

# Epidemiological Studies for Regulatory Agencies

by Vilma R. Hunt\*

In regulation of exposures to hazardous environmental agents, epidemiologic evidence is especially important in defining human risk estimates. The process of developing appropriate regulations is complex, however, and depends on many considerations beyond those established to a high degree of scientific certainty. Thus the needs of regulatory agencies are involved in the way epidemiologic data are developed and presented. To coordinate and review common problems associated with preventive and regulatory activities among the federal agencies concerned with regulation, an Interagency Regulatory Liaison Group (IRLG) was established in 1977. Because of difficulties encountered by these agencies or Congressional committees in evaluating epidemiologic evidence, a subcommittee of the IRLG has developed in draft form guidelines for human population studies to be used in public health decision-making. Although these guidelines have attracted much controversy, their aim is to present criteria for design and documentation of epidemiologic studies, without interfering with the initiative of investigators. Some aspects of the IRLG guidelines are discussed. The need for epidemiologic research in providing evidence for regulatory purposes is increasing, but such studies must be well done if they are to be useful.

In today's society, we are faced with the quandary of balancing the risks and benefits of economically useful industrial and commercial products, which themselves may offer some public health benefits against the potentially increased risk and costs of disease in populations exposed to chemicals. The burden of determining such tradeoffs falls on the shoulders of regulatory agencies, and, to serve as the foundation for policy decisions, they hope to have at hand the most thorough and complete evidence on the health risks of exposure to environmental contaminants as is possible at a given point in time. Further, since the goal of most environmental legislation is, first, to protect the public health—that is, to protect people—the best sort of health data for use in policy-making come from epidemiological studies.

I would prefer to discuss the role that epidemiological research and data play in regulatory decision-making, and, further, how the special research and reporting needs of regulatory agen-

cies should affect the design and conduct of epidemiologic studies.

Environmental and occupational legislation designed to protect the health and welfare of the general public and workers has been enacted in the United States over the last 25 years. This legislation has focused on cleaning up the environment and regulating permissible entry of substances into the atmosphere, water and food supplies, workplaces and homes. The first Federal law on air pollution was passed in 1955, and subsequently the Clean Air Act of 1963, the intent of which was to initiate and accelerate a national research and development program to achieve the prevention and control of air pollution. Other environmental acts that were passed throughout the 1960's and early 70's, such as the Safe Drinking Water Act and Solid Waste Disposal Act, similarly mandated programs to address pollution reduction in water and on land.

The primary thrust of the various legislative acts was, for the pertinent government agency, to determine the risks—especially the health risks—posed by pollutants or hazardous substances and then establish safe levels of exposure, below which

---

\*Office of Health Research, Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460.

health should be adequately protected. This, then indicates how regulatory agencies must view health research data in order to accomplish their mission. Regulatory agencies are in the "numbers-setting" business and, thus, want the data which form the scientific basis of their regulations and guidelines to either provide the "numbers" directly or, at least, be so constructed as to allow development and estimation of safe levels.

In terms of health data in support of regulation, data from three types of research approaches are important. These three sources are: first, toxicological data from studies in animals, and, now, more and more, *in vitro* test systems; second, clinical study data, that is, data derived from controlled experimental trials in human volunteers; and, third, epidemiological data from studies in human populations. The three approaches are interrelated and each plays an integral role in risk assessment and in determining safe levels of exposure, bringing their own special data to the process. Animal studies are critical, since they can provide data on high doses and target organs, for example, and allow development of dose-response curves. Yet the problem of translating animal data to a human context is likely to remain with us, even when multiple species information is available. Clinical studies can be used to verify, under controlled conditions, estimates derived from field or population studies, and to develop a dose-response series in some cases. They are constrained, however, by the type of agent and health or physiological endpoint under study. Epidemiological studies can provide statistical associations between agent and health endpoint and can be weakened by problems with ascertainment of exposure and health endpoint, validity and reliability of data collection methods, and population enumeration, to name a few. Nevertheless, despite any limitations of the epidemiologic approach, it still is the most critical for the regulatory process because it provides information on real people in real environments. For example, even though dose-response data may be unattainable, consistently reported effects from various studies in different populations adds great credence to a regulatory or policy stance as to whether a hazard exists or not.

