Epidemiology in the Regulatory Arena

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While epidemiologic evidence and, particularly, results of individual studies is often highly controversial, epidemiologic findings often play a significant role in the development of many environmental standards and regulations. This prominence reflects the direct relevance of epidemiologic evidence to public health, which was a focus for new policy initiatives over the first 5 years of the Clinton administration. Federal environmental statutes state that protection of human health is a major goal in ensuring, for example, clean water, clean air, and responsible management of waste. At times in the past, however, there was less focus on public health and greater reliance on projections of theoretical tools, such as modeling and risk assessment as the basis for selecting among policy options. With the implementation of the Government Performance and Results Act of 1993 (1), a government-wide effort began to identify ways for measuring and tracking outcomes of governmental efforts, including those of the US Environmental Protection Agency (EPA) and other regulatory agencies. At the same time, there is increased appreciation of the relevance of epidemiology in the public policy arena (2). A demand for more surveillance and other epidemiologic data can be anticipated. There are numerous other forces that have pushed regulatory agencies in the direction of relying more on epidemiology. Industry has questioned the applicability of animal toxicology data to human health risk and has wanted human data to be used to validate this practice. Public health advocates have pushed regulatory agencies to look beyond cancer and other diseases that are more readily assessed using animal models to include other diseases (e.g., reproductive, neurologic, and respiratory) where epidemiology studies have indicated there may be additional risks. The National Toxicology Program has recently begun to incorporate more epidemiology information into its cancer assessments for the Report on Carcinogens. Epidemiologists and the findings of epidemiologic studies have probably played a more significant role in environmental regulation in the future.

This presentation offers the perspective of a physician-epidemiologist on the role of epidemiologic evidence in the regulatory arena. It draws on selected examples and experiences of the author as a basis for general considerations on epidemiology and regulation. While the presentation is thus based around a particular era of one administration, it offers more general lessons concerning epidemiology and policy. It is hoped that these perspectives will help to promote a greater understanding of the policy process among epidemiologists, and how their data are likely to be used (and misused). It is also hoped to promote a greater understanding and appreciation of the need to incorporate epidemiology among risk assessors (who predominantly are toxicologists).

ROLE OF EPIDEMIOLOGY IN REGULATION

Epidemiologic evidence has long held a central role in diverse aspects of public health policy and regulation. Data from many well-conducted epidemiologic studies have identified threats to public health and served as the basis for estimating attributable risk, thereby quantifying the significance of those threats. Epidemiologic studies have also raised awareness of public health issues in specific jurisdictional areas. Consider the example of childhood lead poisoning. Initially the focus was on clinically apparent childhood lead poisoning, but as epidemiologic studies showed that lead levels well below clinical toxicity were associated with neurocognitive effects, the focus of prevention shifted towards reduction of higher exposures and the population mean. Success has been confirmed by tracking blood lead levels through national samples (3, 4). While the hazards of lead exposure to children and adults are now well understood and documented in the scientific literature (5–7), lead remains in gasoline and industrial emissions are inadequately controlled in many countries around the world. Local studies of the prevalence of lead poisoning are proving invaluable in persuading governments to take steps, such as removal of lead from gasoline, that have long been known to be beneficial as a result of the experience in the United States and elsewhere. For example, the EPA and the Centers for Disease Control and Prevention (CDC) were recently involved in studies in Russia on lead exposure in children that have played an important role in that country’s decision to take steps to reduce environmental lead. These steps include the reduction of lead emissions from stationary sources and a transition to unleaded gasoline (8).

