Human Studies of Human Health Hazards: Comparison of Epidemiology and Toxicology

David A. Savitz

Abstract. The two principal methods of evaluating environmental health risks are observational epidemiologic studies of exposed populations and laboratory studies of the effects of agents on experimental animals. The principal advantages of the laboratory approach are random exposure assignment and precise exposure assessment. Epidemiologic studies have the virtue of studying the species of ultimate interest (humans) under natural exposure conditions. Given these characteristics, a strategy is offered for resolving contradictory results from these approaches. Epidemiologic evidence of a hazard with contradictory laboratory data may indicate confounding of the human data from other risk factors or bias due to systematically erroneous data. Animal studies might have erred in selecting an inappropriate species or exposure conditions. Where animal studies suggest a hazard but human studies do not, the human studies may be in error due to random exposure misclassification. Animal studies may have overstated risks due to high exposure levels or selection of an unusually sensitive species for study. Studies of electromagnetic fields suggest an effect on cancer risk based on epidemiologic data with negative results from the laboratory, possibly reflecting confounding or bias in the human research or poor selection of the species or exposure conditions in the laboratory. Improved coordination across these disciplines would benefit those who must reconcile these lines of research in assessing risks to human populations.

Key words and phrases: Electromagnetic fields, epidemiologic methods, risk assessment, environmental health hazards, animal toxicology studies, research method comparisons.

1. INTRODUCTION AND OVERVIEW

Research on environmental hazards is usually, but not always, intended to characterize risk to human populations. There are situations in which other effects clearly take precedence, e.g., acid rain is of concern for its effects on the ecosystem even though human health is not directly affected by such pollution. In other situations humans are not the most sensitive species, e.g., aquatic organisms are harmed by increased iron and zinc levels in surface waters at far lower levels than would be required for human toxicity (National Academy of Sciences, 1977). In most of the environmental exposures of greatest concern (and in the following discussion), however, the health of human populations is the predominant issue.

David A. Savitz is Assistant Professor, Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina 27599.

Society expends substantial resources to protect humans from toxic pollutants, through monitoring the levels of environmental agents, restricting release of hazardous substances and creating financial incentives for reduction of exposure. All of these implementation strategies are predicated on evidence that the pollutants pose a real threat to human health, ideally including the quantification of the risk at different exposure levels necessary for rational cost-benefit decisions. The scientific basis for such interventions is largely derived from parallel information provided in studies of laboratory animals and epidemiologic studies of humans. Methodologic issues pertaining to these different sources of evidence must be appreciated for optimal use of such data in risk assessment.

The attributes of epidemiologic studies of humans exposed to potentially hazardous agents compared to laboratory investigations of animals receiving such exposures are outlined in Table 1. Although there are variants in study design and methods, e.g., human

TABLE 1
Comparison of typical human and animal studies of environmental health hazards

Human studies	Animal studies
Observational: exposures observed	Experimental: exposures randomly assigned
Confounders controlled	Confounders controlled or randomized
Exposures reconstructed	Exposures induced and precisely measured
Species of interest (humans)	Extrapolation of results to humans
Exposure levels and patterns of interest	Extrapolation to naturally occurring exposures

experimentation and observational studies of free-living animal populations, the typical research methods will be discussed. The intention in this paper is not to describe the methodologic principles of epidemiology or toxicology, but rather to compare and evaluate the strengths and limitations of these approaches in assessing health risks to human populations. Situations in which animal and human studies provide contradictory results are discussed by considering why each source of data might be in error. The literature on electromagnetic radiation and cancer serves as a useful illustration of suggestive epidemiologic findings in the absence of corroborative laboratory data. Finally, suggested methods will be offered for improved coordination between these realms of research on environmental health hazards.

2. COMPARISON OF HUMAN AND ANIMAL STUDIES OF ENVIRONMENTAL HEALTH HAZARDS

Exposure Allocation

The first and most critical distinction concerns experimental control over exposure assignment (Table 1). Classically, epidemiologic studies of hazardous agents are limited to the natural occurrence of exposures which result from choice of employment, housing location or other chosen or externally imposed exposures. It would obviously be unethical to randomly impose exposures thought to be injurious to health, although it is ironic that circumstances of employment (e.g., in the manufacture or use of hazardous agents), residence location (e.g., in areas of air or water pollution) and especially individual choice (e.g., tobacco smoking) produce a wide variety of potentially hazardous exposures from which epidemiologists can learn about the causes of disease. In spite of the variation in exposure to hazardous agents, they cannot be randomly assigned because they are not subject to the control of the investigator.