As an aside, I'd like to mention that, in some cases, data from all three research tools may not be available to support regulatory actions. But why regulate if you are not yet confident with the current body of knowledge? One reason is that regulatory timetables are frequently prescribed by legislative mandates. The various amendments to the Clean Air Act have, for example, required the

Environmental Protection Agency to propose a short-term NO<sub>2</sub> standard and to reconsider and revise all the National Air Quality Standards (NAQS) at least every five years. In terms of epidemiological studies, suitable populations may not have been identified or followed for a sufficient period of time for the data to be available to add to regulatory evaluation. Epidemiological studies usually require relatively long periods of time for completion, in comparison with animal or measurement studies, yet regulators frequently are not at leisure to await the results.

Implementation of congressional mandates related to the environment has been based on the assumption that sufficient data exist to set and implement standards concerning unhealthy levels of exposure to pollutants. Congress has recognized, however, that gaps and deficiencies exist in the data required for environmental research and regulatory decisions. The passage of several congressional mandates for improved data and interagency research coordination provides evidence of this awareness. For example, the Toxic Substances Control Act of 1976 (P.L. 94-469) specified that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health." One year later, the Clean Air Act Amendments (P.L. 95-95) established the Task Force on Environmental Cancer and Heart and Lung Diseases, whose purpose, in part, was to "coordinate research and stimulate cooperation between the Environmental Protection Agency and the Department of Health, Education, and Welfare and other involved agencies."

Another example of recognition of the need for greater regulatory and health research coordination occurred in 1977, with an important government initiative to improve protection of the public from toxic substances. At that time, four U.S. agencies which administer laws designed to protect the public health and safety formed the Interagency Regulatory Liaison Group (IRLG). This interagency was formed in response to President Carter's promise to eliminate waste and duplication in government. The four agencies are the Environmental Protection Agency (EPA), the Consumer Product Safety Commission (CPSC), the Food and Drug Administration (FDA) and the Occupational Safety and Health Administration (OSHA). They established a formal relationship for cooperation in protecting the public from exposure to harmful levels of toxic substances by use of consumer products, foods and drugs, in the workplace or through exposure to contaminants in land, air or water. They were joined in 1978 by the Food Safety and Quality Service of the Depart-

ment of Agriculture. Through the IRLG, these agencies hope to enhance and coordinate their preventive and regulatory activities by such means as developing compatible testing guidelines and common approaches to the problem of health risk assessment and by coordinating, when possible, their research efforts to ensure the best use of their collective research capability.

One high priority area of mutual concern is the use of epidemiological research in support of each agency's regulatory mission. Under the auspices of the IRLG, an Epidemiology Work Group was formed which has developed draft documentation guidelines for population studies used in public health decision-making.

Some of you may have already seen and reviewed these guidelines, since they were circulated to the membership of the Society for Epidemiological Research and a notice of availability was published in the *Federal Register*. A great number of comments have been received and, based on these, the draft guidelines are in the revision forms. Although welcomed by many people, the guidelines have stirred up a great deal of controversy in the epidemiological community; much of this controversy centers, I believe, on some misconceptions about the purpose and eventual use of the guidelines, evidently not made fully clear in the draft.

Let me first assure you that the intent of these guidelines is not to pigeonhole or stifle creative research or scientific exploration. Rather, they instead reaffirm the IRLG member agencies' commitment to the principles of good, basic epidemiological design in their own research and further, seek to engage the assistance of the scientific community in the difficult task of public health protection by advising researchers of the data and documentation needs peculiar to the standard setting process. They do not prescribe research methods, but rather lay out for policy-makers the key elements for regulatory decision-making activities.

These guidelines present the type and extent of information considered important for both adequate documentation and the objective evaluation and interpretation of epidemiologic studies. In addition, they are intended to provide a framework for evaluation by policy-makers, who are not themselves epidemiologists. The guidelines will also provide guidance for those who sponsor and undertake such studies, the findings of which may be used in regulatory decision-making. For example, instructions for writing grant proposals do not always lend themselves well to epidemiological proposals. The guidelines can be used to inform

potential grantees of the type of information we would like to see considered in their proposals.

