Developing Scientific and Policy Methods that Support Precautionary Action in the Face of Uncertainty—The Institute of Medicine Committee on Agent Orange

Joel A. Tickner, ScD[a]

SYNOPSIS

To be precautionary, decisions must be made to prevent the impacts of potentially harmful activities even though the nature and magnitude of harm have not been proven scientifically. The Institute of Medicine's Committee on the Health Effects in Vietnam Veterans of Exposures to Herbicides provides a novel example of science and policy structures that support precautionary action in the face of uncertainty. What makes this example unique is the clear set of precautionary decision rules that lowered the standard for evidence, which formed the basis for policy. These rules, established by Congress, strongly influenced the way scientific information was weighed and the subsequent compensation decisions. They encouraged committee members to think outside the confines of their disciplines and develop new tools and methods to fit their unique mandate. The result was a methodology, supported by strong institutional structures, that allowed scientists to discuss the evidence as a whole, reach decisions as a group, and clarify uncertainties.

[a]Department of Work Environment, University of Massachusetts Lowell, Lowell, MA

Address correspondence to: Joel A. Tickner, ScD, Dept. of Work Environment, Univ. of Massachusetts Lowell, One University Ave., Lowell, MA 01854; tel. 978-934-2981; fax 978-934-2025; e-mail <joel_tickner@uml.edu>.

© 2002 Association of Schools of Public Health

Anticipatory and proactive action in the face of uncertainty is a fundamental aspect of the precautionary principle. To be precautionary, decisions must be made to prevent the impacts of potentially harmful activities even though the nature and magnitude of harm have not been proven scientifically. Nonetheless, it is often difficult for policy makers to take precautionary action because of the high standards of proof that are required in science and reinforced in legislation, through regulation, or in the courts.

Establishing statistically significant causal relationships between exposure and human diseases is difficult for a number of reasons: (1) the rare nature and subtlety of many environmentally related diseases; (2) difficulties in quantifying exposure; (3) confounding exposures; and (4) the difficulty of following exposed individuals over long periods of time. Quantitative methods focusing on risk and individual risk-factors frequently serve to compact information about exposure and disease into single numerical estimates, losing a wealth of qualitative information in the process. They can provide a sense of certainty and precision about a particular adverse effect that may not be warranted by the data at hand.

The Institute of Medicine's Committee on the Health Effects in Vietnam Veterans of Exposures to Herbicides—the Institute of Medicine Committee on Agent Orange—provides a novel example of science and policy structures that support precautionary action in the face of uncertainty. The Committee was established to provide an impartial review of the association between exposure to herbicides (including Agent Orange and its contaminants) and a range of diseases in veterans and, later, their offspring. The Committee's results were then used by the Department of Veterans' Affairs (DVA) to inform compensation decisions. What makes this example unique is the clear set of precautionary decision rules that lowered the standard for evidence, which formed the basis for policy. These rules, established by Congress, strongly influenced the way scientific information was weighed and the subsequent compensation decisions.

This article details the decision-making process and methods instituted by the Committee in weighing evidence about associations between herbicide and dioxin exposure and disease, and how those decisions were used by the DVA. The Congressional mandate to impartially review the scientific evidence encouraged the Committee members to think outside the confines of their disciplines and develop new tools and methods to fit their mandate. The result was a methodology, supported by strong institutional structures, that allowed scientists to shed the constraints of their individual disciplines and discuss the evidence as a whole, reach decisions as a group, and clarify uncertainties. This process then permitted governmental compensation decisions to be made in the face of significant uncertainty about whether any individual veteran's disease had been caused by exposure to herbicides in Vietnam.

HISTORY OF THE COMMITTEE—A LEGACY OF CONTROVERSY

During the Vietnam War, from 1965 through 1971, about 11.2 million gallons of an herbicide preparation known as Agent Orange—consisting of equal portions of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)—were sprayed over Vietnam.[1,2] Herbicides were sprayed to strip the jungle canopy that helped conceal enemy forces, to clear tall brush surrounding U.S. base camps, and to destroy food crops that enemy forces might depend upon. Although the true number of combatants was not recorded, it is estimated that more than three million American soldiers could have had transient or significant contact with these herbicides.[1,2] Few precautions were taken to prevent exposure, as the herbicides were not, at that time, considered harmful to human health at exposure levels experienced by troops.

