Regulatory Impact Analysis Project, Inc.

Choices In Risk Assessment

The Role of Science Policy in the Environmental Risk Management Process

Prepared for
Sandia National Laboratories

Sponsored by
The U.S. Department of Energy
Office of Environmental Management and
Office of Environment, Safety and Health

REGULATORY IMPACT ANALYSIS PROJECT, INC.

CHOICES IN RISK ASSESSMENT

THE ROLE OF SCIENCE POLICY IN THE ENVIRONMENTAL RISK MANAGEMENT PROCESS

Prepared for
Sandia National Laboratories

Sponsored by
The U.S. Department of Energy
Office of Environmental Management and
Office of Environment, Safety and Health

Library of Congress Catalog Number 94-69099

International Standard Book Number 0-9643747-1-4

FOREWORD

This report is a product of the Science Policy Impact Analysis Project sponsored by the office of Environmental Management (EM) in coordination with the Office of Environment, Safety and Health (EH) of the U.S. Department of Energy (DOE). The project was initiated to assist EM and EH's Office of Environmental Guidance in gaining insight into the use of "science policy" in the environmental risk assessment and management processes, and the development of environmental regulation. In particular, EM's mission is to use cost-effective and technically sound approaches:

- To ensure that risks to the environment and human health and safety posed by active, inactive, and surplus facilities and sites are reduced to prescribed and acceptable levels; and
- To minimize, handle, treat, store, transport, and dispose of DOE waste safely. Rational risk Management is essential to accomplish EM's mission, especially given the current resource constraints and projected growth of its program.

The report is intended to describe science policy issues and decisions, and how they have been addressed and used in risk-based environmental regulatory decision making. For the purposes of this project, "science policy issue" is defined as a gap or uncertainty in scientific knowledge or data arising in the risk assessment process, and "science policy decision" is defined as the policy decision made to bridge the gap or uncertainty in scientific knowledge and data. Science policy decisions are frequently the driving force in the environmental risk assessment and management processes. DOE's need for information relating to the use of science policy developed as a result of a number of efforts, including those:

- To revise environmental directives and promulgate radiation rules for protection of the public and the environment and to develop supporting guidance documents;
- To develop and integrate risk and environmental management strategies for site remediation; and
- To improve and develop more consistent environmental risk assessment methodology and decision-making processes through coordination with other government agencies and organizations via interagency working groups.

Knowledge of the existence of science policy issues and how science policy decisions are made may be important to DOE in the development or implementation of many programs and directives. For example, EH's Office of the Environment is in the process of promulgating the DOE rule concerning radiation protection of the public and

environment (to be codified at 10 CFR Part 834) and revising DOE's principal environmental protection directive (DOE 5400.1).

The foundation of the environmental and public radiation protection system in the proposed rule is the as low as reasonably achievable (ALARA) process. The ALARA process employs a systems-type approach to ensure that protective and cost-effective controls are implemented in public and environmental protection matters. It requires consideration of and comparisons between radiation doses and health effects to the public and workers, environmental impacts, costs, and natural and cultural resources. Similarly, in the development of DOE 5400.1, DOE is considering applying a systems approach to environmental management of DOE facilities. This systems approach will require that the development of site-specific environmental protection strategies consider all media, pathways, impacts, and risks in a manner that, on balance, results in the most effective, protective, and practical approach. As with the ALARA process, this approach requires that benefits and costs of different health and environmental endpoints be compared and assessed equitably. Hence, a clear understanding of science policy issues and decisions, and their possible impacts to the decision-making process may be an important consideration in the implementation and development of these environmental protection requirements.

In the development of DOE environmental risk management strategies relating to cleanup and remediation programs, it is necessary to assess and characterize as rigorously as possible the impacts and risks to human health, the environment, and cultural, natural, and other resources associated with sites and facilities operations. The fair comparison of these varied impacts and benefits requires a clear understanding of the assessments. Toward this end, and consistent with recommendations from the National Academy of Sciences, it is desirable to distinguish the objective, science-based elements from the policy-based elements of environmental risk assessment and management decisions. Additionally, to characterize impacts or risks, it is necessary to have an understanding of the effects of policy-based decisions on the assessments and management decisions.

The Sandia National Laboratories (SNL), a DOE national laboratory, was tasked to conduct the Science Policy Impact Analysis Project. As part of the project, the Regulatory Impact Analysis Project, Inc. (RIAP), a nonprofit research organization, was tasked to prepare this report. In developing this report, RIAP sought and received input from a large number of individuals and organizations with expertise and experience in regulatory risk assessment and risk management. Contacts included scientists and risk assessors in government, academia, and industry and nonscientist risk managers, policy makers, and regulatory experts (see Appendix I for a list of project information sources). We express our deep appreciation to these individuals and organizations.

RIAP collected more than 1,500 studies, reports, documents, and analyses concerning environmental, safety, and health regulatory actions involving risk assessment. Despite the large number of documents collected, the project's data collection effort does not

and is not intended to reflect the total information on environmental risk assessment and risk management in print. Nonetheless, we are confident that sufficient information was collected and analyzed to produce a report that factually and fairly discusses and characterizes the role of science policy in environmental risk assessment and management.

The project was conducted in two stages. In the first stage, RIAP collected information through: (1) interviews with individuals in the public and private sectors who are knowledgeable about regulatory risk assessment and science policy and (2) research into environmental protection and regulatory issues that were raised by project information sources known to RIAP staff, or developed through project research efforts.

From the many regulatory topics and decisions identified through project research efforts, eight were selected as vehicles through which to discuss science policy and its regulatory impacts. Factors considered in selecting these topics for presentation in the final report were: (1) the nature and extent of the science policy issues involved; (2) the nature and extent of the regulatory impacts of the associated regulatory program; (3) familiarity of the regulatory topic among the public; and (4) variety among topics with respect to regulatory programs and agencies. The second stage of the project involved comprehensive research of the selected topics and preparation of the final report. While the examples selected for review may or may not impact DOE, the analyses of science policy issues are pertinent to DOE's efforts to develop environmental protection strategies or requirements, insofar as such development uses environmental risk assessment methodology.

This report discusses science policy primarily in the context of cancer risk assessment. Science policy is addressed only briefly in the context of ecological risk assessment and only incidentally in the context of noncancer risk assessment. The lack of attention to ecological and noncancer risk assessment or the assessment of their impacts or benefits should not be viewed either as a shortcoming of the report or a dismissal of such issues as unimportant or uninteresting. As a matter of fact, much of DOE's desire for an improved understanding of science policy issues and decisions is derived from the need to compare and balance competing ecological and resource related impacts to cancer and noncancer health risks in the decision making process. Risk assessment has historically focused on the likelihood of inducing cancer in humans. However, as the recent Environmental Protection Agency reassessment of dioxin risks indicates, noncancer effects may be triggered at very low levels of exposure. Noncancer risk assessment is an emerging area, not nearly as well studied as carcinogenicity, that m may become a driving force in risk assessments and cleanup decisions in the near future. The focus of the project was science policy, not cancer, noncancer, or ecological risk assessment. Because it is a more seasoned process, cancer risk assessment is a more convenient vehicle through which to discuss science policy. We expect that lessons learned in cancer risk assessment will be applicable to risk assessments for other ecological and health endpoints.

Given that much has been written on environmental risk assessment and risk management over the last twenty or so years, some may wonder what the value of yet another exposition on these issues might be. This report addresses these issues from a unique perspective. We do not intend to be critical or complimentary of the regulatory risk assessment process. Recommendations for improving environmental risk assessment per se or for further scientific research are not made in this report. Although advances in scientific knowledge and assessment methodology are clearly desirable and are occurring, advances in either area will not come soon enough to assist regulators in addressing the onslaught of genuine and manufactured, known and hypothetical, and significant and insignificant environmental, safety, and health risks and issues currently facing DOE and other federal agencies. We accept environmental risk assessment for what it is—a tool to assist regulators in making decisions concerning difficult issues. This tool has its strengths and its limitations, which are the focus of this report. Wider recognition and better understanding of these strengths and limitations will not make regulatory decisions easier but may result in more informed, unbiased, and transparent decisions.

We would like to express our deep appreciation to DOE's Office of Environmental Guidance, in particular Mr. Andrew Wallo, III, for input to and oversight of this project, and SNL staff, particularly Dennis Berry, Ph.D.; Charles Massey, Ph.D.; and Ms. Teresa Sype for their valuable assistance. Additionally, we would like to thank the reviewers of this report, including William Raub, Ph.D. (Science Advisor to the Administrator of the Environmental Protection Agency); Michael Gough, Ph.D. (Manager, Biological Applications Program, Office of Technology Assessment, U.S. Congress); William Mills, Ph.D. (Senior Scientist/Policy Advisor to the Committee on Interagency Radiation Research and Policy Coordination); Bryan Hardin, Ph.D. (Director of the Washington, D.C., Office of the National Institute for Occupational Safety and Health); Ronald Lang, Ph.D. (President, American Industrial Health Council); Ernest S. Rosenberg, Ph.D., J.D. (Director of External Affairs and Compliance Support, Occidental Petroleum Corp.); and Joe Findaro, Esq. (Bayh, Connaughton, Fensterheim & Malone). Finally, we would like to thank our staff who worked very hard in the preparation of this report: Ms. Martha D. Kaufman and Ms. Hollie Burdt Sheaffer.

