Contrasting Roles of Epidemiology in Dioxin-related Policy: Lessons Learned

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Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)) and related congeners (polychlorinated dibenzo-p-dioxins, referred to generally as dioxins) are among the most widely known and perhaps feared environmental contaminants. The laboratory findings of extreme potency of dioxin as a carcinogen and its documented widespread presence in the environment have raised concern that it contributes to the population’s burden of cancer. As understanding of dioxin’s interactions with cells has grown, the list of possible health effects has expanded (1). Risks of dioxin exposure have been presented to the public in dramatic ways—its potency as a carcinogen, the evacuation of Times Beach, Missouri, and the exposure of the military in Vietnam to dioxin-contaminated defoliants—and it has become one of the most feared environmental carcinogens as a result.

The resulting need to characterize the risks of dioxin for risk management purposes has challenged laboratory scientists and epidemiologists. Following the observation that dioxin is extremely potent in animal bioassays, researchers turned to finding the mechanism for its action. Dioxin is now thought to be toxic through its interaction with the aryl hydrocarbon (Ah) receptor, raising the possibility that it may increase risk for cancers of multiple sites and for other diseases through this mechanism (2). Complementary support for dioxin as a human carcinogen has been sought using epidemiologic approaches with two broad purposes: 1) validating the animal findings for carcinogenicity; and 2) quantifying the exposure-response relation. Human data on quantitative cancer risk have been needed to address the uncertainty inherent in using exposure-response estimates from animal studies in quantitative risk assessment.

The epidemiologic evidence has been considered in several distinct policy-making settings in the United States and elsewhere. This case study focuses on two: the use of epidemiologic evidence in quantitative risk assessment and its use in identifying conditions for compensation among veterans exposed to herbicides in the Vietnam conflict. The limited role played by epidemiologic findings in the fashioning of current regulatory and public health policies contrasts sharply with the approach for compensation of Vietnam veterans for adverse health effects associated with their exposures to the dioxin-containing herbicide Agent Orange. For this exposure, the committees formed by the Institute of Medicine, National Academy of Sciences to assess the scientific evidence on Agent Orange chose to focus on the epidemiologic data, as they were mandated to determine if associations could be found with adverse outcomes (3).

EVOLUTION OF THE EPIDEMIOLOGIC EVIDENCE AND ASSESSMENTS OF RISK

The decades-long story of concern about dioxin exposure and associated health effects began with the 1949 Nitro, West Virginia, industrial accident in which a process reactor overheated and released trichlorophenol and contaminants into the building housing the process. Over the next 8 months, some workers who cleaned up the building or were present during the accident developed acute health effects including chloracne. At the time, these effects could not be linked to specific substance(s) in the trichlorophenol manufacturing process. Following other case reports and clinical observations of chloracne and organ system effects (e.g., liver toxicity) (4–7), these acute toxic responses in chlorophenol and phenoxy herbicide workers became the hallmark of human response to the compounds later identified as dioxins. These early observations prompted a concerted effort towards improved work practices to avoid worker exposure, and also led to scientific inquiry into the nature of the toxic agent associated with these processes and products.

The concern over dioxin and cancer did not arise until a 1978 publication from the laboratories of the Dow Chemical Company showing not only that 2,3,7,8-TCDD was carcinogenic in animals, but that it produced its effects at doses far smaller than those found to be carcinogenic for other agents (8). In fact, based solely on the criterion of the magnitude of the minimally effective carcinogenic dose, 2,3,7,8-TCDD remains the most potent known animal carcinogen yet identified. The Dow findings were later supported by 1982 results from the National Toxicology Program (9, 10),
although differences in risk were noted across species, strain, and tumor site.

The earliest epidemiologic studies from the 1970s addressed concerns for occupationally-exposed populations, primarily chemical industry workers and herbicide mixers/applicators. A case report of three soft-tissue sarcomas among phenoxy herbicide workers was followed by a case-control study on soft-tissue sarcomas in Sweden conducted in 1978 which showed a sixfold excess increase in risk among workers exposed to phenoxy herbicides or chlorophenols (11, 12). By that time, dioxin was recognized as a contaminant of phenoxy herbicides and chlorophenols, and because of the prior findings of the Dow cancer study (8), the authors speculated that dioxins could be the cause of the excess, although the animal bioassays on 2,3,7,8-TCDD did not offer directly parallel findings. Despite the initial research focus on animal toxicology and an inadequate epidemiologic database, federal agencies in the United States soon began to implement policies to prevent high-level exposure. For instance, the Department of Defense moved away from its use of phenoxy herbicides (Agent Orange), and the US Environmental Protection Agency (EPA) canceled uses of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in 1983 because of dioxin concerns.