Development of these guidelines arose from a concern that inadequate documentation or description of evidence needed to evaluate, for example, the appropriateness of study design, adequacy of data, and choice of analytic methods sometimes led to conflicting decisions by agencies with related responsibilities. Continuing debate over the amount and type of evidence needed to make public health policy may result in two courses of action: first, public health actions may be delayed on the assumption that further research is necessary before regulatory action can be taken and supported; secondly, unnecessary regulation may be imposed because epidemiologic studies are inadequately conducted and documented in a way that serves standard-setting purposes. A variant on this last point is that legal timetables for regulation must be met despite the absence of well-developed human data, thus, weakening the set regulation.

Therefore, the IRLG determined that it is appropriate and necessary to provide guidelines for the documentation of epidemiologic studies to be used in public health decision-making.

Within EPA, we are instituting procedures which we call "problem-definition" prior to undertaking an epidemiology study. So that our limited resources can be put to best use in addressing the many problems that confront the Agency. Not to be confused with pilot or feasibility studies, the problem definition approach established a framework to determine the need for and utility of undertaking an epidemiology study in a given population or on a particular agent. The major areas we want to consider as fully as possible prior to undertaking a research project are: (1) statement of the problem, including an assessment of how the data to be derived from such a study could meet EPA objectives and regulatory and enforcement needs and whether the proposed study would generate or test hypotheses; (2) a review of the relevant literature; (3) the projected health and exposure data needs and likely sources; (4) a listing of the potential confounding variables; (5) probable methods of data collection, including potential biases or limitations; (6) the potential problems of data access such as confidentiality; (7) identification and selection issues for study subjects and comparison groups; (8) analytical and statistical procedures that could be applied and their attendant biases and limitations; (9) a preliminary assessment of the types of limits that could be imposed on study inferences and finally (10) a recommendation of the appropriateness of the

epidemiological method to address the question at hand.

I'd like to draw upon both the IRLG Epidemiology Documentation Guidelines and problem-definition approach to highlight several criteria for planning and presenting epidemiologic studies that are intended to support regulatory activity:

- Study hypotheses should be biologically plausible
- Any covariates included in the study design should be biologically plausible
- Studies should be designed to disentangle the effects of other pollutants or risk factors
- Studies should focus on a clearly defined health endpoint and enumerate limitations implicit in the particular data source employed
- Whenever possible, studies should be designed to quantitate the exposure-disease relationship, incorporating all available information into a dose-response framework
- Study designs should in most cases be replicable—the study methods must be completely documented and clearly reported
- Suitable exposed populations and exposure information must exist to ensure the null hypothesis can actually be tested.

Because of such problems, I'd like to discuss these items in greater detail because they are extremely critical to health evaluation and risk estimation in regulatory agencies.

One issue that must be dealt with in research planning is sample size or the statistical power of any given study to detect excess risk. I believe, in many cases in the past, inadequate attention has been paid to statistical power yet regulatory agencies must frequently make decisions on the basis of epidemiological data that can be criticized for looking at two few cases over too short a time. If resources are adequate and several populations are available in which chemical agents may be studied—that is, if choices are available—I believe power should be an important criterion applied in planning studies to meet regulatory research needs and in weighing the merits of undertaking one study versus another.

This is not to say, however, that if statistical criteria cannot be met in a given circumstance that all research should be abandoned. The power of detection of effects, if present, is an important design consideration, but the inability to rule out effects at the low levels characteristic of environmental exposures should not preclude epidemiologic studies. Much information is to be gained from well designed research, even if identification of

safe levels of exposure cannot be accomplished. This is particularly true when the investigations are exploratory in nature with little known about the strength of the risk factors and several populations are available in which chemical agents may be studied—that is, if choices are available. I believe power should be an important criterion applied in planning studies to meet regulatory research needs and in weighing the merits of undertaking one study versus another.