In regulatory settings, epidemiologic data often figure prominently because these data address “real-world” exposures. Humans live in diverse environments and have diverse genetic makeups; thus, epidemiologic research provides
information on risks across the range of responses to stressors and human susceptibility. This diversity of exposures and susceptibility cannot be mimicked in animal models, and it is, consequently, difficult for regulators to set aside epidemiologic data. For some health outcomes there are also no clear analogues in animal models; for example, what is the animal model equivalent of a learning disability for a 6-year-old child? and certainly a regulator could not dismiss epidemiologic data on an environmental agent and reading ability because an animal model had not been developed. Epidemiologic data remain paramount for understanding variability of response and often critical but subtle endpoints, such as neurologic outcomes. Using the new tools of molecular and cellular biology, we should soon gain a deeper understanding of determinants of variation in response to environmental agents, particularly genetic determinants.

Animal data are an important complement to epidemiologic data; in fact, for many agents we rely largely or even solely upon animal data for making policy decisions. For example, the EPA follows standard modeling procedures and assumptions in analyzing animal carcinogen bioassay data and extrapolating to humans (9, 10). Epidemiologic data can be used to test the assumptions underlying such extrapolations of risks from animals to humans (11). We use relatively crude but now ingrained principles to extrapolate from laboratory tests to human risks. For example, for effects with a threshold, there is a routinely applied assumption of a 10-fold intraspecies variability and a 10-fold interspecies variability (12). For effects considered to follow a no-threshold risk relation (e.g., cancer), the upper 95 percent bound for risk from the dose-response curve is used to account for human variability, thereby conservatively inflating the magnitude of risk (13, 14). These assumptions have not been well validated, but epidemiologic data have been used to assess their appropriateness (11, 15). In cases where there is both dose-response data for animals and humans, for the same (or similar) endpoints, it has been possible to assess the ability of toxicology studies to predict human health impacts. In the case of a number of neurotoxic compounds, for example, it was found that more sensitive measures of neurologic damage (“functional” batteries) and different means of assessing dose (body burdens rather than average daily doses) could increase the ability to predict low level effects in humans (16).

Better understanding of mechanisms of injury should enhance regulation, providing a stronger foundation for using animal data and interpreting epidemiologic data. Federal policies in many agencies (e.g., EPA, National Toxicology Program, and US Food and Drug Administration (FDA)) are moving in the direction of accepting mechanistic information as part of the risk assessment process (17–19) with direct implications for regulation. As mechanistic understanding advances, we will be able to develop a wider array of modeling techniques that incorporate specific mechanisms, and modeling will move away from the use of defaults (19). A more mechanistic approach to modeling epidemiologic data can be anticipated.

Surveillance for disease indicative of risks from exposures has long been an element of disease control using epidemiologic approaches. The historic role of epidemiology in investigating infectious disease outbreaks has evolved to include tracking occurrence of some chronic diseases (e.g., cancer) and investigating outbreaks of illness due to inadvertent exposures to environmental agents. Epidemiologic investigations of outbreaks may identify unregulated risks and help to elucidate dose-response relations and sequelae in human populations. For example, investigation of an unusual pattern of asthma occurrence in Barcelona, Spain, led to the identification of soy beans as a cause of asthma (20). Post-marketing surveillance is a more formal means for tracking consequences of chemicals and pharmaceuticals after they are introduced. Such tracking may identify unanticipated hazards as agents come into widespread use and persons having a range of susceptibility are exposed. For example, during the time I served at the EPA, surveillance reports of outbreaks of cholinesterase inhibitor illness and hospitalizations among farm workers led to EPA action to seek the ban of the pesticide Mevinphos. In 1995, the EPA and the manufacturing company entered into a voluntary agreement to phase it out.

**EPIDEMIOLOGY AND RISK ASSESSMENT**

Risk assessment is increasingly prominent as a tool for integrating epidemiologic evidence into regulatory decision-making. The role of epidemiology in environmental regulation is most prominent and clearly defined in the risk assessment process. “Risk assessment” describes not only the formal scientific paradigm that the EPA and most agencies use for assessing risks, but also the policy framework for regulating risks (21). There are many policy considerations that are weighed in regulating risks, such as the precautionary approach, equity, feasibility, and costs of preventing pollution and citizens’ right-to-know. This discussion focuses on risk assessment in the scientific context and how it is used within the existing framework of US environmental laws.