Steven J. Milloy, Project Manager
Pamela S. Aycock, Research Manager
Jason E. Johnston, Senior Research Associate
Regulatory Impact Analysis Project, Inc. October1994

TABLE OF CONTENTS

EXECUTIVE SUMMARY

What Is Science Policy?

In the context of this report, “science policy issues” are the gaps and uncertainties in scientific knowledge and data that arise in the assessment of risks to human health and the environment associated with exposure to substances, conditions, activities, and sites. “Science policy decisions” are the policy choices made to bridge such gaps and uncertainties. Science policy decisions are vital to the regulatory risk assessment and management processes. Science policy decisions enable regulators to justify the costs of regulatory programs in terms of estimated health and environmental risk reductions.

Default Assumptions

Default assumptions are science policy decisions that are applied automatically when certain science policy issues arise. Examples of science policy issues and the corresponding default assumptions are presented in Table ES I. Default assumptions are perceived—and criticized—by some as being conservative. There are others who criticize them for insufficient protectiveness. The selection of default assumptions generally is driven by the policy decision to avoid underestimating potential risks. Given the frequent use of quantitative risk assessment in health and environmental regulation, for any individual science policy issue, use of a default assumption may be the most practical option for getting the work done. Departures from default assumptions have been rare in the past, but alternate assumptions have been adopted in limited cases. Attempts to depart from default assumptions in future risk assessments may invite increased scrutiny, which could result in a reluctance to consider or adopt alternatives based on new scientific information. Continued reliance on default assumptions can be problematic in two scenarios:

1. Multiple conservative science policy decisions, known as "compounded conservatism," may result in inconsistent or unduly biased decisions; and
2. Whether or not compounded conservatism results, policy makers, risk managers, the media, and the public are often unaware of:
    a. The gaps and uncertainties in scientific knowledge and data used in conducting a risk assessment;
    b. The policy-based default assumptions that are used to bridge these gaps and uncertainties; and
    c. The extent to which default assumptions may determine the outcome of the risk assessment.

Table ES-1. Basic Science Policy Issues and Default Assumptions	
Science Policy Issue	**Default Science Policy Assumption**
In the absence of adequate human data, what is the relevance of animal bioassay data to the estimation of human risk?	A substance that is carcinogenic to animals is also a human carcinogen.
Is the occurrence of benign tumors in experimental animals relevant to estimating human cancer risk?	Benign tumors are combined with malignant tumors in animals to establish carcinogenic potential in humans.
When both positive and nonpositive cancer incidence data exist, should the nonpositive data be used for quantitative risk assessment purposes?	In the presence of positive data, nonpositive data do not indicate safety and should not be used in quantitative risk assessment.
What is the relevance of data from animal bioassays conducted with MTD protocols to estimating potential human risk?	Carcinogenic effects observed at the MTD in animals are predictive of effects in humans at much lower doses.
Which animal species should be used to represent humans in terms of carcinogenic response?	The animal species exhibiting the greatest sensitivity is the most appropriate for risk assessment.
When predicting human health risk on the basis of animal data, how should mechanistic variations between species be taken into account?	Differences between species in mechanisms of carcinogenicity are not taken into account when extrapolating data from one species to another.
Data indicate that ingestion of a substance may be associated with cancer. If inhalation exposures are of concern, what is the relevance of the ingestion data to the assessment of risk?	A carcinogen by one route of exposure is a carcinogen by any other route of exposure.
The available data do not demonstrate the absence or existence of a threshold for carcinogenesis.	There is no nonzero dose below which an increase in cancer risk does not occur.
Data indicate a dose-response relationship at high doses, but few or no data concerning the dose-response relationship at lower levels exist.	The dose-response relationship is linear at low doses.
If data on human exposure are unavailable for a particular substance or site, how can exposures be estimated for purposes of quantitative risk assessment?	Chosen values for exposure variables are upper-bound point estimates which, when taken together, do not result in unrealistic exposure estimates.

Current scientific knowledge cannot determine which default assumptions are correct. Science may never be able to answer certain questions that transcend the capabilities of the scientific method. These "trans-scientific" questions include: "What is the shape of the dose-response curve at low doses?" and "Do thresholds for carcinogens exist?" Therefore, it is likely that policy-based default assumptions will always be necessary in risk assessment. However, continued reliance on default assumptions in all cases represents and promotes the stasis of science and risk assessment, and research will continue to identify plausible alternatives for default assumptions. Pressure to incorporate alternative assumptions in risk assessment is increasing.

Alternatives to the Default Assumptions

Plausible alternatives to the default assumptions are available in many, specific instances. In most cases, justification of an alternative relies on chemical- and species-specific data and arguments. Consequently, it is unlikely that any default assumption will be completely replaced. A justifiable alternative may be identified for a class of chemicals, but at present there is no universally justifiable and acceptable alternative to any of the default assumptions. Replacement of default assumptions will occur only after sufficient research and data have indicated that an alternative is more likely to be correct than the default. The alternative must also still be protective of public health. Thus, in the near future, research on alternatives will be limited in impact and will likely result only in incremental changes in the risk assessment process.

The Comprehensive Methodology developed by the American Industrial Health Council represents a potential revolution in the way risk assessments are conducted. Some believe that, if combined with physiologically based pharmacokinetic models and distributional exposure assessments, this methodology could be a dramatic improvement over current risk assessment methods. Full and complete incorporation of all uncertainty and variability would be achieved, and exposures and risks would be expressed in terms of probabilistic distributions. Regulatory decision makers would be presented with complete probabilistic descriptions of the ranges of expected exposures and risks, rather than point estimates. Probabilistic distributions would enable decision makers to consider the likelihood that various exposure and risk estimates will occur and determine explicitly the appropriate degree of conservatism in regulations. This would allow for a degree of separation of risk assessment and risk management, as advocated by the National Research Council that cannot currently be achieved.

Such a change in environmental regulatory decision making within federal agencies will require a commitment to the need for such a change as well as a commitment to funding the required research. If regulatory agencies indicate a willingness to evaluate and incorporate alternatives to default assumptions in regulatory risk assessments, the regulated community will have an incentive to conduct the necessary research. In the end, all parties likely will benefit as knowledge of mechanisms of carcinogenesis and understanding of the hazards posed by environmental contaminants is increased.

Case Studies on Science Policy

Fluoride in drinking water

Fluoride has been artificially added to drinking water as a public health measure to reduce the incidence of dental caries since the U.S. Public Health Service (PHS) first identified an optimal fluoride concentration in 1943. Nevertheless, communities have debated the relative benefits of reduced dental caries and improved oral health versus the potential risks of adverse health effects on teeth and bones. The public health community has long held that the benefits of fluoridation far outweigh any potential risks. Potential long-term health effects, however, are poorly understood. Recent animal studies associating increased cancer risk with fluoridated drinking water provoked renewed concern. Epidemiologic studies have not conclusively established an association between fluoride and bone cancer risk in humans. The major science policy issue considered in this case study is the evaluation of fluoride as to its potential to cause cancer in humans. Two recent reviews of the available animal and human data concluded that there is no evidence that fluoride is a human carcinogen. The Environmental Protection Agency (EPA) subsequently announced that the existing fluoride drinking water standards would not be revised. Given the benefits of fluoridation and the ease with which cosmetic and potentially adverse effects can be minimized or avoided, it would have been imprudent to suggest a change in the regulation of fluoride in drinking water on the basis of inconclusive evidence of carcinogenicity in male rats. A possible additional motivation behind the decision not to change the regulatory standard for fluoride in drinking water might have been fear of the tumult that would have ensued in the public health community and in the public at large if fluoride were judged to be carcinogenic. Classification of fluoride as a possible human carcinogen could have critically damaged the credibility of the PHS, which has aggressively promoted fluoridation for fifty years.

Asbestos in consumer products

Due to its durability and heat-resistant properties, asbestos has been used in a variety of consumer products since the late nineteenth century. Concern about asbestosis and lung cancer associated with asbestos exposure has grown throughout the twentieth century. Asbestos is regarded by EPA and the International Agency for Research on Cancer (IARC) as a known human carcinogen. New uses of asbestos have been banned in the United States since the 1980s. Considerable resources have been devoted to removing asbestos from public buildings, especially schools. In response to growing concerns about adverse health effects associated with asbestos, EPA promulgated a ban on the manufacture, importation, processing, and distribution of existing consumer products containing asbestos in 1989. The ban was remanded by the U.S. Court of Appeals for the Fifth Circuit in 1991 because EPA had not sufficiently justified the ban and had not fulfilled the requirements of the Toxic Substances Control Act (TSCA). The science policy issues supporting the court's decision were EPA's inadequate

consideration of risks to health and safety posed by potential asbestos substitute Products and EPA's use of analogous exposures to estimate benefits of the ban without provisions for public review and comment. EPA has yet to take further action. If the regulation of asbestos-containing products is revisited, special attention should be paid to substitute risk issues. A risk analysis supporting a proposed regulation is not complete unless the full consequences of the regulation are evaluated.