Over the next 20 years there have been additional occupaional studies, using either case-control approaches in the population or follow-up of specific cohorts. Together, the results of the animal studies and the Swedish study (12) convinced Dow and Monsanto Company to examine cancer rates among workers exposed to trichlorophenol releases (13, 14). These studies, both involving workers at levels sufficient to have caused chloracne, found no overall cancer excess. The cohorts were small, 61 for the Dow cohort and 121 for the Monsanto cohort. Each included a case of soft-tissue cancer, making rates of soft-tissue sarcoma greater than expected (15, 16). The authors offered the potential for misdiagnosis of soft-tissue sarcoma as a barrier to a causal interpretation of the findings. Larger cohort studies were soon implemented for these and other chemical industry workers as well as of herbicide sprayers.

Subsequently, in an attempt to address the limitation of power affecting interpretation of findings from the individual cohorts, both the US National Institute for Occupational Safety and Health (NIOSH) and the International Agency for Research on Cancer assembled larger cohorts from multiple sites for chemical workers and workers involved in production or spraying of phenoxy herbicides and chlorophenols, respectively. The NIOSH Dioxin Registry was established in the 1980s, and results of follow-up were reported in 1991 by Fingerhut et al. (17) and in 1999 by Steenland et al. (18). The NIOSH study showed significant increases in mortality from soft-tissue sarcoma, respiratory cancers, and all cancers combined among the subcohort with at least 1 year of exposure and a minimum of 20 years of latency. The International Agency for Research on Cancer study involved over 18,000 persons in 20 cohorts in 10 different countries (19). It showed a sixfold significant excess of soft-tissue sarcomas for those with a latency of 10-19 years from first exposure. Among sprayers in particular, the excess was ninefold for the same latency period.

Further epidemiologic data have come from persons exposed by an accidental release of dioxin in Seveso, Italy, in 1976. A formal epidemiologic study of this accident was initiated in 1980 (20) with follow-up addressing cancers (21) and birth defects (22). While birth defects were not significantly associated with dioxin, several causes of death were significantly increased among residents of contaminated areas (i.e., female biliary cancer, brain cancer, and lymphatic and hemopoietic neoplasms). The results were exploratory in nature, however, with multiple outcomes and small numbers of cause-specific deaths. Nonetheless, the Seveso accident and the subsequent study expanded concern about dioxin exposure from the workplace into the community. Because the Seveso release occurred at a time when methods were available for community studies, data needed for a prospective epidemiologic study and biologic materials were collected, environmental monitoring was implemented, and birth outcomes and cancer incidence were tracked. This accident is particularly informative because exposure was widespread. Follow-up of industrial accidents, such as those in Nitro and Seveso, provided an expectation that human evidence from the population might be available for comparison with the toxicologic findings implying high levels of risk.

In the 1980s, work continued on dioxin characterization. Data on sources, fate and transport, exposure, and human body burdens began to suggest the ubiquity of these compounds and to improve understanding of sources. Additional members of the same chemical class (with similar mechanisms of actions) were identified and characterized using a toxicity equivalence concept. About this time, results from the Dow study were used by the EPA, the US Food and Drug Administration, and the Centers for Disease Control and Prevention to develop cancer potency factors, or upper bounds on lifetime risks per unit of dose. Risk estimates derived from the application of these potency factors to specific exposure situations were used to justify various federal regulatory actions and to provide guidance to State agencies (23). Taking regulatory actions based solely on animal evidence had become, by this time, well accepted, so that the lack of substantial and conclusive epidemiologic data was not a barrier to policy formation.

Even if epidemiologic data are inadequate to serve as the basis for regulation, they can offer a point of validation for risk extrapolations made on the basis of animal studies. The early epidemiologic findings were seen by some, however, as not supporting extrapolation of the animal data. The argument was advanced that if dioxin were as potent in humans as in animals, its effects would be detectable in epidemiologic studies (24). This argument was countered by others with the lack of statistical power of epidemiologic studies involving populations exposed at low doses and having high background cancer incidence rates (24). When analyses of cancer mortality from occupational cohorts and from veterans’ studies failed to reveal a consistent epidemiologic association, dioxin cancer potency estimates were challenged on this basis, in spite of the limitations of the epidemiologic studies.