Agent Orange spraying was stopped in 1970 after a concerted campaign—by scientists and anti-war activists against the practice—was bolstered by a scientific report that stated 2,4,5-T could cause birth defects in laboratory animals. In the early 1970s, scientists discovered that the Agent Orange preparation was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) or dioxin, one of the most toxic chemicals known to science and an unintentional by-product of the production of several chlorinated feedstocks, including chlorophenol, from which 2,4,5-T was made.[1]

Initial indication of impacts on veterans and the government response

Concern about the possible long-term health effects of exposure to herbicides in Vietnam began to grow in the 1970s, as a result of increasing reports by veterans attributing cancer or birth defects in children to wartime herbicide exposures. The acute health effects of herbicide exposure had already been evidenced in a number of people meeting the case definition of chloracne—a dioxin-related skin ailment. At the same time, international concern about the long-term health effects of occupational and environmental exposure to dioxin began to increase.[1–3]

At first, the armed forces and administrative agen-

cies denied that a problem existed. Nevertheless, in the late 1970s and early 1980s, Presidents Carter and Reagan established committees to study the long-term health effects of herbicides used in Vietnam. Studies were undertaken by the Air Force and Centers for Disease Control and Prevention (CDC) as early as 1979 to examine whether adverse effects observed in veterans could be related to wartime exposure to herbicides.[4] The Reagan Administration established a clear precedent of not compensating veterans (in part to avoid liability for dioxin-related claims from communities). One way the government attempted to avoid compensation was by setting a high standard of proof before compensation could be awarded.

Congressional action leading to the Agent Orange Act of 1991

The evidence that a problem might exist, combined with concerns raised by veterans and their support organizations, led to a series of congressional hearings on the effects of herbicide spraying in Vietnam as well as to an important court case defining standards of evidence for compensation (Nehmer vs. U.S. Veterans Administration, 1989).[1] Congressional debates and eventual legislation focused on three areas, corresponding to veterans' concerns: (1) access to health care for illnesses that might be a result of herbicide exposure; (2) scientific research into the health effects of Agent Orange and other herbicides; and (3) compensation for disabilities related to exposure. Senator Tom Daschle of South Dakota noted that the job of Congress was to demand continued independent, scientific inquiry while promoting a "sound, cautious policy to meet the public health and environmental concerns related to dioxin."[5] In other words, *intelligent public policy need not wait for perfect science.*

The Agent Orange Act of 1991 (PL 102-4) codified compensation policy for Agent Orange-related diseases by:

- Establishing the presumption that any veteran who served in Vietnam during the Vietnam era had been exposed to herbicides and dioxin, in the absence of evidence to the contrary;
- Establishing the presumption that non-Hodgkins lymphoma, soft-tissue sarcoma, and chloracne were service-connected (thus initiating disability compensation payments);
- Setting procedures for establishing service-connection for other diseases found to have a positive association with exposure to herbicide and calling for research into veterans' health effects; and
- Instructing the Veterans Administration to enter into a contract with the National Academy of Sciences (NAS) to review the scientific literature concerning the association between herbicide exposure and disease.

The law required the Secretary of Veterans Affairs to initiate regulations for compensation when "the Secretary determines, on the basis of sound medical and scientific evidence, that a positive association exists between (*a*) the exposure of *humans* to an herbicide agent and (*b*) the occurrence of a disease in *humans*." [emphasis added] A positive association was said to exist when "the credible evidence for the association is equal to or outweighs the credible evidence against the association." The Secretary was then to make compensation determinations and to explain any decision denying service-connectedness.

The Committee's mandate

The NAS is a private institution, chartered by Congress in 1863 to provide a mechanism for eminent scientists to investigate and report upon subjects of science and technology requested by the government. The Institute of Medicine (IOM), a branch of the NAS, was established in 1970 to advise the federal government on policy matters pertaining to the health of the public as well as to act independently in identifying important issues of medical care, research, and education. To ensure independence and objectivity, all IOM reports are carried out by expert volunteer committees, without conflicts of interest. IOM committees meet to evaluate the evidence and prepare findings and recommendations, but often conduct public meetings to gather information. Committee reports are released after peer review. The Agent Orange Act of 1991 established firm decision rules for IOM about how to weigh scientific evidence, but the political decision of determining whether compensation should be afforded was left to the DVA. The principal IOM charge is described in the Act as follows:

> For each disease reviewed, the Academy shall determine (to the extent that available scientific data permit meaningful determinations) whether a statistical association with herbicide exposure exists taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association.[6]

The critical aspect of this mandate was its explicit direction to scientists to determine the existence of a

statistical association rather than a cause and effect relationship. The Act called on the NAS scientists to fully discuss the evidence and their reasoning, and to recommend additional research that might resolve areas of continuing scientific uncertainty.

WEIGHING SCIENTIFIC EVIDENCE ON THE COMMITTEE—DEVELOPMENT OF A NOVEL SCIENTIFIC METHOD

In 1992, IOM established a multidisciplinary group of experts on environmental and occupational health and etiology of specific diseases, including occupational and environmental physicians, and researchers on cancer and reproductive epidemiology, biostatistics, neurology, toxicology, and exposure assessment. An initial literature review was conducted by IOM staff, and the vast universe of studies (some 6,000) was narrowed down to approximately 300 on which the Committee would focus its attention. Public meetings with various stakeholders, commissioned research, and expert meetings supplemented the Committee's review.[1]

The Committee quickly recognized that the existing epidemiologic database contained very little information on veterans' exposures to herbicides and dioxin. Nor had adequately designed epidemiologic studies been conducted among veterans. Furthermore, some diseases with long latency may not yet have appeared among veterans. The Committee therefore decided to review studies of occupationally exposed groups and groups suffering from elevated environmental exposures in addition to Vietnam veterans. These studies included agricultural and industrial workers, Vietnamese citizens, and populations around the sites of industrial accidents. They provided better (though often still questionable) exposure measures, higher exposures, and longer exposure durations than the Vietnam veteran cohort and enhanced the ability of the Committee to determine whether these compounds could be associated with particular health outcomes in veterans.

