnetic fields. In: Assessments and viewpoints on the biological and human health effects of extremely low frequency (ELF) electromagnetic fields. Washington, DC., American Institute of Biological Sciences, pp. 295-311.

Sikov, M.R., Montogomery, L.D., Smith, L.G, and Phillips, R.D. (1984). Studies on prenatal and postnatal development in rats exposed to 60-Hz electric fields. Bioelectromagnetics *5*:101-112.

Sikov, M.R., Rommereim, D.N., Beamer, J.L., Buschbom, R.L., Kaune, W.T., and Phillips, R.D. (1987). Developmental studies of Hanford miniature swine exposed to 60-Hz electric fields. Bioelectromagnetics *8*:229-242.

Silney, J. (1979). Effects of electric fields on the human organism. Institut zur Enforschung Electrischer Unfalle, Cologne, Medizinisch - Technischer Berichte, p. 39.

Silney, J. (1981). Influence of low-frequency magnetic field on the organism. *Proc. EMG*, Zurich, pp. 175-180, Proceed 4th Symposium on Electromagnetic Compatibility, March 10-12, 1981.

Silney, J. (1985). The influence thresholds of the time-varying magnetic field in the human organism. In: Berhardt, J. (ed.). Proceedings of the Symposium on Biological Effects of Static and ELF Magnetic Fields. Neuherberg, May 13-15, 1985, BGA-Schriftenreibe, Munchen, MMv Medizin Verlag.

Smith, R.F., and Justesen, D.R., (1977). Effects of a 60-Hz magnetic field on activity levels of mice. Radio Sci. *12*:279-285.

Stern, S., Laties, V.G., Stancampiano, D.V., Cox, C., and De Lorge, J.O. (1983). Behavioral detection of 60-Hz electric fields by rats. Bioelectromagnetics *4*:215-247.

Sulzman, F.M., and Murrish, D.E. (1987). Effects of electromagnetic fields on primate circadian rhythms. Report to the New York State Power Lines Project, Albany, NY., Wadsworth Center for Laboratories and Research.

Takashima, S., Onaral, B., and Schwan, H.P. (1979). Effects of modulated RF energy on the EEG of mammalian brains: effects of acute and chronic irradiations. Radiat. Environ. Biophys. *16:*15-27.

Tarakhovsky, M.L., Sambroskaya, Y.P., Medvedev, B.M., Zaderozhnaya, T.D., Okhronchuk, B.V., and Likhtenshtein, E.M. (1971). Effects of constant and variable magnetic fields on some indices of physiological function and metabolic processes in albino rats. Fiziol. Zh. RSR-*17:*452-459. (English translation JPRS 62865:37-46).

Tenforde, T.S. (1985). Biological effects of ELF magnetic fields. In: Biological and human health effects of extremely low frequency electromagnetic fields. Arlington, VA., American Institute of Biological Sciences, pp. 79-128.

Tenforde, T.S. (1986). Interaction of time-varying ELF magnetic fields with living matter. In: Polk, C., and Postow, E. (eds). Handbook of biological effects of electromagnetic fields. Boca Raton, FL., CRC Press, pp. 197-228.

Tenforde, T.S., and Kaune, W.T. (1987). Interaction of extremely low frequency electric and magnetic fields with humans. Health Phys. *53:*585-606.

Thomson, R.A.E., Michaelson, S.M., Nguyen, Q.A. (1988). Influence of 60-Hz magnetic fields on leukemia. Bioelectromagnetics *9:*149-158.

Ubeda, A., Leal, J., Trillo, M.A., Jimenez, M.A., and Delgado, J.M.R. (1983). Pulse shape of magnetic field influences chick embryogenesis. J. Anat. *137:*513-536.

Vasquez, B.J., Anderson, L.E., Lowery, C.I., and Adey, W.R. (1988). Diurnal patterns in brain biogenic amines of rats exposed to 60-Hz electric fields. Bioelectromagnetics *9:*229-236.

Veicsteinas, A., Margonato, V., Conti, R., and Cerretelli, P. (1987). Effect of 50-Hz electric field exposure on growth rate of chicks. In: Anderson, L.E., Weigel, R.J., and Kelman, B.J. (eds.). Interaction of biological systems with static and ELF electric and magnetic fields. Proceedings of the 23rd Annual Hanford Life Sciences Symposium. DOE Symposium Series CONF 841041, Springfield, VA., National Technical Information Service, pp. 341-346.

Weigel, R.J., Jaffe, R.A., Lundstrom, D.L., Forsythe, W.C., and Anderson, L.E. (1987). Stimulation of cutaneous mechanoreceptors by 60-Hz electric fields. Bioelectromagnetics *8*:337-350.

Weigel, R.J., and Lundstrom, D.L. (1987). Effect of relative humidity on the movement of rat vibrissae in a 60-Hz electric field. Bioelectromagnetics *8*:107-110.

Welker, H.A., Semm, P., Willig, R.P., Commentz, J.C., Wiltschko, W., and Vollrath, L. (1983). Effects of an artificial magnetic field on serotonin N-acetyltransferase activity and melatonin content of the rat pineal. Exp. Brain Res. *50*:*426*-432.

Wever, R., (1971). Influence of electric fields on some parameters of circadian rhythms in man. In: Menaber, M. (ed.). Biochronometry, Washington, DC., National Academy of Sciences, pp. 117-132.

WHO (1984). Extremely Low Frequency (ELF) Fields. Environmental Health Criteria 35. Geneva, World Health Organization.

Wilson, B.W., Anderson, L.E., Hilton, D.I., and Phillips, R.D. (1981). Chronic exposure to 60-Hz electric fields: effects on pineal function in the rat. Bioelectromagnetics *2*:371-380.

Wilson, B.W., Anderson, L.E., Hilton, D.I., and Phillips, R.D., (1983). (Erratum) Chronic exposure to 60-Hz electric fields: effects on pineal function in the rat. Bioelectromagnetics *4*:293.

Wilson, B.W., Chess, E.K., and Anderson, L.E. (1986). 60-Hz electric field effects on pineal melatonin rhythms: time course for onset and recovery. Bioelectromagnetics *7*:239-242.

Wolpaw, J.R., Seegal, R.F., Lowman, R.I., and Satya-Murti, S., (1987). Chronic effects of 60 Hz electric and magnetic fields on primate central nervous system function. Final Report to the New York State Power Lines Project, Albany, NY., Wadsworth Center for Laboratories and Research.