The epidemiologist's ideal "natural experiment," in which observed exposures were fortuitously random-

ized, rarely occurs. Occupations, residences and behaviors are imposed or self-selected in a clearly nonrandom manner such that other attributes often differ between exposed and nonexposed populations. The "healthy worker effect," describing the superior health of industrial workers compared to the population at large, is an example in which exposure to certain work environments occurs more frequently for physically fit and disease-resistant individuals. Because environmental exposures are not randomly assigned, epidemiologic investigations must address the possibility that observed associations between exposure and disease are distorted by a mixing of effects (confounding) with other disease determinants. For example, persons who live in areas of higher air pollution tend to smoke more cigarettes (Weinberg, Kuller and Redmond, 1982). Studies of air pollution and lung cancer which do not take cigarette smoking into account will overestimate the effect of air pollution unless the confounding by cigarette smoking is controlled.

Treatment of Confounders

Valid results can be obtained even when exposure has not been randomly assigned through considering and eliminating the effects of confounding variables through restriction (e.g., only studying nonsmokers) or measurement of those extraneous variables and adjustment in the analysis (e.g., calculating the effect of air pollution with adjustment for cigarette smoking). Although such control without randomization is challenging, an awareness of the possible confounding factors enables the investigator to design and conduct the study to minimize such effects.

Randomized exposure assignment is the norm in animal studies, in that the determination of which organism receives which exposure level is random. Major extraneous health determinants are carefully controlled through restriction, such as diet, caging conditions and even genetic predispositions. With random exposure assignment for a large study population, there is the extra assurance that even unrecognized risk factors for disease will be equitably balanced among the exposure groups, a clear advantage over observational studies. In principle, only random biologic variation prevents obtaining the correct answer. This is one reason for statistical significance testing having more value in the interpretation of results from experiments than from epidemiologic studies: Random error is often the major source of uncertainty. In epidemiologic studies, in contrast, bias or systematic error is of much greater concern, so that an emphasis on significance as a basis for determining the credibility of an association is inappropriate (Rothman, 1986).

Exposure Measurement

A by-product of experimental control over exposure is enhanced accuracy of exposure characterization. The investigator-controlled exposures to chemical and physical agents in the laboratory can be achieved with a high degree of precision. In contrast, epidemiologic studies are concerned with measuring existing exposures, or even more problematic, measuring past exposures through such surrogates as employment at a factory, assignment to a job category, self-reported exposures or in rare circumstances, biologic markers of exposure (Calabrese, 1978). Further complicating the epidemiologist's ability to reconstruct accurate exposure histories is the temporal variation in exposures within a given job or residential setting. If this imprecision in exposure characterization is similar for those who do and do not develop disease, there is a predictable effect: the study results are biased toward the null, i.e., toward an underestimation of the true effects of that exposure (Copeland, Checkoway, McMichael and Holbrook, 1977). This imperfection biases all epidemiologic studies to some degree, in that even such ostensibly clear exposure measures as tobacco smoking history fail to account for depth of inhalation, puffs per cigarette, etc. This random misclassification of exposure dilutes all measures of exposure-disease associations to some degree (Rothman, 1986). The major compensation for these difficulties in assessing causality and measuring exposures in epidemiologic studies is the virtue of working with the species of ultimate interest, human beings.

Extrapolation across Species

Because humans are both the species of interest and the objects of epidemiologic study (Table 1), results are directly applicable to the evaluation of human health risk. In contrast, the results of animal experiments, no matter how well designed and executed, are diminished in value by the need to extrapolate across species. Although there are biologic principles regarding metabolic processes and elimination rates, for example, which can guide interspecies extrapolation (Calabrese, 1978), there is still substantial uncertainty introduced in applying results from experimental animals to humans.

There is also the challenge of extrapolating from the homogeneity of laboratory animals to the diversity of human populations. For example, some agents may only be effective in special subpopulations, e.g., among pregnant women, those with metabolic disorders, heavy alcohol drinkers. The designer of a laboratory experiment cannot possibly build in all the complexities of human populations into the experiment, but exposures to free-living humans naturally include such diverse subgroups.