Process for weighing the evidence: research synthesis

One of the most arduous tasks Committee members faced was to determine how to weigh the evidence, because it required them to think outside traditional scientific parameters and methods for establishing causality. The challenge was to learn whether exposure to herbicides and dioxin increased the risk of disease in humans, not how large that risk was for any individual.[7]

The Committee developed relatively straightforward procedures. Subcommittees were developed to review evidence on different diseases. Each subcommittee member took a disease, reviewed the evidence, and wrote an analysis. This analysis was discussed and consensus reached at the subcommittee level and then at the whole Committee level. Group deliberations, not fully captured in the final report, covered issues of uncertainty, study quality, and comparisons to previous determinations. Consensus and long, open discussion was a critical element of the review.

The method used by the Committee to weigh evidence on an association between exposure and disease has been characterized as a research synthesis method—a way to summarize and integrate studies, drawing conclusions on the whole of the evidence, but also uncovering variability, as well as consistencies.[8,9] A systematic research synthesis includes: (*a*) development of an explicit protocol for study identification, inclusion, and exclusion; (*b*) methods for review of and presentation of the evidence; and (*c*) methods for identifying research gaps and uncertainties requiring more research.

The research synthesis method employed by the Committee combined qualitative and quantitative approaches, but because of the vast differences among studies, quantitative meta-analyses were rarely performed. The synthesis process was an iterative, qualitative review of all the available human evidence.[1] It was driven by comprehensiveness to guard against serious omission, fairness in weighing evidence, and openness in discussion of strengths and weaknesses of the evidence. The process was described by one Committee member as "synthesis by careful thinking." (Personal communication, Graham Colditz, Associate Professor, Harvard Medical School, April 20, 1999.)

It was critical for the Committee, in reaching its decisions, to examine patterns in the evidence as a whole, based on knowledge of the disease being examined, and to avoid getting bogged down in debating details of individual studies. Experience and judgment played a central role in determining whether a pattern was reasonable and indicative of an association. Committee members also examined the strengths and weaknesses of individual studies, looking closely at study quality (size, power, exposure data, dose-response, biases, and confounding). No single study was deemed a decisive basis for a determination, although some larger, well designed studies, with good exposure measures, carried a lot of weight. It was important for Committee members to learn from, rather than suppress, the heterogeneity between studies.

Answering the Congressional Mandate

The Committee was required under the Agent Orange Act of 1991 to answer a particular set of questions regarding the association between exposure to herbicides and dioxin and disease:

1. *Whether a statistical association exists—development of categories of evidence of association.* A difficult aspect of the Committee's charge was to present its results in a way that informed policy, yet did not dictate policy decisions or present more certain results than could be inferred from the available evidence. Early in the process the Committee determined that the available data did not allow the precision of making a yes-or-no determination of association or even to place probabilities on conditions with varying shades of gray. The Committee saw their role as identifying the level of knowledge as well as uncertainties, without going beyond what science could say based on that knowledge. (Personal Communication, David Tollerud, Professor, School of Public Health, MCP Hahnemann University, March 22, 1999.)

   The Committee developed four categories to describe the strength of the evidence of a statistical association between exposure to herbicides and disease in humans (see Table). The categories were based on ones developed for a previous IOM committee and established by the International Agency for Research on Cancer (IARC).[10]

   These categories describe qualities in the evidence that would lead to a particular placement (types of studies, presence or absence of bias, and so on) and allow an honest description of uncertainty in the available data. For example, the *Inadequate/Insufficient Evidence* category allowed the Committee to say that no determination could be made based on the science at that time, although this did not mean that there was no evidence of an association. Most diseases fell into this category by default because of the lack of data. The *Sufficient Evidence* category included diseases for which the evidence of association (from one or more studies) was strong, and bias and confounding were ruled out. *Limited/Suggestive Evidence* was the "red flag" category, allowing the Committee to say that though there was still some uncertainty, there was evidence of an association. Finally, the *Limited/Suggestive Evidence of No Association* category allowed the Committee to conclude that the exposure did not appear to be associated, although the nature of the evidence did not allow the possibility of an association to be ruled out.

   The use of categories allowed for open debate, comparisons, and presentation of the evi-

Table. Categories of association established by the IOM Committee on Agent Orange

Sufficient evidence of an association: Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence for an association.

Limited/suggestive evidence of an association: Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent.

Inadequate/insufficient evidence to determine whether an association exists: The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency.

Limited/suggestive evidence of no association: Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

SOURCE OF DATA: Institute of Medicine. Veterans and agent orange: health effects of herbicides used in Vietnam. Washington: National Academies Press; 1994.

dence, limited as it was. Defining the categories involved significant group deliberation, and the definitions were critical, because they bounded the final weighting of evidence. The final report presented detailed rationales for the categorization of each disease.

