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Animal Studies of Human Hazards

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Abstract. Animals have provided a surrogate for the study of human health. This has been particularly important in the definition of the effects of pollutants generated in our society. Electromagnetic fields provide an example of the use of animals as models. A review of the animal model literature provides the following information in response to three basic toxicologic elements in defining whether electromagnetic fields are a hazard:

1. Various scientific committees have determined that, in general, exposure to electromagnetic fields, individually or combined, causes a response in animals. Exposure facilities must be carefully constructed and characterized to ensure that artifacts or environmental factors are not actually the cause of the reported effects.
2. It would appear that various components of the nervous system, some circadian rhythms of the body and the pineal gland are responsive to electromagnetic field exposure. Data for other systems are either negative, contradictory or inconclusive. With the exception of the pineal gland, there is little reliable information on dose response, minimum duration required for the effect and whether the effect is reversible or permanent.
3. There are very little animal data available to reliably conclude that exposure represents a hazardous situation. There are questions of the significance of some of the animal data, such as changes in circadian rhythms or suppression of melatonin production. There are also concerns raised by human epidemiology data not addressed by the animal data base.

The statistical community is being approached to consider two questions: (1) Can the large amount of negative data be utilized in a quantifiable risk assessment methodology to provide a reasonably reliable definition of risk? (2) Can data from similar studies be statistically combined resulting in larger experimental groups, reducing variability, and potentially clarifying trends or contradictory results?

Key words and phrases: Electromagnetic fields, animal models, negative data, contradictory conclusions, health effects.

INTRODUCTION

In biomedical research, animals are frequently used as a surrogate or model of the human, defining how the body works, how it responds to external stimuli, and in recent years, whether the pollutants generated by our society are hazardous to our health. For example, during the past several years, animals have been used to determine whether exposure to electromagnetic fields (EMFs) is a potential threat to human health and safety. Although there is a rather extensive data base, no one can conclusively state that there is or is not a health hazard. This dilemma is due in part to the inherent limitations in the use of animals as models of the human and in part to factors unique to the study of EMFs. One of the major problems associated with the EMF bioeffects data base and the assessment of potential human health risks relates to statistical considerations. This paper describes the use of animals in EMF bioeffects research, including whether animals are appropriate as a model for humans; identifies areas of concern with the use of available data in the assessment of risk to humans

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from exposure to EMFs; and suggests areas for additional statistical involvement in the EMF bioeffects program.

EMFs are an interesting toxicologic problem. They are ubiquitous in our environment, occurring naturally and from manmade sources. The study of EMFs encompasses a broad range, from direct current used for magnets in fusion reactors to the gigahertz frequencies used for radar. This paper limits discussion to the 60 Hz frequency associated with the electric currents available in our homes and occupational environments. Concern that exposure to 60 Hz fields may cause health consequences arose with reports of mental and reproductive problems in utility workers. Those reports and subsequent European studies, recently reviewed by Bonnell (1982), stimulated an interest in the study of possible health effects of EMF exposure. A workshop held in 1975 resulted in the formation of two ongoing research programs by the Energy Research and Development Administration—now the Department of Energy (DOE) and the Electric Power Research Institute (EPRI). Other organizations such as individual utilities have funded smaller programs, and in 1982, the State of New York funded a larger, short-term effort.

USE OF ANIMALS AS HUMAN MODELS

The major programs approached EMFs as a classical toxicology problem, with research projects studying multiple systems for any evidence of effects. The screening studies, using both large and small animals, were somewhat limited in experimental group size because of limitations imposed by the size of exposure facilities and exposure procedures.

In classic toxicology, three basic elements are required: (1) there must be an agent that is responsible for producing a biologic response, (2) a biologic system that is responsive to the agent must be identified and (3) the response must be considered deleterious.