The four elements of a formal risk assessment process are hazard identification, dose-response assessment, exposure assessment, and risk characterization, the last bridging to risk managers (agency staff who carry out regulatory assessments) and decision-makers (who are career managers or political appointees) (22). While this paradigm was never intended to build a wall between scientists and decision-makers, to an extent a gulf has developed (23). Scientists may be concerned about the use of their findings and the influence of decision-makers on research. Decision-makers are at times uncomfortable with the complexity and ambiguity of scientific evidence and frustrated by a seeming inability of scientists to provide sufficiently certain and appropriately framed evidence for policy decisions. A recent review by the National Academy of Sciences concluded that better decisions would flow from earlier and more extensive interactions between decision-makers and scientists (23). Epidemiologic data most often come into play in the hazard identification and exposure assessment components of risk assessment and, in some instances (e.g., lead) also in dose-response assessment.
Hazard identification

Hazard identification includes examination of all available data on toxicity, weighing the evidence as to the existence of a causal effect between agent and adverse effects (24). There are numerous sources of data relevant to hazard identification. For human health effects, the sources range from descriptive studies and case reports to controlled studies. The use of epidemiologic studies in risk assessment has recently been reviewed (25). Toxicologic data are typically far more abundant than epidemiologic data.

All of these data are relevant to hazard identification. Even case reports can be critical. In fact, many environmental hazards were initially identified by clinicians who saw patients coming from highly exposed or more susceptible populations, as with diethylstilbestrol and adenocarcinoma of the vagina (26) and vinyl chloride and angiosarcoma of the liver (27). The case of Mevinphos illustrates the public health value of physician reporting of pesticide illnesses (which is required in only a handful of states, including Washington, California, Arizona, and Florida). Another example is the recent use of a poison-control system data-collection system to look at patterns of pesticide poisoning in children. The researchers found that exposures to pesticide products are most likely to be reported among children less than 2 years of age, and that (not surprisingly) the most toxic pesticides were responsible for the most serious illnesses. These data can help inform policies about registrations of pesticide products and child resistant packaging (28). Approaches are needed for more systematically using the hazard surveillance potentially afforded by clinical contacts (29). Ecologic information may also be informative for human hazard identification as ecologic effects may serve as sentinels for human effects. For example, concern has been raised about environmental endocrine disruption, based in part on observations in wildlife (30). Although many environmental scientists (including epidemiologists) are uncomfortable with extrapolating from ecologic data to human risks in the absence of epidemiology data, we obviously have learned how to utilize laboratory animal studies and need to better utilize ecologic studies, which may be more relevant given that they reflect exposures that actually occur in the environment.

Exposure and dose-response assessment

Epidemiologic data are also relevant to exposure assessment and to characterizing the dose-response relation. Several dimensions of exposure are relevant to risk assessment (31, 32). Exposure assessment, while now partially separated from environmental epidemiology in a companion discipline, is a component of many epidemiologic studies directed at environmental agents. Epidemiologic studies often provide some description of the exposures of participants but not usually with extensive detail. Epidemiologic data may be refined for risk assessment purposes by using nested approaches that supply more detail for some participants and also by using biomarkers of exposure and dose. Often, the circumstances of epidemiologic research mandate use of exposure or dose surrogates, with the attendant consequence of misclassification. Data at an ecologic level may also be used rather than data at an individual level.