2. *Increased risk of disease among those exposed during Vietnam service.* The second charge of the Committee was to determine the magnitude of the increased risk of disease among veterans exposed during Vietnam service. Early in its deliberations, the Committee realized that "given the large uncertainties that remain about the magnitude of potential risk from exposure to herbicides in the studies that have been reviewed, the inadequate control for important confounders, and the uncertainty about the nature and magnitude of exposure to herbicides in Vietnam, none of the ingredients necessary for a quantitative risk assessment are available."[1] Although quantitative and qualitative evidence indicated that Vietnam veterans as a whole had relatively low exposures compared to occupationally and environmentally exposed cohorts, the Committee could not rule out that some subgroups did have high exposure.
3. *Plausible biologic mechanism or other evidence of a causal relationship.* The third charge was to examine any biologic mechanisms or other evidence of a causal relationship between exposure to herbicides and disease. The Committee examined biologic plausibility in a broad sense, not focusing particularly on mechanistic plausibility for each disease. They examined such things as carcinogenic potential demonstrated in animal studies, capacity to disrupt DNA, and evidence that certain types of cancer are caused by chemical exposures.

   Since TCDD acted as a systemic toxicant in animals through a receptor known to exist in humans, it could plausibly be assumed to act similarly in humans, according to the Committee's findings. Reasonable epidemiologic evidence linking dioxin exposure and specific diseases in humans supported the plausibility of an association with other diseases. The Committee concluded the "lack of specific biological support for a given health outcome did not rule out a conclusion of sufficient evidence."[1]

Results from first Committee report

In its first report, released in July 1993, the Committee placed five diseases and conditions in the *Sufficient Evidence of an Association* category: soft tissue sarcoma, non-Hodgkins lymphoma, Hodgkins disease, chloracne, and porphyria cutanea tarda. In the *Limited/Suggestive* category it placed respiratory cancers, prostate cancer, and multiple myeloma. The report listed four diseases in the *Limited/Suggestive Evidence of No Association*: skin cancer, gastrointestinal tumors, bladder cancer, and brain tumors. The rest of the conditions reviewed were placed in the *Inadequate/Insufficient* category. The Committee also presented research recommendations, in particular calling for the establishment of better exposure assessment through exposure reconstruction models. Three updates of the *Veterans and Agent Orange* study have been published.[11–13] For each update a new Committee, consisting of nearly equal numbers of former Committee members and new members, was established to address specific scientific questions and to review new evidence as a whole. Using a mix of former and new members provided consistency and history in terms of Committee knowledge of the original mandate and how the categories of association were established, but allowed for diversity and a new range of opinion.

PRECAUTIONARY ASPECTS OF THE COMMITTEE—HOW IT SUPPORTED ACTION IN THE FACE OF UNCERTAINTY

The Committee on Agent Orange presents a unique case in which scientists and policy makers were asked by Congress to "take care" in weighing scientific evidence and making policy decisions. This explicit policy mandate was coupled with strong institutional structures that supported scientists in examining scientific evidence in a policy-relevant manner.

Explicit and carefully worded policy mandate and presumptions

A critical aspect in this case was the role of a Congressional policy mandate in steering the subsequent scientific analysis of the evidence and compensation decisions. In describing his support for the bill that would eventually become the Agent Orange Act of 1991, Senator Murkowski stated:

> The evidence is not perfect, but it will never be perfect. Our understanding of cause and effect is still incomplete but we will never have a complete understanding of disease and its causes. . . . Leadership is a willingness to take action in the face of incomplete and imperfect data rather than accepting the paralysis inherent in a never-ending wait for understanding. . . . The search for answers must continue; however, the constant desire for just one more study should not be an excuse for inaction.[14]

Congress members recognized both the need to act in the face of uncertainty and the need to continue searching for scientific answers. Particular aspects of the Act's mandate that drove a precautionary analysis are worth noting:

1. *Precautionary standards for scientific and policy review.* The Act established criteria for evaluating the scientific evidence and a threshold for taking action that are consistent with the precautionary principle. Congress realized the difficulties in establishing a causal relationship between exposure to Agent Orange and disease, and thus wanted to make it possible for decisions to be made based on limited knowledge.

   In conventional scientific inquiry scientists are reluctant to make pronouncements of effects without an established causal relationship, such as evidence of a biological mechanism, clear dose-response relationship, or consistency across many studies. Such relationships are typically considered established when a set of considerations for judging causal associations, called the "Hill Criteria," are fulfilled.[15] The Agent Orange Act of 1991 instructed the Committee to consider only the evidence regarding statistical associations, not causal relationships. A finding of a statistical association required that some scientific evidence demonstrate that an observed effect was not likely to have been caused by chance alone. Congress predetermined that some of Hill's causal criteria had been fulfilled. Compensation would be afforded if the available evidence for an association was as strong as or stronger than the evidence against an association.