In addition, certain assumptions are required in using animals as models. First, it is assumed that responses in animals can be extrapolated to humans. This means that the same dose, scaled from animals to man, will cause the same effect. For chemicals, this generally means scaling on the basis of amount of chemical per unit of body weight. On a body weight basis, animals apparently can tolerate higher doses of most chemicals than humans, and a safety factor of 10 is considered necessary (Klaassen and Doull, 1980). Second, presentation of very high levels of the hazardous substance to animals may be required and is a valid means of identifying possible human hazards. This further assumes that there is a linear relationship between the level of the hazardous substance that is delivered and the degree of the biologic response. Generally, a defined amount of a substance will cause a response in a statistically defined number of people. Because animal experiments are limited to small experimental numbers compared to the total human population, it is assumed that relatively large doses are required so that the effect will occur in a sufficient number of the animals and the effect can be detected statistically.

AREAS OF CONCERN

The following discussion addresses whether 60 Hz EMF exposure should be considered an environmental hazard based on the three elements of toxicology. The available literature is be used to address the various elements. This is not intended, however, to be an extensive review of the literature. References are limited primarily to representative data pertinent to the toxicologic elements.

Is EMF Exposure Capable of Producing a Biologic Response?

Three recent reports prepared by committees of scientists knowledgeable in this area concur that exposure of an animal to electromagnetic fields produces a biologic response (American Institute of Biological Sciences, 1985; Florida Electric and Magnetic Fields Science Advisory Commission, 1985; West Associates, 1986). This conclusion does not necessarily denote that there is a health hazard, although some people contend that there are human health risks associated with exposure to 60 Hz EMF.

There are several factors associated with exposure methodologies that could induce biologic effects. Exposure of an animal requires construction of special facilities—generally a series of parallel plates to produce electric fields and Helmholtz coils to produce magnetic fields. Facilities, when activated, can produce vibrations and heat, which are not experienced by comparable control or sham-exposed animals. If a facility is not properly constructed, corona, which is an ionization of the air, results in crackling sounds (believed to be an auditory annoyance) and produces the toxic compound ozone.

Most animal studies require a water source. Care must be taken to ensure that the water and its delivery tubes do not pick up an electric charge and subsequently deliver a shock to animals each time they drink. Animals receiving shocks drink less and may exhibit dehydration and weight loss.

With the exception of corona, most exposure facility artifacts are not a part of the real-world considerations for human residential or occupational exposure to 60 Hz EMF. Thus, although the biologic results would be interesting, they would be of little substance in determining risk of exposure.

Another major consideration is the actual intensity of the field experienced by the animal. The expected field intensity can be affected by various factors such as the presence of conducting surfaces, the cleanliness of the cage, the position of the drinking system and the presence of adjacent animals. If these factors are not considered by the investigator, it is possible that fields experienced by the animals are actually substantially below that originally expected, so low in fact as to be below a "threshold of effect."

Environmental conditions are another factor to be considered. Recently reports indicate that humidity may have a role in perception or the occurrence of effects.

All of these secondary considerations are important in ensuring that the biologic responses recorded are actually the result of electric or magnetic field exposure and not due to some artifact. Additionally, full characterization and documentation of the actual exposure of animals is important in being able to compare results between laboratories.

What Systems Are Responsive to the Agent?

The study of EMF bioeffects involves most of the physiologic systems in the body, either individually, such as the cardiovascular or nervous system, or integrated, such as behavior or reproduction, which involve several systems. The following discussion lists the major physiologic parameters that have been addressed and discusses available data. There is also an extensive data base on in vitro studies; however, such data are not necessarily applicable to a discussion of animal models. In vitro research is included only where it is necessary to substantiate a discussion point. The animal data to be discussed are representative and not all-inclusive. Several major reviews are available and evaluation of the data base is beyond the scope of this paper. Finally, the studies referenced in this paper utilized exposure facilities that were independently reviewed and documented for field uniformity and artifact consideration.

The majority of research to date involves exposure to electric fields. Only recently has there been a major effort to use combined electric and magnetic fields. Some studies remain incomplete. Others are in preparation for publication and thus are yet not available in peer-reviewed journals. Much of the combined fields data were presented orally or in posters at scientific meetings and are available in abstract form. If abstract data are used for discussion, a reference notation will be included.