The use of epidemiology for dose-response assessment can be critical to the assessment of environmental standards. Recently, the EPA and the FDA found themselves in conflict over the appropriate regulatory standard for methylmercury. In the early 1980s, both agencies had utilized studies in Iraq that documented severe neurotoxicity among people who inadvertently ate methylmercury contaminated seed grain. Since there were no baseline data and exposures were determined retrospectively, there were large uncertainties in the exposure assessment. Moreover, there were uncertainties in extrapolating from presumably higher acute exposure levels to the levels that might be present in the US population on a chronic basis. To resolve the issue, the federal government supported two major prospective epidemiology studies of mercury poisoning and child neurologic development, both in island nations where much of the population eats significant quantities of fish that contain methylmercury (33, 34). One study, conducted in the Seychelles Islands, was a null study that tended to support the FDA’s higher standard, and the other, conducted in the Faroe Islands, showed small but significant neurodevelopmental effects that persisted into school age. A consensus process was conducted by the National Research Council (NRC) to develop a dose-response assessment, taking into account all of the available epidemiology and toxicology information on methylmercury (35). (Although the conclusion of the committee supported EPA’s risk assessment, it was on the basis not of the Iraqi study but the more recent Seychelles study.) As this case demonstrates, modern epidemiologic studies can indeed inform regulators about dose-response and assist in the development of public health standards. It also illustrates the difficulty and complexity of analyzing and interpreting epidemiologic data and that, at this time, the use of outside consensus processes is often critical to the understanding of epideiologic data by regulatory agencies. However, it is too soon to know whether the NRC report will resolve the interagency conflict. The FDA has not yet announced whether it will change its assessment.

A more current example that illustrates how difficult it can be to use epidemiology for dose-response assessment in the regulatory arena is the EPA’s struggle to develop an arsenic standard for drinking water. The EPA worked for a number of years to propose and issue a final standard in 2000, which would have lowered the allowable level of arsenic in drinking water from 50 to 10 ppm. Historically, a number of studies had indicated that arsenic could cause skin cancer by dermal routes and lung cancers by inhalation, but it was thought that oral ingestion might be “safe” because of conversion to less toxic forms in the liver prior to exposures (36). In 1992, evidence from well conducted epidemiologic studies began to support the notion that people who have higher levels of natural arsenic in drinking water have higher rates of cancer of the liver, lung, kidney, and bladder (37). As the evidence mounted, the EPA went to the NRC for advice, and the conclusion of the NRC was in essence to lower the standard (38). Yet, in 2001, the EPA
and waste management. While the costs of environmental health benefits that we receive from clean air, clean water, Overall, the expenditure seems small—a bargain—given the taxes or user fees and the rest via the private sector (43).

percent of these expenditures have been supported through without substantial error. Together, inadequate sample size and exposure misclassification tend to blunt the description of dose-response relations, sometimes resulting in too much imprecision for risk assessment purposes. Epidemiologic analyses of dose-response may also not adequately respond to the needs of risk assessment. Nonetheless, many informative analyses of dose-response have been reported from epidemiologic research—ionizing radiation and asbestos, for example (39–41).

EPIDEMIOLOGY AND ECONOMIC ANALYSIS

Risk assessment is only one component of a comprehensive risk management framework (42). Economic analysis for costs, benefits, and effectiveness also figure in decision-making. Unlike regulatory toxicologists, few epidemiologists have any understanding at all of the legal, policy, and technical framework for economic analysis of regulatory decision-making. Yet, epidemiologic characterizations of risk play a significant role in economic analyses, which, among other purposes, guide the allocation of resources into the many competing areas. If epidemiology is to play a more important role in policy, epidemiologists need to be more informed about this framework and, in particular, of how their data eventually may be incorporated into economic analyses.

It is helpful for epidemiologists to understand why economics has come to play such a major role in decision-making. One reason is the cost of regulation to society and to industry. The regulated community and states have pushed economic policies as a way of trying to make regulation less costly to them. According to a survey by the US Department of Commerce’s Bureau of Economic Analysis, the United States allocated about $123 billion in 1994 for environmental protection as follows: about $35 billion for control of air pollutants sources, $14 billion for sewers, $27 billion for waste water treatment, $41 billion for solid waste, and relatively little, about $2 billion, for research and development (43, 44).