Extrapolation across Exposure Conditions

Another dimension to extrapolation concerns extension of study results to different exposure conditions (Table 1). In spite of the difficulties in measuring exposures in epidemiologic studies, these natural exposure conditions are (by definition) the appropriate exposures for making health risk assessments. The complex, time-varying exposures in the workplace or general environment reflect precisely the exposure patterns which are of concern for their health impact. In contrast, in studies of laboratory animals the investigator must make a judgment regarding pertinent components of exposure to be evaluated with respect to intensity, temporal pattern and concomitant exposures. After the investigator determines the relevant exposure conditions to study and carries out an experiment, there is a need to extrapolate those results back from the precisely measured but artificial laboratory conditions to the humans exposure circumstances.

There are several dimensions to the exposure extrapolation from the laboratory to the community or workplace. The most obvious need for extrapolation is across exposure level. Laboratory studies tend to assess much higher exposures than those actually experienced by human populations. There are valid logistical concerns which require such extreme exposure conditions, but the potential limitation in extrapolation to lower exposure conditions experienced by human populations is apparent. Another issue is the contrast between a pure exposure to a single agent, the usual mode of laboratory investigation, and human exposure to complex mixtures of pollutants, the norm in the real world. If there are synergisms or antagonisms among exposures, then the laboratory studies of individual agents will provide an inaccurate result for judging human risk. Exposures studied in the laboratory are often more acute (brief and intense) than those of concern in human hazard assessment. The epidemiologist's lack of experimental control becomes an advantage in interpretation of data for risk assessment in that there is not a need to determine the precise exposure attributes which affect health, because the exposures studied are experienced as the complete "package" which exists in the workplace or home environment.

3. INTERPRETATION OF CONTRADICTIONARY RESULTS FROM HUMAN AND ANIMAL STUDIES

The methodologic strengths and limitations of human and animal studies of health hazards provide some guidance in the interpretation of contradictory results from the two data sources (Figure 1). For discussion purposes it will be assumed that animal studies and human studies each provide a consensus

		ANIMAL STUDIES	
		Hazard Present	Hazard Absent
HUMAN STUDIES	Hazard Present	Conclude hazard is present	Human studies in error: 1. Positive confounding 2. Misclassification (differential) 3. Selection bias Animal studies in error: 1. Species differences 2. Inappropriate exposures 3. Missing co-requisite exposures
	Hazard Absent	Human studies in error: 1. Misclassification (non-differential) 2. Negative confounding 3. Selection bias Animal studies in error: 1. Excessively high exposures 2. Species differences	Conclude hazard is absent

FIG. 1. Schematic representation of patterns of results for human and animal studies.

of internally consistent positive (the presence of a relationship between exposure and adverse health effects) or negative (no relationship between exposure and health) results. When the evidence from animal and human studies are in agreement, the interpretation is straightforward. The most parsimonious explanation for such consistent positive (negative) results is the presence (absence) of a causal association (Figure 1). Although there may be errors in which both types of studies produce false-positive or false-negative results, the methodologic strengths and weaknesses of the approaches outlined above make this an unlikely explanation for corroborated positive or negative findings.

The more interesting and problematic situation is when the evidence from animal and human studies is contradictory. Although not amenable to simple interpretation, the methodologic attributes of the two types of studies do provide some suggestions regarding the likely basis for such contradictions and a suggestion of how they might be resolved.

Positive Human Studies, Negative Animal Studies

First is the situation in which human studies show positive results and animal studies are negative. There are several possible reasons why positive human results might be in error. There may be positive confounding, in which the true cause of adverse health effects is mixed with the exposure of interest, so that the etiologic impact is falsely attributed to the exposure of interest. In the earlier example regarding air pollution and lung cancer, failure to consider tobacco use would lead to false-positive results implicating air pollution as a cause of lung cancer. This is probably the most common reason for contradictory results, in that hazardous exposures (including personal habits, work-

place hazards and environmental contaminants) tend to occur together. This is obviously not a fact of nature so much as a sociologic phenomenon in which the segment of the population which is exposed to a hazardous environment tends to be societally disadvantaged in diet, education, as well as in health behaviors and access to medical care.