2. *Presumption of exposure and service-connection presumption.* Given great uncertainties regarding exposure to Agent Orange, dioxin, and other herbicides (though high exposure could not be ruled out for some veterans) and the near impossibility of demonstrating that an individual veteran's disease was caused by exposure to herbicides in Vietnam, Congress established rebuttable presumptions of exposure and service-connection. Together, these precautionary presumptions instituted a "benefit of the doubt" policy—if a person had a disease associated with exposure to herbicides, and if that person had served in Vietnam, then his or her illness should be considered to have occurred as a result of service, unless there was evidence to the contrary.

3. *Weighing all the available evidence on veterans and non-veterans.* Acknowledging the lack of studies of herbicide and dioxin-related effects on veterans, the Act instructed scientists and policy makers to make determinations of association based on disease in humans, not only veterans. This wording allowed the Committee to base its determinations on all the available observational studies involving veteran, environmental, and occupational exposures to herbicides and dioxin—an inclusive evidence approach. The latter types of studies had better defined exposure measures and higher exposures in general than did the studies in veterans. This language facilitated decision-making in spite of very limited evidence of association in veterans per se.

4. *Rapid analysis of scientific evidence and rapid policy decisions.* Acknowledging the slow pace of science and policy and the interface between them (especially on contentious, uncertain environmental health issues), the Act mandated a rapid but thorough process. The short deadlines—18 months for the first IOM report and 60 days for DVA compensation decisions—helped facilitate difficult scientific decisions and policy action. The case demonstrates that thorough scientific analysis, detailed policy review of the science, and ultimate decisions can be accomplished in a relatively short time.

5. *Scientific analysis to inform policy.* The Act mandated an independent analysis of the scientific data, separating science and policy, but at the same time instructed that science be conducted to inform policy decisions. An independent review was important to the veterans, who had developed a strong mistrust of the government's ability to analyze the evidence in an unbiased manner.

   From the outset, Congressional leaders noted that the scientific standard of association was more appropriate to public policy in the face of uncertainty than the scientific standard of causality. Committee members recognized that their scientific analysis was driven by the questions asked and served a particular policy purpose, and that they accepted this purpose when signing onto the Committee. That mandate did not impinge on the Committee's ability to develop its own scientific methods to examine the evidence flexibly, fairly, and comprehensively. Though some Congressional staff challenged

the Committee to make probabilistic determinations, Committee members reiterated that such judgments were impossible based on the available scientific literature.

Strong institutional structure behind science supports action in the face of uncertainty

Successful implementation of the Congressional mandate required a strong institutional structure that could engage scientists in analyzing evidence in an unfamiliar way and protect their standing in the scientific community in the process. IOM provided this structure as well as the necessary research to support the scientific review process.

IOM had a 20-year history of providing independent, unbiased information to support public policy and extensive experience in building diverse, multidisciplinary panels to analyze complex, uncertain public health debates. In contrast to the multistakeholder approach typical for other agencies driven by competing interests, such as the Environmental Protection Agency (EPA), the Committee process allowed a diversity of scientific opinions, but deliberately avoided such competition. This allowed for rapid resolution of a contentious issue.

The IOM structure and Committee review process were critical to supporting Congress' precautionary mandate in the following ways:

1. *Lay expert scientific process.* In establishing the Committee on Agent Orange, IOM made an early decision to choose committee members who had not published or made public statements on the human health risks of Agent Orange, dioxins, or other herbicides. Given the controversial and emotionally charged nature of the topic, IOM leadership felt the need for a "fresh analysis of the issue."[1] Committee members could be considered lay or naïve experts who brought expertise in various disciplines to the discussions, but not the biases and positions of those who had examined the issue for a long time. Hearings, meetings with experts, and internal and external research compensated for the Committee's lack of expertise on the particular subject.

   A committee comprised of experts with preconceived conclusions about the subject might have had a difficult time setting aside causal criteria and accepting the categories of association developed.[10] The scientists' lack of established positions on the subject, combined with their multidisciplinary skills in interpreting data, allowed them to reach consensus—and not simply recommend more research. It allowed discussions to focus on the literature rather than on personalities and positions.

   Consensus was critical to the Committee so it could provide a clear statement to the government and public, and feel satisfied with its findings. Considerable time was spent reaching consensus on the methods before any literature search was begun. This was especially problematic with a volunteer committee that had to examine, learn, and understand a large base of literature on herbicides, dioxin, and diseases potentially associated with exposures to them.

   The lay expert process was not without its detractors. Early in the process several experts in dioxin research noted that the Committee had left out important pieces of information in its deliberations, e.g., toxicological data, that might have led to more determinations of association.[16,17]

2. *Ability of scientists to buy into the process.* The mandate of a review of the evidence on association, with only a secondary analysis of individual risk or causality, was a challenge to most Committee members. This was particularly true for experts in specific diseases—often clinicians with little epidemiologic training. Their acceptance of the process was facilitated by strong IOM staff leadership in providing assistance, training, reinforcement, and opportunities for open debate.