These are substantial expenditures that contribute to maintaining environmental quality and improving public health and quality of life. The cost in 1994 to the United States was about $470 per person per year (45). About 40 percent of these expenditures have been supported through taxes or user fees and the rest via the private sector (43).

Overall, the expenditure seems small—a bargain—given the health benefits that we receive from clean air, clean water, and waste management. While the costs of environmental regulation are widely discussed, they are modest in comparison with the costs of medical care, for example. Nonetheless, costs and economic impacts of new regulations need examination. Even relatively small overall costs (and benefits) can fall unequally on the population, creating unacceptably high compliance (or disease) burdens.

President Clinton’s Executive Order 12866 on regulatory planning and review (46) provided direction to the federal government on steps that should be taken to examine economic impacts of proposed regulations. Such a review process has been in place in the Federal Government since the Carter administration. Executive Order 12866 directs agencies to assess all, both quantifiable and non-quantifiable, costs and benefits from a regulation. This broad mandate extends to the many human health effects that are quite difficult to quantify and to consider in monetary terms. For example, how are subtle neurotoxic effects to be quantified? How can associated costs be estimated? In choosing among alternative risk management approaches, agencies seek to maximize the net benefits, and to take into account economic, environmental, public health and safety, and other benefits as well as the impact on distribution and equity within society. So not only total costs and benefits, but also concerns of fairness are to be considered. Executive Order 12866 requires this analysis unless a statute requires another regulatory approach.

How can epidemiologic evidence contribute? Primarily by providing quantitative and qualitative information about health benefits. Data on exposures and risks can be used to calculate disease burden under scenarios of exposure and mitigation. For example, the EPA recently proposed standards that identify dangerous levels of lead in soil and dust (47). Required by the Toxic Substances Control Act, the economic analysis for those standards evaluated alternative levels for lead in soil and dust, requiring substantial effort by epidemiologists and other scientists (48) and peer review by the EPA’s Science Advisory Board (49). In the end, this economic analysis was only one of the supporting documents to meet regulatory requirements under the Executive Order. Epidemiology data also have been important in regulatory decision-making where not required by law. For example, under the Clean Air Act decisions on priority air pollutants are to be made solely on the basis of public health. At the same time, under Executive Order 12866, the EPA is required to do economic analyses and the Office of Management and Budget and industry are very concerned about the additional costs of such regulations. In 1998, when the EPA proposed stricter standards for ozone and PM$_{1.5}$ (fine particulate matter) in air, epidemiology studies formed much of the basis for the EPA’s conclusion that the benefits would justify the costs. Samet (2) has documented the manner in which these studies thereby became the focus of controversy and the processes that ensued as a result. More recently, the epidemiology studies on arsenic and cancer were used to compare the costs of lowering the EPA arsenic standard for drinking water with the number of cancers that might be prevented (50). Although the assessment indicated that the costs were commensurate with the benefits, there were remaining concerns about the inequities of the distribution of the costs, since many of them will be borne by...
small water systems, as well as the strength of the epidemiology data as described elsewhere in this presentation.

The issue of discounting of the value of life is very interesting. Economists use discounting to assure that investments in government expenditures will yield the same rate of return as financial investments. Given that capital investments depreciate over time (i.e., the computer on which this paper is written will be worth very little in 3 years), they also use discounting to estimate the future value of purchases that are made today. Most of us would be surprised to learn that on our birthday, according to economists, our lives are worth 3–12 percent less! Yet economists do indeed assume such an annual (and linear) decrease in value of a life for each day. This is a serious issue in that techniques for discounting that are applicable to financial decisions may not make sense when applied to human lives and nonrenewable resources. Children are of particular concern, and they have a greater potential for years of life lost as well as for long-term disability or impaired productivity. Yet, as a society, we very willingly invest a lot of money to keep older people alive, since we cannot ignore opportunities to prevent morbidity and premature mortality in either older citizens or in the young. No financial advisor would ever recommend purchase of college bonds for our great-great grandchildren; yet, would be irrational to fail to take actions to assure the survival of future generations.