Nonetheless, both regulatory initiatives and voluntary industry actions reflected the public health concern raised by

the expanding toxicologic database for both cancer and non-cancer health effects of dioxin. Both process and product changes to limit dioxin exposures illustrate this point, as with the paper industry which generates dioxin as a by-product of chlorination. Over time, there was a clear expansion of the populations of concern, beyond occupationally exposed workers, to the general population. There was also a gradual shift in concerns from herbicide exposures in general to exposures to dioxin and related compounds (23, 24).

In using the animal findings for risk assessment and management, another key issue was the form of the exposure-response relation for cancer, and particularly whether a threshold should or should not be assumed. Because the compound appeared to have no gene-damaging potential, many argued that it was "only a promoter" and that its risks should not be estimated under a linear "no-threshold" model, as routinely assumed by the EPA and US Food and Drug Administration. Regulatory authorities in several European countries adopted threshold models and assigned Tolerable Daily Intake values for dioxin based on application of various safety factors (in the range of 100–1,000) to data from the Dow study. The resulting Tolerable Daily Intake values varied from 1 to 10 pg/kg/day (23, 25).

Since the 1980s there has been a substantial increase in the extent of information on dioxin's health effects. During the 1990s, multicenter epidemiologic studies of dioxin-exposed populations were reported with more cases, adequate latency, and quantitative exposure assessment that suggested an association between dioxin exposure and certain types of cancer. Findings were reported from four studies that pooled worker groups from multiple plants where there was a potential for high dioxin exposure (19, 26–28). The 1991 study by Fingerhut et al. (26), using the NIOSH Dioxin Registry, was the first of the four to report findings. This first study found excess rates of lung cancer and soft-tissue sarcoma among workers with potential exposure to dioxins lasting more than 1 year and after 20 or more years had elapsed since first exposure. This study provided new evidence that dioxin may be a human carcinogen. The 1996 study by Ott and Zober (29) of workers in the 1953 trichlorophenol processing accident in Germany was the first to include biologic measurements of exposure, using blood lipid levels of 2,3,7,8-TCDD from survivors to estimate exposures of dioxin for all members of the cohort. Rates of cancers among smokers were found to increase with increasing dioxin exposure.

Newer population exposure studies provide an indication of the magnitude of the difference in dioxin body burdens between the occupational cohorts and the population at large. Findings have been reported on dioxin body burdens in the general population and on the toxicity of other chlorinated dioxins, chlorinated furans, and polychlorinated biphenyls relative to that of 2,3,7,8-TCDD. The body burdens measured in the general population were 10–100 times below those in the populations included in the epidemiologic studies, introducing uncertainty in extrapolating the results of the studies (24). Concerns were also raised about other adverse health effects of dioxin, some coming from the growing epidemiologic database as well as from mounting experimental data. As understanding of the interaction of dioxin with cells advanced, the unifying hypothesis was proposed that all of dioxin's adverse effects result from the same underlying mechanism of action (30).

The experimental evidence prompted regulatory actions and necessitated the conduct of supporting risk assessments. Since 1991, the EPA has been conducting an extensive assessment of the human health risks of exposure to 2,3,7,8-TCDD and related compounds. The resulting multi-volume work is not yet in its final form, but has been subjected to several reviews by the EPA's Science Advisory Board (24, 31); a revised draft was released in September 2000 (32), and it has now been the subject of further review by the Science Advisory Board. The carcinogenicity data on dioxin have also been reviewed by a working group convened by the International Agency for Research on Cancer (33), which characterized dioxin as a "known" human carcinogen. In addition, the US Department of Health and Human Services, in their "Report on Carcinogens," has recently listed 2,3,7,8-TCDD as a "known" carcinogen based on its criteria (34). In these three reviews, epidemiologic studies were cited as contributing to our current understanding of the carcinogenicity of dioxins.

To date, however, the epidemiologic findings have not led to new regulatory and public health policies for control of dioxin exposures, although technologic controls on dioxin emissions continue to be proposed, and a comprehensive health-based regulatory strategy is contemplated (24, 31). While uncertainties are seen as limiting the utility of the epidemiologic findings for assessing dioxin's risks to the general population, the EPA's latest draft risk assessment (32) found risk estimates from epidemiologic studies to be not much different from estimates based on animal studies used since 1985. Quantitative dose-response data from the epidemiology database were used to make these estimates, and this may signal an increased, perhaps dominant, role for epidemiology data in future regulatory policy.