Lethality. In the study of most hazardous substances, the toxicologic approach is to deliver enough of the substance to induce death and then determine which organ system(s) failed. From these data, future studies would involve progressively smaller doses of the substance for longer periods of time to determine whether other organ systems are involved or whether there is a threshold level of the substance that the animal can tolerate.

For EMFs, there are physical limitations on the strength of the electric field that can be delivered and thus a lethal level of exposure has not been identified. It is known that sufficient current can be directly induced, such as by touching live wires to cause death, but acute exposure to air fields is not known to be directly responsible for death.

Endocrinology. A broad range of hormones were measured in rodents exposed to field intensities from 3.5–100 kV/m. Circulating corticosterone levels were reported to be elevated in a multigeneration rat study (Seto, Dunlap, Fox, Hsieh, Lymangrover, Walker and Majeau-Chavgois, 1984) with associated increases in adrenal gland weight. Differences in corticosterone occurred only in the first two generations; adrenal weight differences were evident only in the third generation. In two separate studies reporting corticosterone levels in rats, 1-month exposure of rats to 1.5 kV/m resulted in reduced circulating hormone levels (Marino, Becker and Ullrich, 1976); the second study reported changes after exposure to 100 kV/m for a similar period (Free, Kaune, Phillips and Cheng, 1981). After replicate 120 days of exposure, conducted 1 year apart, Free reported a statistical reduction in corticosterone in exposed rats in the first experiment, while in the second there were no differences between exposed and sham. Hackman and Graves (1981) measured corticosterone in mice, in some cases repetitively in the same mice by retroorbital puncture. A transient increase in corticosterone occurred immediately after field onset and returned to normal. Preliminary data from sequential measurements in rats by means of implanted cannulas have to replicate the transient charge (Michaelson and Quinlan, 1985).

Circulating testosterone levels decreased in rats after 120 days of exposure to 100 kV/m electric fields, but not after 30 days of exposure (Free, Kaune, Phillips and Cheng, 1981). The decrease was considered statistically significant in the first of two replicates, but in the second, the probability of occurrence was 0.07, with the traditional definition of effect established at 0.05. The trend was considered sufficient to represent a replication of the original results. The investigators suggest, however, that the results may not be representative of the human situation. The rat scrotal sac touches the ground in the normal rat stance, providing a possible current path. In a multigeneration study, there was no difference in testosterone between treatments, despite a recorded increase in testicular weight in exposed rats (Seto, Dunlap, Fox, Hsieh, Lymangrover, Walker and Majeau-Chavgois, 1984).

The daily cyclic accumulation of melatonin in the pineal gland was found to be suppressed following a minimum of 3 weeks of exposure to 65 kV/m electric fields (Wilson, Chess and Anderson, 1986). Exposure apparently inhibits the activity of the melatonin producing enzyme, serotonin *N*-acetyltransferase (Wilson, Anderson, Hilton and Phillips, 1981).

A number of other hormones were measured after 30 and 120 days of exposure and in multigeneration exposure but in no case was there any indication of effect (Free, Kaune, Phillips and Cheng, 1981; Seto, Dunlap, Fox, Hsieh, Lymangrover, Walker and Majeau-Chavgois, 1984).