Another possible source of erroneously positive epidemiologic studies is from misclassification or information bias, i.e., when exposed persons produce an inaccurately high frequency of disease or diseased persons produce an inaccurately high frequency of exposure. This may arise when there is some suspicion regarding the association under investigation and either the exposure or disease measures are vulnerable to bias. If radiologists who make judgments from x-rays regarding the presence of coal workers' pneumoconiosis are aware of the individual's mining history, then they will be prone to overdiagnose disease among miners, falsely elevating the association. Similarly, in a case-control study, mothers of children with birth defects may erroneously "remember" more pesticide exposure than mothers of healthy infants. Note that the misclassification must be nonrandom to inflate the association; random errors in measuring exposure can only cause a bias toward null results. Critics who claim an association has been inflated by misclassification must argue not just that the measures are imperfect but more specifically that the pattern of errors would raise rather than lower the risk estimate.

On the other hand, animal studies may produce false-negative results for assessing human risk, i.e., even though the results may be valid in characterizing the absence of health risks to rats or guinea pigs in a laboratory environment, they are incorrect for risk assessment in human populations. The sensitivity of the selected species may be less than that of humans due to metabolic differences. Also, the vulnerable segment of the human population (e.g., fetuses, persons with pre-existing chronic disease) may not have been considered in the laboratory study. Some critical aspect of exposure (intensity, temporal pattern, concomitant exposures) may have failed to adequately simulate the human exposure circumstances. For example, it has been suggested the difficulties in producing cancers in animals exposed to arsenic (in spite of known human carcinogenicity) is that arsenic acts as a co-carcinogen and the necessary concomitant exposures were not provided in the laboratory (Pershagen, 1983). In general, toxicologists attempt to produce extreme exposure conditions to be certain of not overlooking a true risk to humans, but this error may still occur. If, for example, an investigator concerned with radiation carcinogenesis examined extremely high exposures which caused cell killing

rather than genetic changes in viable cells (Committee on the Biological Effects of Ionizing Radiations, 1980), the erroneous conclusion might be drawn that radiation does not induce cancer.

Negative Human Studies, Positive Animal Studies

This form of contradiction is probably more common or at least of greater interest, with data on saccharine and bladder cancer and preliminary studies of formaldehyde and nasal cancer providing highly visible current examples. There are several important reasons why epidemiologic studies might fail to identify health risks which are present. As noted above, all epidemiologic studies suffer to varying degrees from random exposure misclassification resulting in underestimation of risk. This misclassification includes outright errors of exposure assignment, imprecision in the subtleties of dose estimation (e.g., the actual dose to the target organ), as well as examination of exposures occurring at the inappropriate times to be related to disease occurrence (Rothman, 1981). For this reason, any negative epidemiologic study should include a consideration of the magnitude of risk which may have been overlooked given plausible estimates of imprecision in exposure measures. In many instances, there would be no contradiction in that the negative results of human studies are readily attributable to dilution of very modest associations which may really be present. There are practical limitations in the ability of epidemiologic studies to identify minimal (although real) elevations in risk.

Another set of reasons for risk underestimation in epidemiologic studies are analogous to those discussed as the basis for overestimation of risk: confounding and bias. If the more highly exposed persons are favored by other attributes (e.g., diet, smoking) then the mixture of adverse effects of the environmental exposure and beneficial effects of the associated exposure could produce no overall association. Similarly, if exposed persons were less likely to report disease or diseased persons underreported past exposures, the epidemiologic study would underestimate risk. These conditions are much less likely or common than the converse in which risks are falsely elevated. Random misclassification of exposure remains the most likely source of risk underestimation in epidemiologic studies.

Animal studies are prone to overestimate health risk, often by design. When the most sensitive species is selected and the highest tolerable dose is used, the investigator has made the choice to risk false-positive results. Note that the inaccuracy of the results is not an issue of the validity of findings for that species under those exposure circumstances, but rather inaccuracy if applied directly to humans exposed to the

existing levels of that agent. Although the public sometimes has difficulty in understanding these distinctions, evaluation of apparently contradictory human and animal data must take this into account.

Extrapolation of the results of animal studies across species and across exposure conditions may produce errors of inference regarding human risk in the real world. Some assays are conducted because of their ease and speed (e.g., Ames test for mutations) with the intention of screening agents to determine those most worthy of further study. When further study of human populations convincingly indicates the absence of a human hazard, the cycle of investigation might be considered complete. Both the screening assay and epidemiologic study may be correct, but the latter is the more direct indicator of health hazards.

4. CARCINOGENIC EFFECTS OF ELECTROMAGNETIC FIELDS

The issues in the interpretation and reconciliation of human and animal studies of health risk are well-illustrated in the literature on cancer risk from electromagnetic field exposures. The general hypothesis, rarely formalized, is that persistent exposure to increased levels of magnetic fields in the residential environment acts to promote human cancers. It must be recognized that neither epidemiologic nor experimental studies have produced definitive results, but the general direction of the findings can be characterized by human studies showing evidence of adverse effects with animal data less indicative of a hazard.