There is now a substantial clinical and epidemiologic literature on persons exposed to phenoxy herbicides and dioxins. The epidemiologic data evaluated for veterans of Vietnam are reviewed below in connection with the issue of veterans' compensation.

**VIETNAM VETERANS AND AGENT ORANGE**

The first large-scale human exposure to dioxin-contaminated herbicides occurred during the Vietnam War, where 19 million gallons of Agent Orange, a 50-50 mix of 2,4,5-T and 2,4-dichlorophenoxyacetic acid, were sprayed to defoliate forested areas in South Vietnam. The spraying campaign began in 1962 and reached its peak from 1967 to 1969. In 1969, a scientific report raised concerns about herbicide-induced birth defects in laboratory animals. Largely as a result of these concerns, use of 2,4,5-T was suspended in 1970, and all spraying was suspended in 1971 (35).

Concerns over health effects from herbicide exposure among Vietnam veterans persisted, however, and fueled the political debate over compensation for illnesses among veterans. Epidemiologic studies were initiated by the Centers
for Disease Control and Prevention, the US Department of Veterans Affairs (VA), and the US Air Force to evaluate the risks of adverse health effects, including cancer, from veterans’ exposure to herbicides. Legislation was passed to define the procedures by which service-related disability compensation would be determined for veterans.

In 1991, additional legislation was promulgated to provide for an independent assessment of the potential health risks posed by exposure to Agent Orange and other herbicides used in the war (35). The Agent Orange Act of 1991 directed the VA to enter into an agreement with the National Academy of Sciences to establish a committee to review the scientific literature related to health effects of these herbicides. This would be followed by five subsequent update reports at 2-year intervals. The Academy’s specific mandate was to determine, if possible (36):

1. Where there is a statistical association between the suspect disease and herbicide use, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association;
2. The increased risk of disease among individuals exposed to herbicides during service in Vietnam; and Whether there is a plausible biologic mechanism or other evidence of a causal relation between herbicide exposure and disease.

The committee, formed under the Institute of Medicine, chose to rely primarily on published epidemiologic studies in its deliberations, acknowledging the large amount of toxicologic and other data on herbicides and the contaminant dioxin. The committee released its report in 1994 (36), and the VA used this information to modify its compensation criteria for certain diseases. The report identified five conditions, including three types of cancer, for which there was “sufficient evidence of an association” between herbicide exposure and these health outcomes. Most of the epidemiologic studies that supported this conclusion involved occupational or environmental cohorts exposed to herbicide or dioxin, not Vietnam veterans. Several other types of cancer were considered to have “limited/suggestive evidence of an association” with herbicide exposure. Generally, veterans were compensated if they could demonstrate they had incurred any of the diseases for which the Institute of Medicine committee identified a statistical association with herbicide exposure. Veterans were not required to demonstrate exposure or its magnitude.

The committee was also asked to make recommendations on future research needs to clarify unresolved issues regarding health effects of herbicides used in Vietnam. These recommendations resulted in several governmental actions (3). First, the VA initiated a study on Chemical Corps soldiers. Second, the VA and the Department of Defense began a process to identify as many service men and women as possible who served in Vietnam and to establish procedures to generate a comprehensive list of participants in future military actions. This was a major advance for future studies of health effects related to wartime exposures; epidemiologic studies of Vietnam veterans were severely hampered by the inability to comprehensively list participants in that conflict. Finally, the report’s call for additional research resulted in funding by the VA of an independent, extramural research program to validate proposed biomarkers, and to test the feasibility of developing and using a comprehensive exposure reconstruction model in epidemiologic studies of veterans.

In 1996, the first biannual update of “Veterans and Agent Orange” (3) was released from a newly constituted Institute of Medicine committee. This report extended the range of studies evaluated to include neurologic case reports and addressed the VA request for more information on acute and subacute peripheral neuropathy, and on birth defects. Both of these conditions were judged by the committee to have “limited/suggestive evidence of an association” with herbicide exposure. The majority of the committee’s conclusions continued to rely on epidemiologic studies.