As applied to a nonrenewable resource, discounting can also have irrational consequences. For example, compared with a renewable resource such as a computer, the Chesapeake Bay is not going to become obsolete in 3 to 5 years and it is not replaceable. The Bay will continue to have value to our children, to our grandchildren, and to future generations, in terms of their health. They will want it to provide seafood (hopefully free of hazardous levels of chemicals and pathogens), recreational opportunities, and aesthetic values, all of which contribute to health. So is it really rational in environmental decision-making to discount the value of the Chesapeake Bay every year?

CRITIQUES OF USE OF EPIDEMIOLOGY IN RISK ASSESSMENT

Epidemiologic data figuring prominently in regulatory decision-making are likely to be closely scrutinized and publicly criticized by parties who may be affected by regulation. Observational data have inherent limitations, well recognized by epidemiologists; these limitations are often targeted both generically and specifically. Epidemiologists carrying out research are, of course, fully aware of the potential for bias and confounding to produce possibly invalid associations. They strive to address these potential limitations through rigorous design, data collection, and analysis. Too facilely, however, critics may aggressively dismiss epidemiologic evidence, citing every potential flaw, even if irrelevant. One recent example of this approach can be seen in an op-ed piece that appeared in a national publication (51). The issues of concern cited in the op-ed piece and the corresponding criticisms are listed in Table 1. The particular pollutant and environmental problem to which the authors of the op-ed piece refer in their criticism have been replaced with blanks in Table 1 to illustrate that the concerns are expressed so broadly that they could apply to any number of pollutants and environmental problems in any number of epidemiologic studies. In the op-ed piece, the authors went on to quote from Science: “Many epidemiologists concede that their studies are so plagued with biases, uncertainties and methodological weaknesses that they may be inherently incapable of accurately discerning such weak associations” (52, p. 164). Although this critique of epidemiology has been extensively (and effectively) rebutted within the community of epidemiologists, scientists outside the epidemiology profession remain skeptical and, in my experience, many believe that results can be manufactured in epidemiology studies via manipulation of statistics.

This general, and sometimes unthinking, approach to criticizing epidemiologic data is all too prevalent. Such criticisms, even if ungrounded, are readily made and sometimes difficult to refute. We need criteria and even principles of practice for evaluating data. Critics need to go beyond generalities, approaching the issue of whether bias or confounding has led to findings that are misleading policymakers. It is all too easy to invoke uncontrolled confounding, but the critic should be called on for more—the potential confounders and the associated error in estimation. At times, critics have invoked long lists of confounders without any consideration as to the requirements for confounding in the data of interest. In fact, critics sometimes raise the possibility of confounding for agents for which there is little evidence of association (or at best a weak association) with the outcome.

Similarly, critics turn equally to possible errors in exposure measures. They often imply that exposure measurement error led to an exaggeration of the association between exposure and outcome. However, particularly in studies of environmental agents, exposure misclassification tends to be random, reducing apparent effects. This blunting of the sensitivity of epidemiologic studies is not sufficiently appreciated for its implications in policy-making. Epidemiologic data may also be set aside because of a stated lack of understanding of biologic mechanisms. The tobacco industry, for example, advanced this argument for decades against the evidence on smoking and health. Of course, there are no criteria for gauging that biologic understanding has been achieved, and scientific inquiry pursues mechanistic understanding to ever deeper levels.