Unleaded gasoline

Automobiles and other motor vehicles are a widely recognized source of significant air pollution. Pollutants of concern associated with motor vehicles include lead, hydrocarbons, carbon monoxide, and nitrogen oxides. Unleaded gasoline, which was originally required for use with catalytic converter-equipped cars, has been on the market for more than twenty years. Continuing attention to reducing air pollution has resulted in increasingly stringent exhaust emissions requirements on automobiles and the elimination of leaded gasoline as a fuel. This case study focuses on unleaded gasoline, which has been associated with kidney tumors in male rats. The central science policy issue is determining the relevance of a particular type of kidney tumor in male rats to human cancer risk assessment. As a default science policy decision, cancer in animals is assumed to be predictive of carcinogenic effects in humans. EPA scientists evaluated mechanistic data and determined that the kidney tumors observed only in male rats exposed to unleaded gasoline were of no relevance to potential human cancer risk. If unleaded gasoline had been implicated as a rodent carcinogen, and subsequently suspected of being a human carcinogen, significant upheaval concerning the use of unleaded gasoline could have ensued, potentially damaging the credibility of EPA which has promoted the use of unleaded gasoline over the last twenty years.

Used oil

More than 1 billion gallons of used oil are generated each year in the United States. Used oil contains a variety of toxic and carcinogenic substances and can therefore pose a threat to human health and the environment, especially when improperly managed or disposed. In developing the Hazardous Waste Management System mandated under the Resource Conservation and Recovery Act (RCRA), EPA had to decide whether or not to designate used oil as a hazardous waste. All hazardous wastes must be managed under strict standards in Subtitle C of RCRA. EPA evaluated and re-evaluated the data and requirements of RCRA and other statutes and changed its position several times. As a matter of science policy, EPA determined that the hazards posed by used oil did not meet the criteria for hazardous waste listing under RCRA. Litigation ensued when petitioners questioned the validity of an EPA proposal not to list used oil on the basis that the resulting stigma would have negative effects on recycling. Eventually, EPA fulfilled the RCRA mandate and fostered recycling by instituting special management standards for used oil but not listing it as hazardous waste.

Trichloroethylene

Trichloroethylene (TCE) has long been used in a variety of industries and is therefore a groundwater contaminant at numerous sites. Superfund law and policy require that contaminants in certain groundwater aquifers be cleaned up to drinking water standards. Remediation of contaminated groundwater often drives the cost and duration of Superfund site cleanups. EPA classifies TCE as a probable human carcinogen. However, evidence is gathering that TCE is either not carcinogenic or not as carcinogenic in humans as once thought. Incorporation of alternative science policy decisions could result in less stringent drinking water standards for TCE. The standards applied to groundwater cleanup would also be less stringent, which would reduce remediation costs but not public health protection.

Workplace indoor air quality

The Occupational Safety and Health Administration (OSHA) recently proposed to regulate indoor air quality (IAQ) in the workplace. Improved IAQ is intuitively desirable, but scientific data concerning IAQ are sparse. The lack of data limits OSHA's ability to assess the health risks posed to workers by poor IAQ. The proposed IAQ regulation includes a ban on workplace smoking, except in specially designated and separately ventilated areas, as well as measures designed to address other indoor air contaminants. This case study examines the science policy in OSHA's risk assessment for environmental tobacco smoke (ETS) and the estimated costs and benefits of the proposed smoking ban. Despite a relatively large database of information on human lung cancer risk from exposure to ETS, OSHA had to make a number of science policy decisions to conduct the quantitative risk assessment necessary to justify the proposed smoking ban. Although the estimated costs of the proposed smoking ban appear to be relatively low and the estimated benefits appear to be relatively high, the costs may be incomplete and the benefits may be substantially overstated. The information database for the remainder of the proposed rule for IAQ is not nearly as extensive as that for ETS, and the associated science policy decisions are likely to be more tenuous than those for ETS. Because the estimated costs of the portion of the proposed IAQ rule not addressing smoking are very high, the proposed science policy decisions are even more questionable.

Toxics Release Inventory

The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) requires industrial facilities to report their releases and transfers of toxic chemicals listed on the Toxics Release Inventory (TRI). The purpose of such reporting is to provide communities with information concerning routine local releases and transfers of toxic chemicals. TRI reporting is not intended to reduce or restrict routine or permitted releases of and exposures to chemicals and does not directly reduce health risks. Congress established the initial list of chemicals subject to TRI reporting, but EPA is authorized to add chemicals to and delete chemicals from the TRI. The criteria for listing

chemicals on the TRI are expressly stated in EPCRA, but their broad wording requires EPA to exercise judgment in determining whether a chemical is toxic. Decisions to label chemicals as toxic depend on science policy decisions. This case study focuses on EPA's recent proposal to add another 313 chemicals to the TRI and provides insight on how EPA currently makes science policy decisions in the context of TRI reporting.

Radon in drinking water

The 1986 Amendments to the Safe Drinking Water Act (SDWA) required EPA to regulate eighty-three contaminants, including radon, by June 1989. On July 18, 1991, EPA proposed a drinking water standard for radon of 300 picocuries per liter (pCI/L). The proposed standard is based on the capability of available technology to reduce radon levels in water to less than (100 pCI/L and on detection limits for radon in water. Final drinking water standards for radon have not yet been promulgated due to the controversial nature of the proposal and continued congressional and Science Advisory Board involvement. EPA is under a court-ordered deadline to issue a final standard for radon by April 30, 1995. The assessment of risks associated with exposures to radon in drinking water is highly uncertain. Relevant science policy issues addressed in this case study include the assumption of low-dose linearity for risk extrapolation, the use of surrogate data to estimate risks of nonlung cancers associated with ingestion of radon in drinking water, and the choice of assumed values for exposure variables used in the quantitative exposure and risk assessment. EPA did not use maximally conservative estimates and approaches in calculating the risk attributable to radon in drinking water. Had typical default assumptions been used, the estimated benefits of adopting a standard of 300 p CI/L would have been greater. The uncertainty regarding the risk assessment is illustrated by alternative assumptions, which if used would reduce the published risk estimates by a factor of ten or more. The SDWA does not allow for the consideration of exposures and risks from other sources. Thus, despite widespread dismay that EPA is proposing to devote considerable resources to addressing a small portion of the total potential risk due to radon, EPA is subject to an antiquated, media-specific law that effectively precludes multimedia approaches and relative risk considerations.

Conclusions

Many risks to human health and the environment are "unprovable."

Some risks to human health and the environment are provable. Provable risks can be measured or observed directly and include actuarial risks such as those associated with highway or air travel accidents. In contrast, other risks—such as those associated with low-doses of radiation or exposure to chemicals in the environment—are often too small to be measured or observed directly with existing scientific methods and available resources. Additionally, specific health and environmental effects are often difficult to attribute to specific causes because other competing causes cannot be excluded with reasonable certainty. Such risks are unprovable. However, the fact that a risk is

unprovable does not mean that it does not exist. Provable risks can be calculated, whereas unprovable risks can only be estimated through the risk assessment process. Although unprovable risks may be estimated and expressed in probabilistic terms, they are at best educated guesses and do not constitute knowledge or uncontroverted fact. In other words, the ability to produce a numerical estimate of an unprovable risk does not mean that the risk is proven.

Science policy issues are unavoidable in, and science policy decisions are essential to, the regulatory risk assessment process.

Risks are unprovable because of significant gaps and uncertainties in scientific knowledge, data, and method. When risk assessment is used to estimate unprovable risks, these gaps and uncertainties become science policy issues. Both risk assessors and risk managers make science policy decisions in order to bridge the gaps and uncertainties. Thus, science policy decisions enable the estimation of unprovable risks.

Science policy decisions, particularly when compounded, lead to conservative risk assessment results.

By design, many science policy decisions lead to risk assessment results that are more likely to overstate than to understate risks. In other words, compensation for the lack of knowledge in the risk assessment process is intended to be protective of public health. Risk assessment results are even less likely to underestimate risk when, as is generally the case, a series of conservative science policy decisions is involved. There is nothing wrong with such science policy decisions and risk assessments unless the nature and extent of the science policy decisions made are not fully disclosed to policy makers, risk managers, the media, and the public.

The existence and extent of science policy in risk assessment are rarely fully and fairly disclosed.