A third Institute of Medicine Agent Orange committee was constituted in 1997, and its report was published in 1999 (37). No new health outcomes were added to the “sufficient” or “limited/suggestive” categories of association. A second activity of this Institute of Medicine committee was to hold a workshop to bring together investigators who were responsible for large epidemiologic databases to discuss opportunities for sharing, combining, and re-analyzing primary data related to herbicide and dioxin exposure and human health effects. A fourth committee has recently evaluated the evidence in an updated 2000 report (38) and added type 2 diabetes and acute myelogenous leukemia in children of veterans to the category of “limited/suggestive evidence.” The association of type 2 diabetes with exposure to herbicides is the focus of a supplemental report (39).

THE ROLE OF EPIDEMIOLOGY: LESSONS LEARNED

Except in the mandated reports of Vietnam veterans exposed to Agent Orange, results from epidemiologic studies have thus far played a limited role in the development of regulatory and public health policies related to dioxin and cancer. Because the animal cancer studies gave the first evidence on carcinogenicity, public health and regulatory policies have tended to rely upon their results as the basis for risk management. Regulatory policy regarding chemical carcinogens generally gives more weight to adequate epidemiologic data when available (40), but there are well-established precedents for using clearly positive animal data to develop regulatory policies when epidemiologic data are absent or inadequate. These precedents are based in part on knowledge regarding the predictive power of animal data and in part on the "precautionary principle," that is "when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (41). Thus, while epidemiologic results have had a corroborating role, they have so far not been the primary basis for regulatory policy.

The restricted role of epidemiologic evidence is further explained by the need of regulatory decision-makers for quantitative evaluations of low-dose risks to the general population. The absence of sufficiently definitive findings on quantitative dose-response from the epidemiologic data
limits their use for this purpose, although some progress is being made in deriving sufficiently certain exposure-response relations from the epidemiologic data on dioxin (32, 42). Future regulatory policies may rely heavily on these recent developments.

The historic evolution of concerns about dioxin and cancer has placed shifting and increasingly complex demands for answers on epidemiologic researchers. The initial concerns related to occupational exposures to herbicides and the non-cancer and cancer risks of these higher exposures. As the likely contribution of dioxins in particular to these concerns became apparent, hypotheses moved from herbicides generally to the contaminant dioxins specifically. Emerging information on general population exposures, beginning in the 1970s and 1980s, added broad concern about the public health consequences of dioxins. There was also recognition that the general population is exposed to an array of chemically-related dioxins and dioxin-like compounds which have multiple sources. Research design became more complex as the focus of research moved from relatively highly exposed occupational groups, to less exposed workers and to the general population. Increasingly sophisticated exposure assessment schemes were needed, moving from broad occupational groupings to measurements of body burden of dioxins.

Several observations related to the use of epidemiologic evidence in policy development emerge from the Agent Orange/Institute of Medicine experience. First, unlike other assessments of dioxin-related health effects, the Institute of Medicine reports relied almost exclusively on epidemiologic studies. The primary goal of the additional VA-funded research was to foster further epidemiologic research as the most direct way of determining health risks in the population of interest. Second, while the evaluation of the epidemiologic evidence provided by the committee served to inform policy-makers, the legislatively mandated criteria for compensation of Vietnam veterans for service-related illness were not based on the full spectrum of evidence that epidemiologists use to infer causal relations. Also, because the Institute of Medicine was mandated to evaluate herbicide exposure, not dioxin, the committee relied on studies of occupational, environmental, and military exposure to herbicides, as well as to dioxin. Thus, the Institute of Medicine committees’ conclusions have differed from assessment reports that seek to evaluate health effects of dioxin and dioxin-related compounds, and to assess causality. Despite these distinctions, the 6 years that have elapsed since the first Institute of Medicine Agent Orange committee was convened have witnessed an effective and bi-directional interaction between epidemiology and policy at the national level.

THE CONTINUED IMPORTANCE OF EPIDEMIOLOGY AND OPPORTUNITIES TO IMPROVE METHODOLOGY

The sometimes conflicting and inherently uncertain findings of epidemiologic studies of environmental agents may frustrate researchers and policy-makers alike. The utility of carrying out such studies may be questioned. However, in one view, epidemiologic science, properly oriented and using newly available tools and methods, remains extremely important for dealing with problems such as that of dioxin exposure and cancer risk.