The epidemiologic studies addressing cancer risk in relation to electromagnetic field exposures from power transmission and distribution lines are accumulating, with a general trend toward suggestive, positive associations. Wertheimer and Leeper (1979) initiated this area of research with the finding that children who developed cancer tended to live in homes surrounded by electrical wiring suggestive of increased magnetic field exposure more frequently than controls. The magnitude of effect was modest (estimated rate ratios of 2.0–3.0) and consistent for subgroups defined by type of cancer, age and sex. Potential confounders available from the birth certificate and residence did not alter this association. Fulton, Cobb, Preble, Leone and Forman (1980) published a failure to corroborate these findings in Rhode Island, but the method of control selection resulted in an imbalance in the occupancy dates of case and control homes tending to bias the results toward the null (Wertheimer and Leeper, 1980).

Adult cancers were also found by Wertheimer and Leeper (1982) to be related to occupancy in homes imputed to have elevated magnetic field levels. Most recently, Tomenius (1986) reported a positive

association between measured magnetic fields and childhood cancer risk in Sweden, apparently corroborating Wertheimer and Leeper's (1979) study. Negative results were provided by McDowall (1986) in a British study of adult cancers, but the quality of their exposure assessment is especially weak in that it is based on simple proximity to power lines rather than on estimated magnetic field exposure. Although a variety of methodologic concerns have been raised about these studies (Savitz, 1986), none of the critics have offered a convincing alternative explanation for the data. In the aggregate, these studies of residential electromagnetic field exposures and cancer offer incomplete but suggestive evidence of a positive relationship. Literature on occupational exposures to electromagnetic fields is also providing suggestions of increased leukemia (Savitz and Calle, 1987) and brain cancer (Lin, Dischinger, Conde and Farrell, 1985) risk.

The biologic research on this topic is too extensive to be reviewed in detail, but a recent set of such review papers are available (American Institute of Biological Sciences, 1985). As interpreted by experts in the field, there is little or no direct evidence of carcinogenicity of electric or magnetic fields, e.g., they are not mutagenic (Easterly, 1981). Furthermore, there is no evidence of specific effects on immune function (American Institute of Biological Sciences, 1985) or other biologic processes associated directly with cancer development. On the other hand, there is a growing recognition that 50–60-Hz electromagnetic fields are biologically active, i.e., they do cause biologic responses even with very low exposures. The subtlety of many changes in physiologic function in response to environmental conditions makes the distinction between "biologic response" and "pathologic change" increasingly important and difficult to assess.

Given suggestively positive epidemiologic studies in the absence of a clear biologic basis for such effects, it is useful to speculate on the possible reasons for this situation and suggest methods by which the apparent discrepancy might be resolved. The epidemiologic data may be in error for one of two reasons: (1) There may be positive confounders, i.e., cancer determinants which are positively associated with electromagnetic field exposures and disease risk; (2) there may be selective misclassification in which cases tend to have erroneously high exposures relative to controls.

The likelihood of positive confounding has been addressed to a limited degree in the literature, but the diversity of cancers reported to be associated with electromagnetic fields (childhood cancers, adult leukemias, brain cancers) in both residential and occupational settings makes this unlikely. In studies of residential electromagnetic field exposures, it is difficult to speculate on what cancer determinants might

be associated with the electromagnetic field exposures in the home, but the obvious candidates of social class and age have been addressed (Wertheimer and Leeper, 1979, 1982). It might be argued that some adverse exposures are related to living in homes with higher exposure, but there is little empirical evidence to assess this possibility. The corroborative evidence from occupational studies further reduces the possibility of confounding in that some factor(s) would have to confound both home and workplace exposures.

Selective misclassification is a concern in some specific studies, e.g., Wertheimer and Leeper (1979, 1982), in which case and control homes were not judged blindly for wiring configuration. It is possible that subtle biases of the investigators tended to produce an artificial excess of high exposure case homes and low exposure control homes. Without more detailed information on exposure classification accuracy, it is not possible to definitively address this concern. One often-cited basis for the uncertainty of these studies is concern with the overall accuracy of the exposure assessment (Roth, 1984). The use of wiring configurations as a proxy for electromagnetic field exposure has been challenged, but use of a poor proxy measure cannot account for positive findings. In fact, it can be assumed that such nondifferential misclassification will superimpose a bias toward the absence of any association (Copeland, Checkoway, McMichael and Holbrook, 1977).