The numerical results of risk assessments tend to be emphasized while discussions of the role of science policy in generating the risk assessment results tend to be de-emphasized. For example, given that many risks are unprovable, there is some probability that, in fact, they are zero. For unprovable risks, science policy decisions enable the estimation of nonzero risks. However, this fact rarely, if ever, is clearly presented in a risk assessment. The lack of disclosure causes risk assessment results to be communicated essentially as fact. Such communication is misleading. Lack of full and fair disclosure of the role of science policy in risk assessment is not the fault of regulators alone. Media communication of risk information tends to omit discussions of science policy because such discussions: (1) do not fit into sound bites; (2) tend to detract from the sensationalism of the risk information; or (3) are not simple to communicate, and subtleties are lost.

Science policy decisions are responsible for regulatory programs and regulatory impacts that are justified on the basis of risk assessment.

For regulatory activities and programs that involve or depend upon risk assessment, the science policy decisions made generally determine the existence, extent, and continued credibility of the regulatory activities and programs. As illustrated by the case studies in this report, science policy decisions have been instrumental in determining that:

- Used oil should not be classified as a hazardous waste subject to regulation under Subtitle C of the Resource Conservation and Recovery Act;
- Unleaded gasoline is not carcinogenic to humans;
- Fluoridated drinking water is not carcinogenic, and drinking water should continue to be fluoridated as a public health measure; and
- Commercial uses of asbestos could be banned under the Toxic Substances Control Act.

In the future, science policy decisions will be used to help determine whether:

- Glass wool, food additives, nitrogen dioxide, sulfur dioxide, nitrate ion, phosphorus compounds, and other chemicals will be added to the Toxics Release Inventory,;
- Workplace indoor air quality will be regulated;
- Drinking water standards for radon will be made more stringent; and
- Remediation of Superfund sites contaminated with trichloroethylene will continue to be as stringent as currently required.

As in the risk assessment process, science policy and other assumptions play a significant role in the estimation of benefits and costs associated with regulatory programs.

When risks can only be estimated, the benefits of regulatory programs to reduce those risks also can only be estimated, are not verifiable, and depend on science policy-based assumptions. Similarly, cost assessments often depend on assumptions, are uncertain, and cannot constitute uncontroverted fact. An important distinction between estimates of costs and benefits is in the certainty of their existence. Because it is not possible to prove with certainty the existence of unprovable risks, the existence of benefits from regulatory programs also cannot be proven. In contrast, while there is uncertainty involved in cost assessments, such uncertainty is associated with the magnitude of the estimated costs, not their existence.

Science policy decisions can be made so as to result in desired regulatory outcomes.

The case studies of fluoride in drinking water, asbestos in consumer products, unleaded gasoline, and used oil are examples of decisions where science policy-based assumptions help to justify desired regulatory outcomes.

- In the case of fluoride in drinking water, the weight-of-evidence science policy decision that fluoride was not carcinogenic in humans supported the continued fluoridation of water, a highly valued and desirable public health measure. This science policy decision also helped maintain the credibility of the Public Health Service, which has been promoting the use of fluoride since the 1940s.
- In the case of asbestos in consumer products, the science policy decision to consider only the estimated cancer risk from asbestos brake products and not to consider the potentially offsetting safety risk from the use of nonasbestos brake product substitutes helped justify EPA's decision to promulgate a ban on commercial uses of asbestos.
- In the case of unleaded gasoline, the science policy decision that mechanisms of carcinogenicity varied between rodents and humans provided the basis for concluding that unleaded gasoline is not carcinogenic to humans. This science policy decision helped maintain the credibility of EPA's program to remove lead from gasoline.
- In the case of used oil, the science policy decision that used oil is not a hazardous waste facilitates used oil recycling. Labeling of used oil as a hazardous waste would have resulted in a burdensome cradle-to-grave regulatory scheme for used oil that might have undermined recycling efforts and increased pollution from illegal or improper disposal of used oil.

For the foreseeable future, science policy will remain the key to all regulatory programs that rely on quantitative risk assessment.

Although a great deal of scientific knowledge has been developed over the last twenty years, existing knowledge still cannot answer all the questions we can put to it. Advances in knowledge are not likely to come fast enough to address the onslaught of genuine and manufactured, known and hypothetical, and significant and insignificant risks faced by regulatory agencies, the regulated community, and the public. Although continued scientific research is highly valued, from a practical point of view, regulatory agencies rarely enjoy the luxury of time to wait for new research to aid them in regulatory decisions. Hence, science policy decisions will continue to be relied upon by regulators. For policy makers and risk managers who are aware of the tendency of risk assessors to make conservative science policy decisions, regulatory decisions are easier, because they know their decisions are not likely to be made on the basis of underestimated risk.

Recommendations

Policy makers, risk managers, the media, and the public should be made aware of the role of science policy in risk assessment and subsequent risk management decisions.

Although risk assessors are likely to be aware of science policy issues and decisions, the same cannot be said for policy makers, risk managers, the media, and the public. Risk assessors often fail to emphasize the existence and extent of science policy in risk assessment. Where the role of science policy is not explicitly explained, risk estimates may be erroneously communicated to policy makers, risk managers, the media, and the public as uncontroverted fact. Because these groups are unaware of the role of science policy, they often fail to inquire about its impact on risk assessment. Either failure may result in regulatory decisions that are made on an uninformed basis to an uninformed, misled, or unnecessarily alarmed public. Risk assessors should ensure that such miscommunication does not occur. Policy makers, risk managers, and the media should inquire about the existence and extent of science policy.

The federal government should institute a mandatory training and continuing education program on regulatory risk assessment and risk management for policy makers, risk managers, risk assessors, and their staffs.

Decisions based on risk assessment affect the health and of safety people, the condition of the environment, the operation of the federal, state, and local governments, and the operation of industries and businesses. Remarkably, no formal training in risk assessment or risk management is required of the policy makers, risk managers and risk assessors and their staffs who participate in the making of these weighty regulatory decisions. In contrast, physicians, attorneys, policemen, firefighters, plumbers and electricians, among others, are required to undergo substantial training, apprenticeship, and licensing before engaging in their respective occupations. Although professional societies exist, and regulatory agencies sponsor seminars and workshops from time to time, there is no system in place which attempts to achieve a minimal level of competence in the area of risk assessment and risk management among all policy makers, risk managers, risk assessors, and their staffs. It is quite likely that a mandatory training and continuing education program that explicitly discusses science policy as a matter of policy rather than fact would: (1) improve awareness and understanding of science policy throughout the federal government; (2) result in more effective, efficient, and timely regulatory programs; and (3) pay for itself in a short period of time.

Communication of risk assessment results should emphasize the role of science policy.

Because risk assessments for unprovable risks are educated guesses, risk assessment results should never intentionally or inadvertently be presented as fact. Full disclosure of the role of science policy should accompany risk estimates wherever presented, including Federal Register notices, executive summaries of regulatory documents, press

releases, and other public and media communications. Disclosure is ineffective if it is inaccessible, comprehensive, explicit, and understandable. Disclosure should attempt to address the following questions:

- Is the risk of concern provable, and can it be calculated? If the risk is unprovable, is it because the risk is too small to be detected with current scientific methods or because competing risk factors cannot be sufficiently distinguished?
- If the risk is unprovable, or provable but incalculable, what are the gaps and uncertainties in scientific knowledge and data that preclude the calculation of risk?
- what science policy decisions have been made to bridge these gaps and uncertainties? For unprovable risks, what science policy decisions have been made that concern the existence of the risk?
- could alternative science policy decisions have been considered? What would the impacts have been on the risk assessment of these alternative decisions?
- what are the implications for regulation of the science policy decisions made as well as the alternatives? Do alternative science policy decisions reduce or eliminate the basis for regulation? Does consideration of substitution risks or lifecycle risks affect the basis for regulation?

Answers to these questions will facilitate understanding of the likelihood that a risk exists and its potential magnitude. Improved understanding will enable: (1) policy makers and risk managers to decide on a more fully informed basis whether and what resources should be expended to address the risk; and (2) the public and media to debate the issue on a more fully informed basis.

Risk assessment guidelines may help provide a framework for the use of science policy in risk assessment, but only if such guidelines are flexible and complied with in good faith.

Risk assessment guidelines can provide a framework within which regulators can make science policy decisions. Such a framework would provide the regulated community and the public with the "rules" for science policy decisions in regulatory risk assessment. Flexible guidelines would delineate the factors to be considered in developing a risk assessment and would require explanations for all judgments. Risk assessment guidelines should not establish a cookbook approach. Unless the guidelines are flexible enough to accommodate new scientific developments and specify the level of evidence required to deviate from a default assumption, efforts to develop new knowledge may be stymied or wasted. This could, in turn, inhibit advances in risk assessment. To the extent that risk assessment guidelines actually provide policy guidance, such guidance should be complied with in good faith by regulatory agency staff or it will be of little practical value. With respect to potential judicial review, although it will be difficult for a court to rule on the scientific merits of an agency science policy judgment, a court can

rule whether that judgment has been explained adequately. Ultimately, the merits of the judgment will be evaluated, and the agency's credibility will be weighed in the court of public opinion as well as by the scientific community.