Epidemiologic research findings have also been impugned if the effect estimate is low, perhaps a relative risk below 2 or 3. Associations of this magnitude have been labeled as “weak” and in a range where epidemiologic data should be considered suspect or dismissed. Of course, smaller associations may be more likely to reflect bias or confounding, but this tendency is not a basis for summarily dismissing findings of “weak associations.” The magnitude of effect should parallel the magnitude of exposure. Strong exposures (e.g., active smoking) would be expected to have greater effects than lesser exposures (e.g., passive smoking). In fact, bias may be a consideration if the magnitude of effect seems too large, given the exposure (e.g., passive smoking and coronary heart disease).
reduced (55). The rapid fall-off in mortality from Reye’s syndrome once warnings had occurred is demonstrated in figure 1 (58). The consequence of delay is that there may well have been unnecessary deaths due to Reye’s syndrome.

In other cases, epidemiologic data are likely to be ignored for a longer time. In the case of aspirin/Reye’s syndrome, eliminating the uses of aspirin by young children made an impact in sales of aspirin but did not remove from medical practice an essential pharmaceutical agent. Given that the legal framework for the regulation of over the counter pharmaceutical agents is health-based, it was relatively easy for the FDA to decide to remove a potentially harmful product, which provided little benefit to patients. Contrast this with the current situation with regulation of arsenic in drinking water. Although the epidemiologic evidence is also strong and consistent, the regulatory framework is not a purely health-based framework. Under the Safe Drinking Water Act, the EPA is to establish a “goal” for a standard for any carcinogen of zero. However, the actual standard must take into account “feasibility,” which in practice means technical challenges, like the expense to small drinking water purveyors of removing arsenic (which naturally occurs in many water supplies). At this time, the consequence of the delay in lowering the EPA arsenic standard is unknown, and it will be more difficult to calculate given that cancer develops over a lifetime and that there is no disease (like Reye’s syndrome) that uniquely is associated with arsenic exposure. Similarly, in the case of methylmercury, it is difficult to calculate how much damage to the learning abilities of the next generation of children has resulted from the debates over the mercury risk standard (and the consequent delay on the part of the EPA and FDA to regulate significant sources of exposure to children).

### CONSEQUENCES OF IGNORING EPIDEMIOLOGIC DATA

How does a regulator determine when a situation justifies action? Criteria for causation certainly plays a role. However, in truth, there are no “bright lines.” Although you probably always need strength and consistency of associations, there are times when actions are warranted even when there are no data to examine biologic plausibility. Failing to follow warnings from epidemiologic data may have adverse consequences for the public’s health. Consider the example of aspirin and Reye’s syndrome, a highly severe childhood disease that is now very rare. Multiple epidemiologic studies had identified aspirin dosing, as well as varicella and influenza infections, in very young children as risk factors for Reye’s syndrome (53, 54). With no established mechanism for the disease and lacking animal data, however, the pharmaceutical industry fought restrictions on aspirin dosage for young children until the early 1980s. Figure 1 illustrates the consequence of the decision to finally require labeling of aspirin, showing mortality data reported between 1974 and 1989 in a CDC surveillance program for Reye’s syndrome. Children died from Reye’s syndrome at a relatively constant rate until the early 1980s.

In 1980, the CDC began to issue warnings about a possible link between aspirin and Reye’s syndrome in young children (55). Both the US Surgeon General and the American Academy of Pediatrics issued formal advisories in 1982 (56, 57). In 1986, manufactures were required to label aspirin to warn against giving the medicine to young children, but by that time use of aspirin in young children had been sharply reduced (55). The rapid fall-off in mortality from Reye’s syndrome once warnings had occurred is demonstrated in figure 1 (58). The consequence of delay is that there may well have been unnecessary deaths due to Reye’s syndrome.