There are several general reasons why the animal studies may have produced incorrect negative results for human risk assessment. The problems of interspecies extrapolation are well-known for chemical agents (Calabrese, 1978), but there are particular problems associated with the spatial orientation in electromagnetic fields of humans relative to other species (Kaune, 1985). There is the possibility that experimental animals are not similarly affected by electromagnetic field exposures. Another concern is the potential failure of animal experiments to include the counterparts to vulnerable humans. The suggestion that magnetic fields may act as cancer-promoting agents would imply that the vulnerable human subpopulation consists of those persons whose cancers have already been initiated. The baseline frequency of initiated cancers among laboratory animals might be insufficient for observing a promotional effect.

Some attributes of the exposures used in laboratory studies may be inappropriate for human risk assessment. Much of the work has been done with electric fields in contrast to the presumed human effects from magnetic fields. There may be "windows" of intensity or frequency for producing effects, such that higher or lower exposure levels or frequencies would fail to show a particular effect. Fields in laboratory settings tend to be purely sinusoidal in form, unlike the more erratic

and complex fields in the residential environment. One or more of these exposure attributes may produce errors in the evaluation of human risks in the home or workplace.

It seems that the experimental work in this area has paid insufficient attention to its use in human risk assessment. Much of the effort of laboratory investigators seems to be oriented toward an understanding of the basic mechanisms, which is certainly a valid goal of biologic research. Nonetheless, there needs to be a greater effort to elucidate those mechanisms which are potentially most relevant to the assessment of human health hazards.

The selection of the experimental animal should be guided in part by similarity to humans in their interaction with electromagnetic fields. An obvious need is the direct examination of a possible promotional role of such fields by studying animals with chemically initiated cancers. Exposure conditions should be more directly oriented to the human situations of interest. Complex wave forms should be studied if those are the norm in the real world. The methodology for designing experiments to address human health concerns is in the purview of toxicologists and other laboratory scientists, but an appreciation of the ultimate use of such data in conjunction with epidemiologic information needs to be appreciated at the outset. Epidemiologists cannot manipulate exposures to better simulate the laboratory investigations, so that the laboratory environment must be made to more closely approximate the human exposure conditions. The advantages of randomized exposure assignment and precision in exposure measurement can be retained while improving on the applicability to human populations.

5. CONCLUSIONS

The methods of epidemiologic investigation and laboratory toxicology have evolved and improved independently. Unfortunately, the inexplicable contradictory data which may result are not desirable when combining the information for health risk assessment. These avenues of investigation must converge in risk assessment and policy formulation. When epidemiologists are unaware of laboratory work and vice versa, risk assessment may represent the very first effort at reconciliation, inviting the possibility of inexplicable contradictory data from human as compared to animal studies. Contradictory findings need not be problematic if there is sufficient information to reconcile the findings. Rather than leaving it to policy makers, the media or the general public to reconcile such information, however, the scientists themselves are in the best position to design their studies to facilitate such judgments.

For example, the controversy over the apparent carcinogenicity of saccharine in laboratory animals

led to a large, well-designed epidemiologic study conducted by the U. S. National Cancer Institute (Hoover and Strasser, 1980). The absence of detectable effect in humans led to the conclusion that while there may be a very modest increase in cancer risk, the study data excluded the possibility of a substantial effect. To the public, this leaves open the choice of "believing" the laboratory conclusion regarding carcinogenicity or the epidemiologic conclusion of no effect. The involved scientists are more likely able to recognize that there may be interspecies differences or dose-related effects such that both types of studies are valid and relevant to human health risk assessment.

Better coordination across disciplines is essential for improving our understanding of environmental risks. Laboratory studies should be heeded by epidemiologists in designing their investigations. Where experimental evidence exists regarding mechanisms, latency of effect or vulnerable subgroups, epidemiologists should include such considerations in their choice of study population, exposure measurement and interpretation of results. Similarly, laboratory investigators concerned with hazards derived from epidemiologic data should pay closer attention to the suggested exposure-disease relationship. This includes a consideration of presumably vulnerable subpopulations and the precise exposure characteristics. In the example of electromagnetic fields and cancer risk, the epidemiologic data point toward a promotional effect of magnetic fields. For relevance to human health risk, studies of electric fields or mutations are less concordant and thus less pertinent. Neither line of investigation should be constrained by the other's evidence, in that new discoveries are often made with little justification for conducting the study. Nonetheless, a recognition that one's data will be integrated with the corresponding data from other disciplines would not only help those who must make such an integration for risk assessment, but would promote more useful and interpretable scientific investigations.