Precedent has been established, and agencies should be encouraged to give meaningful consideration to alternatives to the default assumptions used in risk assessment.

Default science policy decisions generally are employed in risk assessment. In some cases, however, regulatory agencies have opted to use alternatives to the default science policy decisions where the alternatives are supported by scientific knowledge or data. This trend should be encouraged. To the extent possible, risk assessment guidelines should provide a timely and effective process for evaluating and implementing potential alternatives to the default science policy decisions. Such a process should include a compliance mechanism, perhaps independent from the particular regulatory agency, to ensure an objective review.

Summary

Risk assessment is a valuable tool through which regulators can gauge the existence and severity of potential risks to human health and the environment. Risk assessment cannot provide the definitive answers policy makers, regulators, the regulated community, and the public would like. Nonetheless, risk assessment based on science policy can frame the debate about whether particular potential risks should be regulated and who should bear the costs of regulation. Full and open disclosure of science policy in risk assessment can take this debate to the next level.

Only when policy makers, risk managers, the public, and the media fully understand the role of science policy decisions in risk assessment can the "real" issue in environmental and public health protection be debated. We must determine what society is willing to pay to reduce or avoid risks to human health and the environment which have been identified and estimated using science policy rather than science alone. These risks may or may not actually exist. If they do exist, they are likely to be relatively small or indistinguishable from other risks. If risks are too small or indistinguishable, it likely will not be possible to know whether regulation produced any benefit. The open debate of the value and priority of regulating these types of risks will enable, but not guarantee, policy and regulatory decisions to be made on a fully informed basis.

1
WHAT IS SCIENCE POLICY? WHAT ARE ITS IMPACTS? A HYPOTHETICAL EXAMPLE

In the context of this report, "science policy issue" refers to the gaps and uncertainties in scientific knowledge, data, and methodology that arise in assessing the risks to human health and the environment of exposure to substances, conditions, activities, and sites. "Science policy decision" refers to the decisions made by regulatory agencies to bridge such gaps and uncertainties. Science policy decisions are vital to the current regulatory risk assessment and risk management processes because they enable regulators to develop a basis on which to justify the costs of regulatory programs in terms of health and environmental risks reduced and benefits obtained.

To understand the role that science policy plays in risk assessment, consider the following hypothetical, but not unrealistic, example. Suppose you are the regulatory official responsible for determining whether and how human exposure to Substance X should be regulated because it may cause cancer. You ask your staff scientists to conduct the necessary risk assessment. Your staff will probably take the following steps:[1]

1. Determine whether Substance X has the potential to cause cancer in humans;
2. Determine what level of human exposure to Substance X causes cancer;
3. Determine whether any individuals are exposed to Substance X at levels which may cause cancer; and
4. Characterize and present all the scientific and risk information gathered.

Based on the information presented by your staff, you will decide whether and how to regulate Substance X. Through comprehensive research, your staff have determined that there are no available studies that directly associate Substance X with cancer in humans. However, the results of several laboratory experiments published in the scientific literature report that rats and mice fed relatively high doses (i.e., 1,000 milligrams of Substance X per kilogram body weight daily [mg/kg/d]) in their diet for two years experienced an increased incidence of tumors of the forestomach. Statistically significant increased tumor incidence was not reported at the other dose levels tested in the experiment (750, 500, and 250 mg/kg/d). The reported increase in cancer was

[1]These steps correspond to the four-step risk assessment paradigm of hazard identification, dose-response assessment, exposure assessment, and risk characterization. See (National Research Council [NRC] 1983).

statistically significant only if both benign tumors and malignant tumors were counted together. Your staff conclude that the observed carcinogenic response in animals indicates that Substance X may be carcinogenic in humans as well.

Your staffs then determine that Substance X is widespread in the environment and that all humans are exposed to levels of Substance X of up to 0.01 mg/kg/d. Exposure to Substance X is estimated to cause 1,000 deaths from cancer annually which would not otherwise have occurred (referred to as excess or premature cancer deaths).

Based on the information presented by your staff, you conclude that a regulatory program should be developed and implemented to reduce human exposures to Substance X. Your staff have determined that Substance X can be virtually eliminated from the environment, thereby avoiding 900 cancer deaths annually at a annual cost of $1 billion. You calculate that such a regulatory program, which would expend approximately $1.1 million per cancer death avoided, is relatively cost-effective when compared to the costs of other regulatory programs. [2]

Your staff were faced with several gaps and uncertainties in scientific knowledge, data, and method in their attempts to estimate the risks associated with exposure to Substance X. Your staff made several science policy decisions—some of which were compelled by existing policy guidelines—to bridge those gaps. You may or may not have been made aware of them or their impact on the conclusions reached by your staff. The science policy issues and decisions relevant to this example are discussed below.

- **Science policy issue and decision #1.** No scientific studies associate human exposure to Substance X with cancer. Your staff had no direct information concerning whether Substance X might cause or be associated with cancer in humans. Only rodent laboratory experiments associated Substance X with cancer. In order to be protective of human health, your staff assumed that Substance X could reasonably be expected to cause cancer in humans because it has been demonstrated to cause cancer in animals.
- **Science policy issue and decision #2.** The animal study reported an increase in cancer in the rat forestomach. Humans do not have forestomachs. However, the human esophagus may be biologically similar to the rodent forestomach and could respond similarly. In order to be protective of human health, your staff assumed that the biological mechanism that led to cancer in the rodent forestomachs has an analogous mechanism in humans.

[2] The cost per premature death avoided has been estimated for a variety of environmental regulatory actions. Example estimated costs per avoided death include $200,000 for trihalomethane drinking water standards, $3.4 million for radionuclide standards in mines, $110 million for the ban on asbestos in consumer products, and $5.7 trillion for the hazardous waste listing for woodpreserving chemicals (Office of Management and Budget [OMB] 1992, 12).

- **Science policy issue and decision #3**. The increases in cancer incidence in the rodent studies were statistically significant only if both benign and malignant tumors were considered to be indicative of the carcinogenic action of Substance X. Benign tumors, however, are not cancerous and do not necessarily progress to malignancy. If only the malignant tumors associated with Substance X in the rodent studies were counted, you could not conclude with certainty that they were associated with exposure to Substance X. However, because some benign tumors do progress to malignancy, in order to be protective of human health, your staff assumed that both benign and malignant tumors are indicative of Substance X's carcinogenicity.
- **Science policy issue and decision #4.** The rodents were fed 1,000 mg/kg/d of Substance X for two years. Estimated human exposures are 100,000 times lower. Although you have no information either supporting or contradicting an association between low-dose exposure to Substance X and increased cancer risk in humans or animals, to be protective of public health, your staff assumed that any human exposure to Substance X will result in increased human cancer risk.
- **Science policy issue and decision #5.** Mathematical modeling to extrapolate the rodent data to human risk estimates is necessary to estimate how much cancer is attributable to Substance X. Using the linearized multistage model, which is designed to calculate an upper-bound limit on the risk at very low doses, in conjunction with population exposure estimates, your staff estimated that human exposures to environmental levels of Substance X are associated with 1,000 excess cancer deaths per year.

Thus, your decision to implement the regulatory program was made possible only by a series of science policy decisions. Each of these decisions was made so as not to underestimate possible risks to public health, and to reflect a desire to be protective of human health in the face of uncertainty. The science policy decisions filled the voids in knowledge which otherwise would have prevented your staff from quantifying potential human cancer risk associated with exposure to Substance X. Without the resulting quantitative risk assessment, you could not have understood the potential magnitude of the problem or been able to make the risk management decision to proceed with a regulatory program.

In the final analysis, if the risks approximate what your staff have estimated, you may have made a good regulatory decision. However, you will most probably never know whether your regulatory program was effective and avoided any cancer deaths. This is because the risk estimate your staff calculated is completely hypothetical in nature. Your staffs risk assessment is not an actuarial estimate, and it is not based on any information concerning known human mortality caused by exposure to Substance X. Furthermore, even if the estimated risk is real, it may be unprovable because it is either statistically too small to be identified or cannot be distinguished from other risks with

reasonable confidence given the limitations of current scientific methods. Finally, even though you do not know whether the risks your staff predicted are real, you do know that real costs will be associated with the regulatory program.[3] Even though the cost estimates might not be entirely accurate, you have made the decision to implement a regulatory program to reduce exposures to Substance X. This decision represents a balance between a certain expenditure and an uncertain benefit.

As this hypothetical example illustrates, risk assessment, particularly quantitative risk assessment, is practically impossible without science policy decisions. Science policy enables risk assessments to be conducted in a rational manner even when ideal data are unavailable and when scientific understanding is incomplete. Thus, because risks to human health and the environment cannot otherwise be calculated, science policy plays a central role in justifying environmental, safety, and health regulatory programs.