This is not to say, however, that if statistical criteria cannot be met in a given circumstance that all research should be abandoned. The power of detection of effects, if present, is an important design consideration but the inability to rule out effects at the low levels characteristic of environmental exposures should not preclude epidemiologic studies. Much information is to be gained from well designed research even if identification of safe levels of exposure cannot be accomplished. This is particularly true when the investigations are exploratory in nature with little known about the strength of the risk factors of concern. This, I might add, is precisely the problem we are facing with the relatively recent emergence of toxic substances as a public health concern. In addition, the situational nature or problem orientation of studies and budget requirements often put realistic limits on sample size and prohibit the design of studies to detect relative risks close to one. In many cases, a small population is well identified and characterized as to exposure, also an area of concern. Adequately sized groups may either be nonexistent or may lack well defined ties to exposure data which also weakens the conclusions that can be drawn. In such circumstances, the knowledge, especially as to trends and consistency, to be gained from a series of well designed, well controlled studies in small, special populations probably overrides the problem of absolute adherence to sample size criteria.

I raise the issue of power and sample size not solely in the interest of good design and analysis, but to emphasize that regulatory agencies must interpret and evaluate negative as well as positive studies and want to be able to define safe levels of exposure with both statistical and technical confidence. More attention should be devoted to the constraints of statistical power in the future. Perhaps we should also place greater emphasis on two areas: first, on developing innovative approaches to detecting and analyzing the relatively small increases in risk likely to be posed by low-level exposure, and second, on developing biological and biochemical markers or screening tests for human subjects to detect preclinical changes and to pre-

dict and identify high-risk groups. Sole reliance on disease or mortality outcome, with associated problems of latency, is often not fully satisfactory and may not reflect prudent public health policy.

It is desirable for any environmental or occupational health study to assess as thoroughly as possible an individual's exposure experience and to relate this to subsequent health status. Typically, studies are not undertaken until many years after the exposure of interest has occurred either because the factor has just been identified as a potential risk or clinical disease is just becoming apparent after the passage of sufficient latency time. Quantifiable exposure data are usually lacking or difficult to obtain or reconstruct. Efforts frequently must be made to estimate exposure qualitatively.

Yet knowing definitively that exposure occurred and, more importantly, at what level, is of great concern to regulatory agencies. There is absolutely no substitute for knowing exposure and how health outcomes vary as exposure varies. Proposed public health regulations can rise and fall on this question. The importance of the application and development of improved exposure assessment techniques in epidemiologic studies cannot be over-emphasized.

Identification of suitable study populations is an important element in research planning in regulatory agencies. For environmental health research, in certain instances it is apparent that occupational groups present the best and sometimes only available study population for examining risks from various chemical exposures. If no effects are found at relatively high levels, then concerns about exposures at much lower environmental levels may be lessened. It is anticipated that the workplace environment will continue to be a primary target for further studies of reproductive hazards to define the sensitivity of this organ system to various chemical insults and to test specific hypoth-

eses regarding exposures and adverse reproductive outcomes.

One area that comes immediately to mind where a suitable study population is needed is that of diesel health effects. Because of the widespread use of diesel engines one might not expect such difficulty in identifying good study populations. However, it appears very difficult to fulfill the major criteria of a stable, long-term group of sufficient size (probably several thousand) with substantial exposure that can be estimated from current measurements. Also, the issue of confounding workplace exposures, such as asbestos, always arises. Knowledge of the obviously critical variable of smoking habit data is also of concern. Although numerous suggestions have been made, a verified study population of diesel exposed subjects is still elusive.

Other populations that may be useful for determining the health risks posed by exposure to chemicals are: occupational cohorts and their families; consumers of products that may contribute to domestic and other exposures; school children attending schools and other groups proximal to point sources of hazardous chemicals; residents in areas of heavy industrialization; populations residing in the vicinity of waste disposal sites; populations proximal to natural emissions of various compounds, i.e., hydrocarbons or sulfates.

The final point I would like to make concerns health endpoints. As we grow more and more concerned with the potential hazards posed by chemicals in the environment, studies to determine effects on the neurological and reproductive systems assume greater importance. I would like to add that we should not only be concerned with pregnancy outcome or sequelae in offspring born to exposed parents, but we must also address the effects on reproductive capacity, fertility, miscarriages, and abortions in adults.