We offer several bases for this view. First, over-reliance or reliance upon animal data only may be misleading, both as to the existence of a hazard and its quantitative magnitude. There is also the inherent uncertainty of extrapolating findings from animal models to humans. Particularly when both public health and economic stakes are large, lack of evidence from human studies hinders informed and cost-effective decision-making. Second, epidemiologic research addresses “real world” exposures; in the dioxin example, populations are exposed to a number of dioxin and dioxin-like compounds, not just a single compound, and exposure levels are well below those of the animal studies. Animal toxicology studies can yield useful information about single compounds at high doses, but their results are not necessarily useful for predicting risks of exposures to “real world” mixtures of the type and level encountered in the case of dioxins. Third, there have been opportunities to integrate knowledge obtained over the past decade regarding dioxin’s pharmacokinetic behavior into epidemiologic studies, so that understanding of quantitative dose-response relations can be improved. For example, with improved analytical methodology for detection of body concentrations of dioxin (in parts per trillion) and knowledge of the long biologic half-life of dioxin in humans (approximately 7 years), models can now be developed to reconstruct body burdens in exposed cohorts decades after their exposure began. Such model building may do much to improve epidemiologic estimates of human exposures.

The converging evidence from these multiple advances—animal data, mechanism of action, quantitation, and sensitivity of detection—can all be applied to human beings, who demonstrate a range of exposures of over 1,000-fold (adipose tissue concentrations). Thus, it is possible to examine a sensitive biomarker from animals which occurs in most tissues, has a large response, is easily quantified, and for which there are excellent dose-response data in animals. For example, cytochrome P-450 induction occurs at dioxin exposure levels at least 100 times less than those associated with toxic effects such as carcinogenesis (30). A study in humans, then, might involve a population whose body burden is known and preferably significantly above background, and testing whether cytochrome P-450 activity is increased. If this enzyme induction can be validated as a biomarker of cancer risk, then a study of this design has the potential to test the hypothesis of low-dose cancer risk in humans.

The design of this kind of study could draw on a solid base of animal data, and identification of an opportune cohort for which both exposure and response data can be collected for comparing to animal models. This type of epidemiologic research requires a comprehensive and multidisciplinary approach that brings laboratory methods to the population.

RECOMMENDATIONS FOR IMPROVING THE PROCESS OF USING EPIDEMIOLOGIC EVIDENCE

This case study shows that epidemiology has had an important but limited role in the development of public policies.
related to dioxin. The data accumulated over a time period during which risk assessment and its use for policy development were evolving. In the example of dioxin and cancer, the contrast between the striking animal data and the ambiguous epidemiologic data was not readily reconciled and the epidemiologic data were perhaps set aside because of this gulf. However, the epidemiologic studies and the use of their evidence for policy purposes might have been enhanced if the following recommendations had been implemented:

Data development

1. For topics for which epidemiologic data will likely carry policy implications, there should be an early and continuing discussion between potential decision-makers and researchers to ensure that the policy questions are in sharp focus, even if they evolve over time.

2. In responding to policy questions, epidemiologists should search for populations and study designs that can yield quantitative measures of exposure and risk. Exposure response data are invariably needed for risk assessment and integral to assessing causality.

3. Early and continuing interactions between decision-makers and epidemiologists are advisable to ensure that the policy questions are carefully framed (i.e., potentially susceptible to scientific investigation) and that decision-makers are fully apprised of the likely limitations in the expected results from epidemiologic studies.

4. Close interactions between epidemiologists and other researchers involved in the study of underlying biologic mechanisms of toxicity are advisable to ensure maximum integration of mechanistic understanding into epidemiologic study designs.

Data applications

1. Continued attention by epidemiologists to the ultimate policy questions should serve to ensure that study results are expressed in the most useable forms.

2. Policy-makers should be fully informed, in language that is understandable to the lay public and also faithful to the underlying science, of the strengths and limitations of epidemiologic results.

3. It is suggested that results from single studies be presented in the context of the existing epidemiologic database, with a discussion of consistencies and inconsistencies and their possible explanations. To the extent possible, the degree to which epidemiologic findings are consistent or inconsistent with estimates of risk projected from animal data should be evaluated and explained.

Before the founding of Environ in 1982, Dr. Rodricks served as Deputy Associate Commissioner for Science in the US Food and Drug Administration, a position he assumed after 15 years at the agency. His entire career has been devoted to the development and use of risk-related information for purposes of regulation; he was involved in the first federal efforts to regulate dioxin exposure in the late 1970s. He has served on 16 committees of the National Research Council, all involving toxicology, risk assessment, and public policy.

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DISCLOSURE

Dr. Joseph V. Rodricks is a Founding Principal of Environ Corporation, a risk assessment and management consulting firm that provides services to clients around the world.