REFERENCES

NATIONAL RESEARCH COUNCIL (NRC) *Committee on the Institution Means for Assessment of Risks to Public Health. 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, D.C.: National Academy Press. (Red Book)*

OFFICE OF MANAGEMENT AND BUDGET (OMB). 1992. *Regulatory Program of the United States Government (April 1, 1991-March 31, 1992)*. Executive Office of the President, Washington, D.C.

[3] It should be noted that estimated costs can be, and often are, every bit as hypothetical as risk estimates. Although costs are easier to know, regulators must, in fact, generally balance uncertain cost estimates with uncertain risk estimates.

2
A HISTORICAL PERSPECTIVE ON SCIENCE POLICY

During the 1970s and 1980s many laws were enacted and amended to clean up and protect the environment and to protect the health of workers and the public. These laws included the Atomic Energy Act (AEA), Clean Air Act (CAA), Clean Water Act (CWA), Toxic Substances Control Act (TSCA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), Comprehensive Environmental Response, Compensation and Liability Act (CERCLA or Superfund), Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), and Occupational Safety and Health Act (OSHAct). These and other laws require regulatory agencies to:

- Identify environmental, health, and safety hazards;
- Establish limits on emissions and releases of various substances from industrial facilities, waste sites, and motor vehicles, *etc;*
- Establish limits on permissible human exposure to substances in food, drinking water, air, and in the workplace; and
- Oversee the cleanup of present and former industrial facilities and waste sites.

Oftentimes, these activities are accomplished through a regulatory process which depends in part on risk assessment. Although some environmental, health, and safety laws contemplate "risk" as a basis for regulation (the Federal Food, Drug and Cosmetic Act, TSCA, and Federal Hazardous Substances Act, for example), risk assessment is not specifically mandated by most laws enacted to protect the public and environment. Rather, risk assessment is a process that has been developed over time to assist regulators in establishing a basis for implementing their statutory responsibilities through regulation.

Risk assessment is defined as "use of the factual base to define the health effects of exposure to hazardous materials and situations." [1] Risk assessment is currently understood to mean the process of estimating the likelihood and severity of adverse outcomes to individuals and populations. Cancer risk assessment, therefore, is a specialized form of risk assessment.

[1] (National Research Council [NRC] 1983, 3) This publication is referred to herein as the Red Book.

The U.S. Environmental Protection Agency (EPA) first issued formal guidelines for conducting cancer risk assessments in 1976.[2] These early interim guidelines recognized two important facts regarding the role of science policy in risk assessment. First, most risks are "unprovable":

> *[I]n very few cases is it possible to "prove" that a substance will cause cancer in man, because in most instances the evidence is limited to animal studies.*[3]

Risks may be unprovable because they are too small to be practically measured or observed by current scientific methods.[4] Risks may be unprovable because for a given adverse health or environmental effect, two or more potential causes may not be distinguishable from each other.[5] Second, science policy decisions are key components of risk assessment that assist in the estimation of unprovable risks.

> *The central purpose of the health risk assessment is to provide a judgment concerning the weight of evidence that an agent is a potential human carcinogen and, if so, how great an impact it is likely to have on public health. Judgments about the weight of evidence involve considerations of the quality and adequacy of the data and the kinds of responses induced by the suspect carcinogen.*[6]

The "weight of evidence" and "quality and adequacy of the data" are broad science policy issues raised by the nature of unprovable risks. The judgments referred to in the quotation above are the science policy decisions.

Because true risks are essentially unprovable, science policy issues are generally addressed so as to be protective of public health. Therefore, by design, science policy leads to risk assessments that are more likely to overstate rather than understate risks to the environment and human health. Conservatism remains a key feature of science policy in risk assessments today. [7] Because risk management decisions are often made based on risk assessment results, conservative risk assessments lead to risk

---

[2] Environmental Protection Agency [EPA] 1976)

[3] (EPA 1976, 21403)

[4] *See* (NRC 1991, 27-47) and (Seiler and Alvarez 1994).

[5] *See* (NRC 1991, 27-47) and (Seiler and Alvarez 1994).

[6] (EPA 1976, 21404). This quotation should not be construed as a complete or accepted definition of risk assessment. The quotation addresses only hazard identification, one of the four parts to the risk assessment process.

[7] Dr. Lynn Goldman, EPA Assistant Administrator for Prevention, Pesticides and Toxic Substances, stated at the 1994 annual meeting of the American Association for the Advancement of Science that risk assessment involves making reasonable assumptions and setting science policies that bridge gaps in data and understanding and that assumptions used by the government are often conservative and risk adverse (Bureau of National Affairs [BNA] 1994a).

management decisions and regulatory programs that may well be overprotective of the environment and public health.[8]

Over time, regulatory risk assessments have spawned litigation, additional regulatory activity, controversy and numerous scholarly efforts to analyze and improve the risk assessment process. Some of the more notable events in the history of risk assessment and risk management since 1976 are discussed below.

- **1980—*Benzene* decision.**[9] In a case involving the Occupational Safety and Health Administration (OSHA) exposure standard for benzene, the Supreme Court held that OSHA must provide an estimate of the actual risk associated with a toxic substance. Although only OSHA was involved in this case, the decision provided a de facto mandate for quantitative risk assessment at all regulatory agencies. The Court recognized that OSHA may use assumptions (i.e., science policy) in risk assessment, but only to the extent that those assumptions have some basis in reputable scientific evidence.
- **1981—Executive Order 12291.**[10] President Ronald Reagan issued this policy directive which instituted a new process for the review of regulatory actions with annual economic impacts exceeding $100 million by the White House Office of Management and Budget (OMB). From its issuance until its revocation in 1993, this Executive Order provided OMB with authority to review and control the fate of environmental regulation on the basis of cost-benefit principles.[11]
- **1981—Office of Technology Assessment.**[12] The Office of Technology Assessment (OTA) of the U.S. Congress issued a report discussing risk assessment methods and estimated the contribution of various factors, including smoking, food, occupation, and environment to cancer risk.

---

[8] We do not intend to imply either that overprotection of public health is desirable or that it is not. In some cases, overprotection may be desirable; in other cases it may not be. Whether overprotection is desirable, and what costs society is willing to pay for it, clearly depend on specific facts and circumstances. Furthermore, because most risks are indeed unprovable, it is unlikely that the degree of overprotection or under protection can ever be known or demonstrated.

[9] Industrial Union Dept., AFL-CIO v. American Petroleum Institute, 448 U.S. 607 (1980) (Benzene).

[10] (Executive Office of the President 1981)

[11] "Principles contained in §2 of Executive Order 12291 include: "(a) Administrative decisions shall be based on adequate information concerning the need for and consequences of proposed government action; (b) Regulatory action shall not be undertaken unless the potential benefits to society for the regulation outweigh the potential costs to society; (c) regulatory objectives shall be chosen to maximize the net benefits to society; (d) Among alternative approaches to any given

[12] (OTA 1991)

- **1983—NRC Red Book.**[13] The National Research Council [14] (NRC) landmark analysis of the regulatory risk assessment and risk management processes, the Red Book, established the four-step paradigm for risk assessment: hazard identification, dose-response evaluation, exposure assessment, and risk characterization. The *Red Book* offered recommendations concerning the development of risk assessment guidelines by regulatory agencies.[15]
- **1984—EPA Risk Assessment Forum.**[16] Formed during the period when EPA began developing risk assessment guidelines, EPA established the Risk Assessment Forum to resolve significant issues arising from the use of risk assessment guidelines and internal agency conflicts over technical risk assessment issues.
- **1985—Executive Order 12498.**[17] This Executive Order explicitly included risk assessment in the regulatory review process established under Executive Order 12291 and required that regulatory agencies comply with the principle that "[r]egulations that seek to reduce health or safety risks should be based upon scientific risk-assessment procedures, and should address risks that are real and significant rather than remote or hypothetical."[18]
- **1985—OSTP cancer risk assessment guidelines.**[19] The White House Office of Science and Technology Policy (OSTP) issued a report entitled Chemical Carcinogens: *A Review of the Science and Its Associated Principles.* This report reviewed the state of cancer risk assessment and established thirty-one general principles for regulatory agencies to use in establishing their own cancer risk assessment policies and procedures. Despite their origin in the Executive Office of the President, the principles were advisory and were therefore not binding on individual regulatory agencies.[20]
- **1986—EPA Risk Assessment Council.**[21] The Risk Assessment Council (RAC) was formed to focus on risk assessment policy issues, leaving the Risk

---

[13] (NRC 1983)

[14] The National Research Council was established by the National Academy of Sciences (NAS) in 1916 to associate the broad community of science and technology with the NAS purpose of furthering knowledge and of advising the federal government.

[15] *See* further discussion below.

[16] (BNA 1986)

[17] (Executive Office of the President 1985)

[18] Section 1(d) of Executive Order 12498, citing §4 of the August 11, 1983, report of the Presidential Task Force on Regulatory Relief, "Reagan Administration Regulatory Achievements."