Reproduction. A series of multigeneration studies reported increases in mortality in the offspring and a decrease in body weight after exposure to 15 kV/m electric fields (Marino, Becker and Ullrich, 1976) and an increase in body weight at 3.5 kV/m (Marino, Reichmanis, Ullrich and Cullen, 1980). Using swine, a protocol specifically designed to study reproduction in detail demonstrated no difference in reproduction or the health and development of offspring from exposed (30 kV/m) and sham-treated animals. There was a statistical increase in the rate of fetal malformations or deformities (Sikov, Beamer, Rommereim, Buschbom, Kaune, Phillips and Anderson, 1985). Two studies (100 kV/m) with rats using the same protocol as used with the swine resulted in an increased incidence in such rates of malformations, the first study and negative results in the second (Sikov, Phillips, Buschbom and Kaune, 1983). Statistical combination of the data indicate no effect of field exposure. A rat multigeneration study also reported no difference in malformation rates of fetuses or other more general reproduction parameters (Seto, Dunlap, Fox, Hsieh, Lymangrover, Walker and Majeau-Chavgois, 1984). Multiple generation studies with two strains of mice exposed to combined electric (50 kV/m) and magnetic fields (10 G) resulted in no basic reproductive effects of exposure (Carsten and Benz, 1986).

Genetics. Chronic exposure of mice to combined fields indicated negative results for sister chromatid exchange tests of marrow cells and dominant lethal counts of fetuses (Carsten and Benz, 1986). Exposure to high intensity electric fields had no effects on mouse sperm function, morphology and DNA repair (McClanahan, 1984).

Bone. Two laboratories reported a delay in bone healing in rodents exposed to electric fields (McClanahan and Phillips, 1983; Marino, Cullen, Reichmanis, and Becker, 1979). Electric field exposure was reported to have no effect on bone growth at one lab (McClanahan and Phillips, 1983) but to enhance long bone growth at another (Walker, Seitelman, McElhaney, Mullen, Hagadorn and Seto, 1982).

Cardiovascular. Exposure to 100 kV/m electric fields had no effects on numerous parameters related to the cardiovascular system including heart rate, blood pressure, and body temperature (Hilton and Phillips, 1980) or on serum chemistry or hematologic parameters (Ragan, Phillips, Pipes, Phillips and Kaune, 1983).

Immunology. Exposure of mice to 100 kV/m for up to 120 days resulted in no difference in multiple parameters assessing humoral or cellular immunologic activity (Morris, 1985). Peripheral leukocytes obtained from normal and antigen-challenged dogs and human volunteers were exposed to combined electric and magnetic fields, but no differences in various biochemical and functional parameters were found (Winters, 1985).

Behavior. Studies reported that rats can reliably detect the presence of electric fields as low as 4.5 kV/m (Stern, Laties, Stancampiano, Cox and de Lorge, 1983), and baboons can detect minimum fields of about 18 kV/m (Orr, Lucas, Smith and Rogers, 1986). Rats are reported to avoid 100 kV/m fields but spent more time in 25 kV/m fields than in shielded conditions (Hjeresen, Kaune, Decker and Phillips, 1980). Recent research indicated, however, that no avoidance threshold can be defined in baboons up to 74 kV/m (Rogers, Lucas, Smith and Orr, 1986), and rats will not work to turn off 100 kV/m fields (Stern and Laties, 1985). Operant behavior tests of animal concentration and ability to maintain awareness of time passage demonstrated no effects of exposure to electric and magnetic fields (Thomas and Liboff, 1985). A second study measured coordination in rats 3 months after in utero exposure to electric and magnetic fields and reported no statistical differences between exposed and sham-exposed groups in seven experiments (Salzinger, Freimark, McCullough, Phillips, Birenbaum and Paduano, 1985). However, there was a consistent trend of a decrease in behavioral activity, and the investigator indicated that this consistency suggested that an effect had occurred.

Rats respond to the onset of high strength electric fields with a startle reaction characterized by increased activity and elevated respiration. With repetitive field onset, the animals adapted by the third trial. A rest period of 40 hr was required between trials for the startle reaction to reoccur (Rosenberg, Duffy, Sacher and Ehret, 1983).

Circadian Rhythms. The daily cycle of a wild type mouse was reported to be shortened during 10 days of constant darkness after short periods of exposure to 100 kV/m (Ehret, Duffy, Groh and Fowler, 1984). In preliminary data for primates exposed to combined electric and magnetic fields, cycles were reported to have been lengthened (Sulzman and Murrish, 1985). In both studies, not all animals exhibited the circadian effect.