   Members also gained confidence in the process as they developed and refined it. The IOM assisted by providing examples of structures used on similar committees and by continuously reminding the Committee of its charge, whenever it strayed into discussions of risk (exposure) or causality. The process encouraged and depended upon scientists being willing to take off their disciplinary hats and work within a novel structure, alien to their traditional scientific thinking.

   Some had more difficulties than others in accepting the mandate. These members were concerned that their independence and professional identity were being violated by being told how to analyze the science. These members felt that scientists were being railroaded through a process, without an opportunity for debate on the most appropriate ways to analyze data.

3. *Qualitative, multidisciplinary review.* With IOM leadership, the Committee was able to weigh the available evidence on herbicides, dioxin, and disease in a manner that best supported policy decision-making, without overstating the boundaries of scientific knowledge. This qualitative, flexible, evaluation process permitted each disease to be reviewed on an individual basis, taking into consideration the available information and accumulated knowledge. By examining all of the available evidence, using group expert judgment to fill in gaps in data, and honestly representing what was known and not known, the Committee facilitated a precautionary weighing of evidence and decision-making.

   The Committee conducted its research synthesis through an in-depth examination of multiple lines of evidence (epidemiologic studies in various populations, toxicology, clinical data on the etiology of disease), the most instructive studies, and heterogeneity and patterns in the evidence, rather than trying to distill a wide range of information into a few numbers. In an effort to support the deliberative process, the Committee attempted to quantify evidence when it could. When it could not quantify the evidence, graphical representations and thorough descriptions were provided to inform the Committee's determinations.

   A critical aspect of this precautionary weighing of scientific information was the role of expert judgment and deliberation. This multidisciplinary group judgment was crucial in evaluating the quality of the evidence and making conclusions to inform policy.[7] Due to the uncertain nature of observational studies on dioxin and herbicides (particularly exposure measures), the skills and experience of Committee members were necessary to tease out patterns and suspicions from a complex web of evidence. The Committee noted that reaching conclusions based on the available evidence required thoughtful consideration of alternative approaches and explicit collective judgment, which could not be achieved through strict adherence to some prescribed formula.[1]

   The deliberative process was described in the following way: "Our job was to take a step back, look at all of the information available, and to see whether or not there was either relatively conclusive information or perhaps some suggestion of information that was not conclusive either way."[18] Deliberation led to the development of categories of association to describe the evidence. Careful, tight wording of the categories ensured that policy makers would be able to understand the rationale behind the Committee's decision.

4. *Honesty and explicitness about uncertainty.* One of the most precautionary aspects of the Committee's review was its explicitness about the uncertainties inherent in determining whether exposure to herbicides and dioxin was associated with disease in humans. This uncertainty provided the rationale for the Committee's decision to use categories of association and its explicit descriptions of the strengths and limitation of the evidence on which determinations were made. The Committee, in detailed fashion, described in its reports what could be inferred from the evidence, what could not, and whether additional research would provide necessary answers in any reasonable period of time.

   In Congressional hearings, the Committee was forced to defend its explicitness about uncertainty and the limits of the science:

   > What we have tried to do in the Committee is to present the evidence and the strength or weakness of the evidence in as precise, clear way as possible to allow you to do all that you need to do on the policy front. There are limitations to science. There are limitations to the statistics, and we can simply provide you with the information, and then you need to deal with it.[18]

   This rigorous, transparent review of the evidence on disease provided a more comprehensive picture of what was scientifically known, not known, and suspected. It exposed the impossibility of achieving certainty and created an opportunity to place pressure on decision makers to take action in the face of uncertainty as well as to support research to reduce uncertainties.

5. *Public involvement/hearings.* Although the Committee deliberations were not traditionally public, IOM typically invited other experts and stakeholders to participate in open hearings so the Committee could be exposed to a wide range of information and positions. A wide variety of stakeholders—including veterans, scientists, Congressional staff, governmental agencies, private corporations, and environmental groups—were invited to hearings, convened at the begin-

ning of each Committee process. The hearings and informal contact with stakeholders forced the Committee to take the issue seriously, to understand what was at stake, and allowed members to be open to refining their traditionally rigid world view.[10] The hearings also helped fill gaps in the scientific base of information and to gather qualitative and anecdotal information—particularly that a small group of veterans had particularly high exposures that were not included in expert models. Finally, they increased the legitimacy of the Committee's conclusions.

LIMITATIONS

A potential limitation in the broader applicability of the Committee example is that the case did not involve the kinds of economic interests most resistant to precautionary decision-making. This was not a case of preventive action. The case involved government compensation, not a marketed product; although the federal government did have some interest in preventing compensation, as did the chemical industry, which feared this would set a precedent for EPA dioxin decisions. Things might have turned out differently if chemical companies, rather than the government, had been forced to pay compensation or if this case involved compensation for general public exposure to dioxin. One can never completely separate the science and policy decision process from the purpose to which it is put.