[19] (Office of Science and Technology Policy [OSTP] 1985)

[20] (Federal Focus 1991, 35)

21 (BNA 1986)

Assessment Forum to focus on technical risk assessment issues. The RAC was replaced by the Science Policy Council in early 1994.

- **1986—EPA carcinogen risk assessment guidelines.**[22] EPA's Guidelines for Carcinogen Risk Assessment were the first revision of the 1976 Interim Procedures and Guidelines. The 1986 guidelines, which remain in use today, enunciate some of the more commonly encountered science policy decisions that EPA relies upon in conducting risk assessments.
- **1987—***Vinyl Chloride decision***.**[23] In this litigation involving EPA's air emissions standard for vinyl chloride, the court interpreted the Clean Air Act (CAA) to require EPA to first determine a "safe" level of exposure for air pollutants before considering economic or technological feasibility of achieving reduced emissions. The rule was remanded to EPA and, in the subsequent rulemaking, EPA decided to emphasize quantitative risk assessment in the establishment of CAA standards.
- **1989—Council on Environmental Quality Risk Analysis Guidebook.**[24] The Council on Environmental Quality (CEQ) published a guidebook to risk analysis which was designed for "consumers of risk information" and offered "a balance between technical and nontechnical literature."
- **1990—Clean Air Act Amendments.** EPA has promulgated emissions standards for only eight hazardous air pollutants in the twenty years since the CAA was enacted in 1970. Therefore, Congress significantly reduced the role of risk assessment in standard setting and required that initial emissions standards be set on the basis of technology, rather than risk. Quantitative risk assessment is to be used to evaluate whether or not the technology-based standards are protective of public health with an ample margin of safety.
- **1990-1992—Interagency risk assessment coordination.** The Federal Coordinating Council on Science, Engineering and Technology (FCCSET), operating under the direction of OSTP, set up two groups to address risk assessment issues from an interagency perspective: (1) the Ad Hoc Working Group on Risk Assessment which reported directly to FCCSET; and (2) the Subcommittee on Risk Assessment which reported to the FCCSET Committee on Life Sciences. In 1991, FCCSET announced that interagency consensus had been reached concerning the cross-species scaling factor.[25]

---

[22] (EPA 1986)

[23] Natural Resource Defense Council v. EPA, 824 F.2d 1146 (en banc) (D.C. Cir. 1987) (Vinyl Chloride).

[24] (Council on Environmental Quality [CEQ] 1989)

[25] (BNA 1992). See Chapter 3 and Chapter 4 for further discussion of the science-policy issue and decision associated with the scaling factor.

- **1991—First noncancer risk assessment guidelines.**[26] EPA has been conducting risk assessments for health effects other than cancer for years. The guidelines for developmental toxicity risk assessment are the first noncancer risk assessment guidelines to be issued in final form by EPA. The developmental toxicity guidelines were originally issued in interim form in 1986, along with guidelines for mutagenicity risk assessment.
- **1992—EPA risk characterization guidance.**[27] Issued in memorandum form, this guidance prescribes how risk assessment results should be communicated by risk assessors and risk managers. This guidance supplements the risk characterization guidance contained in EPA's 1986 cancer risk assessment guidelines.
- **1992—Exposure assessment guidelines.**[28] EPA issued guidelines for assessing exposure as part of risk assessment.
- **1992—OSHA** *Air Contaminants decision***.**[29] In this case, the court struck down permissible exposure limits (PELs) for 428 toxic substances on the basis that assumptions used by OSHA in the risk assessments supporting the PELs were not substantiated by the available scientific evidence. This case reiterates the lesson of the Benzene decision that, although science policy is clearly permissible in risk assessment, science policy decisions must have some basis in fact. Through this rulemaking, OSHA was attempting to update standards that had been set more than twenty years earlier. By requiring a better substantiated scientific basis for assumptions—a requirement which may not be practical or possible— this case may effectively block OSHA's ability to update many of the earlier standards, particularly en masse.
- **1992—Corrosion Proof Fittings decision.**[30] This court decision involved EPA's 1989 ban on the future manufacture, importation, processing, and distribution of asbestos in almost all consumer and commercial products. The court held that EPA failed to include and consider adequately the toxicity and relative safety of asbestos substitutes. In viewing this omission as a fatal flaw, the court stated that an agency is required to regulate on the basis of knowledge rather than the unknown.
- **1993—First CRAM report.**[31] The NRC Committee on Risk Assessment Methodology (CRAM) released the first of a series of reports on various

[26] (EPA 1991)

[27] (EPA 1992a)

[28] (EPA 1992b)

[29] *AFL-CIO v. OSHA*, 965 F.2d 962 (11th Cir. 1992) (*Air Contaminants*).

[30] Corrosion Proof Fittings v. EPA, 947 F.2d 1201 (5th Cir. 1991) (Corrosion Proof Fittings) See Chapter 6

[31] (NRC 1993)

issues in risk assessment. The two key science policy issues addressed in this report were the use of the Maximum Tolerated Dose (MTD) in animal cancer bioassays and the development and implementation of a two-stage model of carcinogenesis.

- **1993—Executive Order 12866.**[32] This Executive Order constitutes the current Administration's policy concerning regulatory review and expressly revokes Executive Orders 12291 and 12498. Agencies are explicitly directed to consider the degree and nature of risks posed by various substances or activities within their respective jurisdictions. Although this Executive Order continues the tradition of regulatory review of risk-based regulation by OMB, it has been implemented so that OMB has relatively less ability to control regulations.[33]
- **1993—Executive Order 12881.**[34] This Executive Order established the National Science and Technology Council and effectively replaced FCCSET as the Executive Branch entity overseeing the coordination of federal risk assessment policy.
- 1993—EPA Science Policy Council. EPA replaced its Risk Assessment Council with the Science Policy Council.35 The immediate priorities for the Science Policy Council are to initiate and guide a process for strengthening EPA's peer review and risk characterization.[36]
- **1994—NRC CAPRA Report.**[37] The CAA Amendments of 199038 required EPA to commission an NRC review and evaluation of EPA procedures for cancer and, to the extent practicable, noncancer risk assessment. The NRC found that EPA's general approach to risk assessment is basically sound, but the report included more than seventy recommendations focused on science policy and improving current risk assessment methodology.[39]
- **1994—Interagency risk assessment coordination.**[40] EPA issued a report designed to be a primer on federal risk assessments of neurotoxicity. The document was prepared by scientists from twelve federal agencies meeting since 1992 under the auspices of the now-defunct FCCSET.

---

[32] (Executive Office of the President 1993a)

[33] See n.49.

[34] (Executive Office of the President 1993b)

[35] (EPA 1993a)

[36] (EPA 1994)

[37] (NRC 1994)

[38] Section 112(o).

[39] See further discussion in text below.

[40] (BNA 1994b)

A useful perspective on how the risk assessment process has evolved and where it is today is provided by a review and comparison of the recommendations contained in the 1983 *Red Book* and in the 1994 *CAPRA Report*. With respect to science policy, *the Red Book* contained the following recommendations.[41]

- *Red Book Recommendation: Regulatory agencies should take steps to establish and maintain a clear conceptual distinction between assessment of risks and the consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessment should be explicitly distinguished from the political, economic and technical considerations that influence the design and choice of regulatory strategies.*

  Although the recommendation that scientific risk assessment should be kept separate from nonscientific, policy-driven risk management seems logical, this recommendation is limited in impact. Science policy decisions are essential to bridge gaps in knowledge so that risk assessments can be conducted. Thus, risk assessment necessarily contains policy elements, and, through these policy elements, risk assessment and risk management are inextricably intertwined. This connection, however, does not justify masquerading science policy decisions as scientific fact. Complete separation of risk assessment and risk management is not feasible. At the very least, the impact of science policy decisions on risk assessment should be clearly and completely described.

  - *Before an agency decides whether a substance should or should not be regulated as a health hazard, a detailed and comprehensive written risk assessment should be prepared and made publicly accessible. This written assessment should clearly distinguish between the scientific basis and the policy basis for the agency's conclusions.*

  This recommendation is potentially the most valuable concerning the use of science policy in risk assessment. Full disclosure of the use of science policy in risk assessment enables a more informed evaluation of and debate concerning proposed regulatory programs. That is, more informed decisions can be made as to whether it is worth expending limited resources to address potential hazards only if policy makers, risk managers, and the public are able to understand what is known, what is not known, what assumptions and guesses have been made, and the range of potential benefits from regulating a potential hazard. However, such disclosure does not just happen. Full disclosure would have to be explicitly required; the requirement would have

[41] (NRC 1983, 150-171)

to be substantially complied with, and compliance would have to be meaningfully enforced.[42]

- ***Red Book Recommendation***: The NRC recommended improving risk assessment through the use of "inference guidelines," which would provide guidance to regulators concerning the use of science policy in risk assessment.