Nervous System. Nerve preparations from rats exposed for 120 days to 100 kV/m exhibited no effects for multiple parameters with only two parameters exhibiting changes, synaptic transmission (Jaffe, Laszewski, Carr and Phillips, 1980), and recovery from fatigue (Jaffe, Laszewski and Carr, 1981).

No difference was reported in reaction time and in central nervous system (CNS) activity in nonhuman primates exposed for 105 days to electric and magnetic fields (Seegal, Dowman and Wolpaw, 1986). Rats exposed in utero were reported to have normal development of CNS function (Jaffe, Lupresti, Carr and Phillips, 1983). Similar results were reported for swine exposed to 30 kV/m electric fields both in utero and during subsequent growth (Lovely, Hjereson, Phillips and Anderson, 1985). Measurements of neurotransmitter indicate that there may be a shift in the daily cycle of amine and metabolite concentration of one brain region of rats and a suppression of another region in rats exposed to electric fields (Vasquez, Anderson, Lowery and Adey, 1986). Among various amines and metabolites, 5-hydroxyindolacetic acid and homovanilic acid were suppressed after 3 weeks of combined field exposure (Seegal, Dowman and Wolpaw, 1985).

Exposure to electric (Albert and Anderson, 1985) or combined fields (Gona and Yu, 1985) appears to have no effect on CNS development in rats exposed in utero.

Thus, there appear to be some biologic systems that are responsive to EMF exposure. There are some biologic effects such as changes in neurotransmitters, pineal melatonin and circadian rhythms. For most other systems, however, there are either no reports of responsiveness, or the reports are contradictory. Some of the contradictions may relate to changes in circadian patterns. For instance, original neurotransmitter measurements made at a single time period indicated no effect of exposure (Vasquez, McNeeley and Adey, 1984). Only when measurements were made over a 24-hr period does a pattern emerge (Vasquez, Anderson, Lowery and Adey, 1986). This could be a major factor in hormonal changes; hormones normally demonstrate large changes in concentrations over 24 hr under normal conditions. A second source of contradiction could involve the various facilities. Independent review of research facilities was not initiated until 1979. Thus, while assessment of facility characteristics was completed, for studies conducted prior to 1979, the assessment was after the fact and may not have involved actual experimental conditions. The assessment procedure further raised questions of actual field intensities of the facility at several non-DOE funded institutions.

It is possible that all the reported effects are attributable to stimulation of the skin surface. High strength electric fields cause vibration of body hair on humans and animals (Bonnell, Maddock, Male, Norris, Cabanes, Gary, Conti, Nicolini, Margonato, Veicsteinas and Ceretelli, 1986). A mechanoreceptor in the skin of cats that does not adapt to continuous stimulation was responsive to electric field stimulation (Jaffe, Lupresti, Carr and Phillips, 1983). These receptors are associated with down fur in animals, and a comparable receptor in humans has not been identified, placing in question the use of animals as a model of human response to EMF exposure.

Is the Response Deleterious?

This question is the driving factor for the EMF bioeffects program. To date, no intensity of EMF that is acutely lethal has been identified and with the exception of the earlier multigeneration studies, no long-term studies have demonstrated reliable, consistent evidence of increased mortality or significant pathologies. There are a number of issues that must be resolved including whether the teratologic effects reported earlier can be reliably replicated and whether there is a difference in teratologic susceptibility between swine and rodents. The nervous system appears to be particularly responsive to field exposure, but in the integrated animal there is no indication of effects on the animal's ability to function. Changes in hormones related to stress, such as corticosterone, are not consistent within or between laboratories, and there is no consistent evidence that field exposure results in a stress phenomenon.