Yet, the situation faced by the Committee, in terms of limits in the available evidence and uncertainty, was similar to the situation faced by most scientists examining the links between hard-to-define exposures and often rare diseases. What was different in this case was the mandate to review science using a different standard from scientific causality and to give the "benefit of the doubt" policy under uncertainty to veterans. The question is whether causality or attributable risk (which the Committee concluded could not be ascertained) are ever appropriate standards of proof when science is conducted for preventive public policy.

CONCLUSIONS

The IOM scientists were instructed to evaluate scientific evidence in a manner that could support action in the face of uncertainty. The Committee's mandate was the result of an understanding of the difficulties inherent in scientifically establishing cause and effect relationships in the face of very limited evidence and an acknowledgement of who bears the costs of uncertainty when the evidence is less than perfect.

The separation of "precautionary science" and "precautionary policy" was critical, though such a separation is never absolute. It allowed a more thorough review and encouraged scientists to think beyond their training, free from vested interests, and decision politics. Given the complexities and difficulties in examining uncertain data, an independent scientific panel may be the most effective means of analyzing a wide range of technical evidence, with public input to ensure that important information is not excluded. Through participatory processes, government decision makers and the public can then incorporate this evidence, evidence of alternatives, and other considerations, such as values, into the ultimate decision.

The Committee's review acknowledged that specific diseases were associated with exposure to herbicides and dioxin, paving the way for greater attention to the public health impacts of dioxin and prospective public policy. Some lessons that can be learned from the Committee's approach to weighing the scientific evidence and future decision-making, include:

1. *Mandates for precautionary science.* A clearly defined precautionary policy mandate outlining the standards by which scientists should weigh evidence is as important as the charge to policy makers. Such a charge need not compromise scientific integrity. Although its policy mandate, with constant reinforcement, heavily shaped its evaluation, the Committee was allowed sufficient flexibility to examine the evidence in a way that would best inform policy yet be honest about the limits of science. The case demonstrates that if decision/scientific criteria are made explicit, scientists may come out with different results than if they had reviewed the same evidence based on their traditional causal paradigm and inherent scientific skepticism. (Personal communication, David Kriebel, Professor, Department of Work Environment, University of Massachusetts, Lowell, July 22, 1999.)

   The precautionary standard of association, rather than causality or proof, is a standard of evidence suitable for policy purposes, if not for scientific purposes—one that can facilitate action in the face of uncertainty. Using standard causality-based rules of weighing scientific evidence would have meant (and did for years) no action. Acknowledging this makes it easier to ask what the appropriate rules should be. In precautionary public policy, it is less necessary to prove a specific exposure caused or will cause

a disease than to determine whether the evidence as a whole indicates harm may be occurring and that compensation should be afforded or specific preventive actions should be taken. This does not mean that causal information, such as biologic plausibility and consistency, should not be considered in decision-making. Rather, it means that in cases where uncertainty is great about impacts on a particular population, yet reasonable knowledge about the hazards posed by an activity exist (as was the case with dioxin), it is appropriate to make decisions on a lower scientific standard—a presumption that a causal relationship is likely. Thus, perfect information or understanding are not necessary before precautionary actions are taken.

2. *Mandates for precautionary policy.* Precaution also requires an explicit mandate to policy makers to act in the face of uncertainty. A mandate to examine science in a precautionary way alone will not necessarily result in precautionary decisions, particularly if the regulatory agency believes such decisions might undermine its authority, lead to court or powerful interest challenges, or result in high financial or resource costs. In the Agent Orange case, Congress recognized the DVA's lack of motivation to act and provided a clear policy mandate instructing the agency to make decisions based on a positive association (weight of evidence) rather than causality; and to assume that all those who had served "in theater" had been exposed. Future mandates of this sort will need to address the potential for agencies to use uncertainty as a rationale not to act, particularly in cases where evidence is lacking—a situation easily confused with evidence of a lack of association.

3. *Strong institutional structures.* A precautionary weighing of science requires strong institutional support structures and a multidisciplinary expert review of evidence. Institutional leadership and insight from IOM resulted in a systematic precautionary process to inform, rather than make policy. Lay scientists from a variety of backgrounds and disciplines entered the review with no preconceived conclusions on the issue of dioxin and herbicides, and were encouraged by IOM to examine scientific evidence in a manner that was initially alien to many.

   An important aspect of the multidisciplinary review was its incorporation of expert judgment and qualitative analysis. Though policy makers often prefer scientific information to be presented in quantifiable point estimates, thus making decision-making easier, more clear-cut, and more defensible, the Committee recognized that such determinations were not possible based on the available evidence and, in fact, would be misleading about the nature of science. Therefore, the Committee focused its efforts on a qualitative, deliberative review that provided a thorough review of the state of the science. This approach avoided the tendency to "push for a number at the expense of thinking," which often ignores important non-quantifiable data and judgment. (Personal communication, Graham Colditz, Associate Professor, Harvard Medical School, April 20, 1999.)

   Decision makers can use uncertainty as an excuse not to act. The illusion of the possibility of achieving greater certainty can also reinforce the belief that decision makers should wait before acting. Once the impossibility of achieving certainty (or substantially reducing uncertainty) is understood, it becomes easier to understand why action is essential (because the failure to act can result in further damage to health and the environment) and to hold decision makers accountable for not acting.