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### TABLE 1. Examples of broad criticisms of epidemiology, with blanks replacing terms that are interchangeable depending upon the environmental pollutant studied*

<table>
<thead>
<tr>
<th>Issue</th>
<th>Criticism (51)</th>
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<tbody>
<tr>
<td>Ecologic fallacy</td>
<td>“The study suffers from a basic epidemiologic problem known as the ecologic fallacy. This simply means that although the most polluted communities may indeed have a ___ percent higher ___ rate than the least polluted areas, this coincidence does not by itself demonstrate a cause and effect relation between ___ and ___.”</td>
</tr>
<tr>
<td>Environmental measures</td>
<td>“The researchers did not measure how much ___ even one study subject was exposed to. Instead, they guess how much ___ these individuals might have encountered.”</td>
</tr>
<tr>
<td>Confounding</td>
<td>“Study subjects undoubtedly differ in many behavioral, occupational, environmental, and genetic factors that were inadequately considered by the epidemiologist. Any one of these factors, or combination thereof, could explain the difference in rates.”</td>
</tr>
<tr>
<td>Plausibility</td>
<td>“A further problem that should make us skeptical of the epidemiologic study’s findings. It turns out that nobody has demonstrated how ___ could cause higher ___ rates.”</td>
</tr>
<tr>
<td>Statistical association vs. causality</td>
<td>“The reported increase in risk is only an artifact of statistics called a statistical association. It is not scientific proof that ___ causes ___.”</td>
</tr>
<tr>
<td>Weak associations</td>
<td>“Among epidemiologists, statistical associations that purport to represent increases of risk less than 100% are considered to be weak associations.”</td>
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* Blanks added by author to replace selected words.
CONCLUSION

Obviously, epidemiology has and will continue to have an important role in environmental regulation, both in assessment of risks and in economic analysis. However, there are several challenges that need to be addressed in order to realize the full potential of epidemiologic data in this arena. As suggested by this presentation, it is important to establish a high standard for evaluation of epidemiologic studies. One effort to do so, organized by Federal Focus in 1995, was a useful starting point for such efforts (59). Federal Focus convened a panel of 18 experts in London, England, to develop principles for evaluating epidemiologic studies for causal associations and using epidemiologic data in regulatory risk assessment. These are referred to as the “London Principles” (59). More recently, the World Health Organization has issued a set of helpful guidelines for evaluation of epidemiologic evidence for health hazard characterization (60).

Establishment of standards is not helpful unless there are people on the receiving end who understand how to apply them. Regulatory agencies require greater access to scientific expertise for the evaluation of epidemiologic evidence, so that they can better integrate it into the risk assessment process. Lack of these capabilities has serious public health implications if decisions are bogged down in consultation and delay. Just as some 20 years ago there was a revolution in toxicology, and a large infusion of toxicology expertise into regulatory agencies, so we now need such an infusion of epidemiology expertise. During my time at the EPA, I was often reminded of how few epidemiologists were available in the agency for review of epidemiologic studies. However, with the benefit of modern epidemiologic approaches, regulatory agencies can no longer rely primarily on toxicologists for assessment of human health risks.

A demand for more epidemiology in regulatory agencies will not be easy to fulfill. We have begun to see an emphasis on training epidemiologists in the application of epidemiology to hazard identification and dose-response assessment. Even so, I believe, based on my observations of how difficult recruitment is at regulatory agencies, that the demand is greater than the supply. One option to consider is to develop programs to train students specifically in regulatory epidemiology. Although this would seem to be a radical suggestion, this has occurred in the field of toxicology and is the reason regulatory agencies and industry can recruit and hire toxicologists to do risk assessments. At present it is clear that the vast majority of epidemiology graduates want to actually perform epidemiologic studies and are not interested in jobs that involve reviews of the studies of others. Another option is to provide (or require) more epidemiology and biostatistics training of regulatory toxicologists.

Hopefully, the day will come when regulatory agencies will be as familiar (and comfortable) with the use of epidemiology information as with toxicology information. However, the possibility of complete comfort with epidemiologic data probably will continue to be elusive. Fundamentally, evidence of direct human impacts will always be more compelling than other data—to decision-makers and to the general public. Given this fact, epidemiology in the regulatory arena will continue to be both highly charged emotionally as well as a lightning rod for critics of regulation.

REFERENCES

4. Blood lead levels in young children—United States and