There are a number of additional issues that require further study. Epidemiologic studies suggest a relationship between various forms of cancer and EMF exposure. (This area will be discussed in a subsequent paper by Dr. Savitz.) There is also some limited in vitro evidence suggesting a linkage between field exposure and cancer (Phillips, Rutledge and Winters, 1986; Phillips, Winters and Rutledge, 1986). However, to date there are no animal data to support the linkage, either from the standpoint of genetic or mutagenic events or immune surveillance. To date, no cancer-related animal studies have been completed by laboratories with documented exposure facilities. One pilot effort will be completed by the end of this year, and plans are forming for other studies.

One investigator suggested a relationship between circadian rhythm changes and various mental problems and possible pathologies (Ehret, 1985). However, there are no laboratory data to support that contention. Additionally, the reported circadian effect from EMF exposure is not consistent within a defined population and may not be consistent between species. Melatonin depression and preliminary data on neurotransmitter concentrations help to substantiate the concept of circadian effects. Research is in progress to characterize these effects and determine their physiologic significance.

Committees of knowledgeable scientists that have reviewed the entire literature base have concluded that no acute deleterious effects have been found to date. EMF exposure does induce various biologic responses but nothing that can as yet be used as substantiation of a hazard. There is also general agreement that additional research is necessary to evaluate the present reported effects and to conduct experiments to address concerns raised by in vitro and epidemiologic reports.

The majority of studies reported in this paper have used field strengths in excess of the threshold of perception of animals, and although they behaviorally adapt to the presence of the field, continuous stimulation of the nervous system from mechanoreceptor firing or hair vibration is possible. Field strength in excess of those experienced by people are required experimentally for two reasons. First there is the problem of small experimental groups referenced earlier in this report. Higher doses are assumed to produce a linearly related higher incidence of effects in small populations. The second reason relates to scaling of dose. Based on surface currents, it is estimated that a 5-fold increase in electric fields is necessary for rats to receive comparable doses to humans. Thus, the 100 kV/m used in many experiments would be comparable to intensities experienced in some occupational settings. This does not allow for the 10-fold safety margin referenced earlier in this paper.

FUTURE NEEDS

There are a number of needs in the bioeffects program in addition to conducting additional experiments. Of special importance is the need to utilize the existing data base from two different perspectives:

- There is some belief that the trends of subtle, inconsistent effects may be due to insufficient experimental numbers. Statistical procedures to combine data from different experiments can be useful.
- Risk assessment methodologies were attempted using either comparative procedures or bounding techniques. Both relied primarily on positive results and were unable to consider the large amount of no effects data. There is a need to develop risk assessment techniques to incorporate negative data into the equations for the estimation of risk.

There are two additional areas of ongoing study that could affect the need for statistical assistance, identifying of the mechanism of interaction between EMF and biologic tissue and defining the scaling relationship between various animal species and man. Defining how biologic tissue interacts with applied fields will aid in determining whether changes are permanent or transitory, whether genetic stability is involved, and whether recovery can be anticipated. The question of mechanism is being addressed experimentally, both in vitro and with animals. The interactive level of study includes both how the electric current and the magnetic field may alter the cell membrane and how the fields may be perceived by an organism. Elucidation of both would aid in defining various reported effects and whether they are applicable to humans.

The last point addresses the ability to extrapolate results from animal experiments to man. A portion of the required information must be completed experimentally, providing similar data for specific systems in animals and man. This, however, requires a reliable biologic marker. Studies are presently in progress involving both large primates for extended exposure and human volunteers for monitoring of acute exposure. With completion of the studies, the data will have to be reviewed for consistency of biologic change with that seen in animal models. A second facet involves modeling of the surface and internal currents generated by field exposure. Differences in body size and grounding governs the distribution of current and thus the actual exposure of various organ systems (Kaune and Phillips, 1980). It is possible that there could be large differences in exposure between the upright and prone positions.

In summary, animals are used as a model for the study of the possible health effects of EMFs. From a classic toxicologic point, electromagnetic fields can cause biologic responses, with primary emphasis on the neurologic system. However, the available animal data do not at present point to an acute hazard. More research, both laboratory and theoretical are required to define whether the accepted effects are indicative of long-term subtle changes that are presently not recognized as being caused by field exposure.

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