The approach applied by the Institute of Medicine Committee on Agent Orange could be expanded in several ways to support preventive, precautionary decisions. The first step is a policy mandate to weigh scientific evidence in a precautionary manner and for decision makers to act in the face of uncertain information. A second step is a strong institutional structure to train scientists in review methods that would more effectively address uncertainty and complexity. An expansion of the types of disciplines and lines of evidence (going beyond epidemiology) used in the review could enhance the possibility of detecting associations and identifying strengths and weaknesses in the data. Further, categories could be established to make determinations on the magnitude and type of exposure. This would permit qualitative estimates of risk. It would also expand the range of information on which preventive interventions could be based.

The wisdom of Congressional leaders in crafting the Agent Orange Act of 1991 mandates ensured that the limits of science to define exposure or to prove cause and effect were reflected in the way science was conducted and, ultimately, in public policy decision-

making. These mandates created an environment for precautionary action. Precautionary action does not negate the need for continuing research and reassessment to understand the links between exposure and disease, to understand if precaution is necessary, and to ensure that the decisions made are the most protective of public health and the environment. The two clearly go together.[19] The Institute of Medicine Committee on Agent Orange case demonstrates that, with clear policy signals and an openness to new approaches, both science and policy can be conducted in a manner that supports precautionary action in the face of uncertainty.

The analysis in this article is the product of interviews with key actors in the Institute of Medicine's review process as well as extensive document review. The author would like to acknowledge the following individuals who either were interviewed or provided information used in this analysis: David Kriebel, Michael Stoto, David Tollerud, Graham Colditz, Jesse Berlin, and Brian Langholz. The final analysis, however, is the author's own interpretation.

REFERENCES

1. Zumwalt, Jr. ER Admiral, statement. Report to the Secretary of the Department of Veterans Affairs on the Association Between Adverse Health Effects and Exposure to Agent Orange. Washington: U.S. Department of Veterans Affairs. (May 5, 1990).
2. Institute of Medicine. Veterans and agent orange: health effects of herbicides used in Vietnam. Washington: National Academies Press; 1994.
3. Rodricks J, Collins J, Farland W, Tollerud D. Contrasting roles of epidemiology in dioxin-related policy: lessons learned. Am J of Epidemiol 2001;154(12 Suppl): S43-9.
4. Stichman B. Between the courts and the congress: leveraging VA benefits for agent orange plaintiff cases. In: Rhoades D, Leaveck M, Hudson J, editors. Legacy of Vietnam veterans and their families: survivors of war, catalysts of change. Papers from the 1994 National Symposium. Washington: Government Printing Office; 1995. p. 300-16.
5. Daschle T, statement. Agent orange legislation and oversight: Hearing before the Senate Comm. on Veterans' Affairs, 100th Cong., 2nd Sess. (May 12, 1988).
6. Agent Orange Act of 1991, Pub. L. No. 102-4, 105 Stat. 11 (Feb. 6, 1991).
7. Stoto M. Research synthesis for public health policy: experience of the Institute of Medicine. In: Stangl D, Berry D, editors. Meta-analysis in medicine and health policy. New York: Marcel Dekker; 2000. p. 321-57.
8. Cooper H, Hedges L. Research synthesis as a scientific exercise. In: Cooper H, Hedges L. The handbook of research synthesis. New York: Russell Sage Foundation; 1993. p. 3-14.
9. Mosteller F, Colditz G. Understanding research synthesis (meta-analysis). Annu Rev Public Health 1996;17:1-23.
10. Institute of Medicine. Adverse effects of pertussis and rubella vaccines. Washington: National Academies Press; 1991.
11. Institute of Medicine. Veterans and agent orange, update 1996. Washington: National Academies Press; 1996.
12. Institute of Medicine. Veterans and agent orange, update 1998. Washington: National Academies Press; 1999.
13. Institute of Medicine. Veterans and agent orange, update 2000. Washington: National Academies Press; 2001.
14. Stout M, statement. Agent orange legislation and oversight: Hearing before the Senate Comm. on Veterans' Affairs, 100th Cong., 2nd Sess. (May 12, 1988).
15. Hill AB. The environment and disease: association or causation. Proc R Soc Med 1965;58:295-300.
16. Schecter A, statement. National Academy of Science Comm. report on agent orange: Hearing before the Senate Comm. on Veterans' Affairs, 103rd Cong., 1st Sess. (July 27, 1993).
17. Silbergeld E, statement. National Academy of Science Comm. report on agent orange: Hearing before the Senate Comm. on Veterans' Affairs, 103rd Cong., 1st Sess. (July 27, 1993).
18. Tollerud D, statement. Institute of Medicine Update on Veterans and Agent Orange: Hearings before the Subcomm. on Hospitals and Health Care of the House Comm. on Veterans' Affairs, 104th Cong., 2nd Sess. (April 16, 1996).
19. Goldstein B. The precautionary principle and scientific research are not antithetical. Environ Health Perspect 1999;107:A594-5.