REFERENCES

- AMERICAN INSTITUTE OF BIOLOGICAL SCIENCES (1985). *Biological and Human Health Effects of Extremely Low Frequency Electromagnetic Fields*. American Institute of Biological Sciences, Arlington, Va.
- CALABRESE, E. J. (1978). *Methodological Approaches to Deriving Environmental and Occupational Health Standards*. Wiley, New York.
- COMMITTEE ON THE BIOLOGICAL EFFECTS OF IONIZING RADIATION (1980). *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*. National Academy Press, Washington, D.C.
- COPELAND, K. T., CHECKOWAY, H., MCMICHAEL, A. J. and HOLBROOK, R. H. (1977). Bias due to misclassification in the estimation of relative risk. *Amer. J. Epidemiol.* **105** 488-495.
- EASTERLY, C. E. (1981). Cancer link to magnetic field exposure: A hypothesis. *Amer. J. Epidemiol.* **114** 169-174.
- FULTON, J. P., COBB, S., PREBLE, L., LEONE, L. and FORMAN, E.

- (1980). Electrical wiring configurations and childhood leukemia in Rhode Island. *Amer. J. Epidemiol.* **111** 292-296.
- HOOVER, R. N. and STRASSER, P. H. (1980). Artificial sweeteners and human bladder cancer. *Lancet* **1** 837-840.
- 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* 25-60. American Institute of Biological Sciences, Arlington, Va.
- LIN, R. S., DISCHINGER, P. C., CONDE, J. and FARRELL, K. P. (1985). Occupational exposure to electromagnetic fields and the occurrence of brain tumors. An analysis of possible associations. *J. Occup. Med.* **27** 413-419.
- MCDOWALL, M. E. (1986). Mortality of persons resident in the vicinity of electricity transmission facilities. *Br. J. Cancer* **53** 271-279.
- NATIONAL ACADEMY OF SCIENCES (1977). *Drinking Water and Health*. National Academy Press, Washington, D.C.
- PERSHAGEN, G. (1983). The epidemiology of human arsenic exposure. In *Biological and Environmental Effects of Arsenic* (B. A. Fowler, ed.). Elsevier, New York.
- ROTH, H. D. (1984). *An Evaluation of Published Studies Analyzing the Association of Carcinogenesis with Exposure to Magnetic Fields*. Electric Power Research Institute, Palo Alto, Calif.
- ROTHMAN, K. J. (1981). Induction and latent periods. *Amer. J. Epidemiol.* **114** 253-259.
- ROTHMAN, K. J. (1986). *Modern Epidemiology*. Little, Brown, Boston.
- SAVITZ, D. A. (1986). Human health effects of extremely low frequency electromagnetic fields: Critical review of clinical and epidemiologic studies. Presented at IEEE Power Engineering Society Winter Meeting, New York City, February 2-7.
- SAVITZ, D. A. and CALLE, E. E. (1987). Leukemia and occupational exposure to electromagnetic fields: Review of epidemiologic surveys. *J. Occup. Med.* **29** 47-51.
- TOMENIUS, L. (1986). 50-Hz electromagnetic environment and the incidence of childhood tumors in Stockholm County. *Bioelectromagnetics* **7** 191-208.
- WEINBERG, G. B., KULLER, L. H., and REDMOND, C. K. (1982). The relationship between the geographic distribution of lung cancer incidence and cigarette smoking in Allegheny County, Pennsylvania. *Amer. J. Epidemiol.* **115** 40-58.
- WERTHEIMER, N. W. and LEEPER, E. (1979). Electrical wiring configurations and childhood cancer. *Amer. J. Epidemiol.* **109** 273-284.
- WERTHEIMER, N. W. and LEEPER, E. (1980). Re: "Electrical wiring configurations and childhood leukemia in Rhode Island" (letter). *Amer. J. Epidemiol.* **111** 461-462.
- WERTHEIMER, N. W. and LEEPER, E. (1982). Adult cancer related to electrical wires near the home. *Internat. J. Epidemiol.* **11** 345-355.