  The theoretical value of formal guidance to assist regulators in addressing science policy issues is unquestioned. However, the practicality of risk assessment guidelines as proposed is questionable. First, it appears to take an inordinate amount of time to produce such guidelines. For example:

  - EPA's interim carcinogen risk assessment guidelines were issued in 1976. However, it was not until 1986 that they were produced in final form. Further, although EPA has been in the process of revising the 1986 guidelines since at least 1989, a final revision has not yet been formally adopted.[43]
  - In 1982, the Center for Food Safety and Applied Nutrition (CFSAN) of the Food & Drug Administration (FDA) published a Redbook [44] which delineates the criteria by which FDA evaluates the safety of direct food and color additives.[45] Although revision of the FDA Redbook commenced as early as 1986, a draft version was not made available for public comment until March 1993. A final version is not expected before the end of 1994.

  Second, expectations of risk assessment guidelines may be too high. Existing guidelines tend to be more of a general description of what the risk assessment process is rather than a set of rules for making specific judgments in the risk assessment process. In individual risk assessments, science policy decisions are made on the basis of available data and scientific knowledge. It is difficult and probably not desirable to "hard code" specific science policy decisions in risk assessment guidelines.

  Third, to the extent that risk assessment guidelines are "rules," they may be applied inflexibly. New scientific knowledge which could modify or replace specific science policy decisions contained in the guidelines may not warrant

---

[42] An additional issue which seems to be overlooked by regulatory agencies is the inevitable simplification of risk findings by the media. The subtleties of the risk assessment process, particularly science policy, are generally lost immediately after release of risk assessment results. The result is an only partly informed or a misinformed public.

[43] EPA published a draft version for public comment in August 1994. As part of efforts to update and revise the 1986 Guidelines, a panel of experts convened in September 1994 to review a document entitled "Draft Revisions to the Guidelines for Carcinogen Risk Assessment (External Review Draft, August 1994)." See 59 FR 43125 (August 22, 1994).

[44] CFSAN's *Redbook* should not be confused with the NRC's Red Book.

[45] (Department of Health and Human Services [DHHS] 1993)

revision or reissuance of the guidelines. This may unduly limit the incorporation of new scientific knowledge in science policy decisions.

Finally, and again to the extent that they are rules, for guidelines to have any meaning, they must be complied with in good faith as they are voluntary in nature. Even congressionally established scientific review bodies cannot compel compliance. For example:

- EPA's Science Advisory Board (SAB) is an independent body that Reviews EPA risk assessments. However, the SAB merely advises the EPA and has no enforcement authority.
- Congress often requires regulatory agencies to consult the NRC. However, the NRC cannot compel a regulatory agency to adhere to its advice.
- The National Council on Radiation Protection and Measurements (NCRP) was established in 1964 to, among other things, develop basic concepts about radiation protection.[46] Yet NCRP recommendations are not required to be incorporated in federal radiation protection programs.[47]

The issue of compliance is sensitive. During the 1980s, the OMB Office of Information and Regulatory Affairs (OIRA) developed a great deal of notoriety for its review and control over EPA regulations under Executive Order 12291.[48] During the Bush Administration, the Competitiveness Council, led by Vice President Quayle, eclipsed OIRA. Under the current Administration, the Competitiveness Council was abolished and OIRA has had a lower profile, which raises questions about its review and enforcement authority.[49]

An alternative would be to allow the public to enforce compliance with the guidelines through judicial means. However, most proposed legislation[50] does not provide for any compliance or enforcement mechanism, including administrative or judicial review.

---

[46] Pub.L. 88-376, §3, July 14, 1964, 78 Stat. 321.

[47] 0ne current example of this is the ongoing EPA rulemaking to issue cleanup standards for sites contaminated with radiation. EPA is considering a cleanup standard that would limit radiation exposure to the public to a dose equivalent of 15 millirem per year beyond natural background levels of radiation exposure (BN A 1994f). This rule may apply to Superfund sites with naturally-occurring radioactive material (NORM) wastes (EPA 1993b). If finalized so as to include NORM wastes, this cleanup standard would be over twenty times more stringent than the most recent recommendations of the NCRP (*i.e* „ 500 millirem per year) for NORM wastes (NCRP 1993).

[48] In 1991, a Presidential Executive Order was recommended which would have vested OIRA with extensive oversight authority concerning Executive Branch risk assessment activities. *See (*Federal Focus 1991). In 1992, a draft of such an Executive Order was being circulated within the Executive Branch by the Executive Office of the President.

[49] It has recently been reported that the number of EPA rules reviewed by OMB under Executive Order No. 12866 has been reduced by 50 percent (BNA 1994c).

[50] One exception is S. 490. See discussion in text.

While disclosure would, and guidelines could be useful in risk assessment, the Red Book did not recommend a mechanism to ensure compliance with either.

The 1994 *CAPRA Report* made a number of recommendations concerning the use of science policy in risk assessment. Some of the general recommendations are discussed below.[51]

- ***CAPRA Report*** Recommendation*: Because of limitations on time, resources, scientific knowledge, and available data, EPA should generally retain its conservative, default-based approach to risk assessment for screening analysis in standard setting; however, several corrective actions are needed to make this approach more effective.*

  In the context of the other recommendations of the *CAPRA Report*, this recommendation acknowledges the reality that conservative, default-based risk assessment is the only practical alternative available to all regulatory agencies, not just EPA. However, without the "corrective action" phrase, this recommendation would be a license for any regulatory agency to use science policy as it sees fit with little accountability.

- ***CAPRA Report*** **Recommendation:** *EPA should develop an iterative approach to risk assessment. This will lead to an improved understanding of the relationship between risk assessment and risk management and an appropriate blending of the two.*[52]

  Although sound in principle, it is not clear that an iterative approach would be practical. Rulemaking is both labor- and time-intensive, thereby creating a disincentive for iteration. For example, for most of EPA's life, it has had insufficient staff to write all the rules expected of it. Usually, the timetable for a regulatory action is far shorter than the time required to do the scientific research necessary to modify or replace a science policy decision. These disincentives, however, do not preclude revisions to risk assessments that can be incorporated in subsequent rulemakings. Revisions to risk assessments affecting existing regulations are difficult because:

  - Regulatory agencies are reluctant to spend their limited resources addressing already "settled" issues (unless there is pressure to do so);
  - Regulatory agencies risk their credibility by being perceived as wrong, regardless of the bases for revisions; and
  - As demonstrated by EPA's ongoing reassessment of dioxin, it can be difficult to reduce previous risk estimates.

---

[51] (NRC 1994, E-7-E14)

[52] The *iterative approach* is a process in which improvements are continually made to a risk assessment until either the risk estimates are below the applicable decision-making level, further improvements in scientific knowledge would not significantly change the risk estimates, or it is determined that further analysis is not warranted (NRC 1994, E l 3).

Thus, it is not clear that regulatory agencies are willing to expend their limited resources addressing the same hazards repeatedly.

- ***CAPRA Report*** **Recommendation:** *For [the iterative approach] to work properly, however, EPA needs to provide justification for its current defaults and establish a procedure that permits departures from default assumptions.*

  The concept of developing criteria for departing from default assumptions is sound, but the NRC did not recommend what form such criteria should take. In any event, such criteria are not likely to provide for wholesale replacement of default assumptions. As demonstrated by past EPA practice, departures from default assumptions will most likely be addressed only on a case-by-case basis.[53]

- ***CAPRA Report*** **Recommendation***: When EPA reports estimates of risk to decision makers and the public, it should present not only point estimates of risk, but also the sources and magnitudes of the uncertainties associated with these estimates.*

  Although not a new concept, this is clearly the most practical recommendation of the *CAPRA Report*. The *Red Book* also contained this recommendation in 1983, but full disclosure of the uncertainties in regulatory risk assessment is not yet routine. This situation persists at EPA despite the issuance of the 1992 risk characterization guidance. Full implementation of this recommendation by regulatory agencies would immensely improve the risk assessment and risk management processes in the shortest time frame. Full disclosure of the uncertainties in regulatory risk assessment would:

  - Facilitate the accountability of risk assessors for their science policy decisions;
  - Enable policy makers and risk managers to evaluate potential regulatory policy options from a more informed perspective; and
  - Enable the media and the public to evaluate from a more informed perspective whether policy makers and risk managers are making acceptable and desired risk management decisions.

In the eleven years from publication of the Red Book to publication of the *CAPRA Report*, it has been learned that:

- Science policy decisions remain essential to the regulatory risk assessment process; and

[53] See Chapters 3 and 4 for further discussion.

- Full disclosure of the uncertainties in regulatory risk assessments continues to be the exception rather than the rule.

This perceived lack of progress may have led the 103rd Congress to become increasingly interested in risk assessment and cost-benefit analysis. Specifically, the following legislative actions related to risk assessment and/or regulatory impacts were pending as of late September 1994:[54]

- **S. 81,** the Economic and Employment Impact Act, would require cost analysis and estimates and evaluation of the likely impact of federal legislation and regulation on the private sector and state and local governments.

  S. 110, the Environmental Risk Reduction Act of 1993, would allocate environmental cleanup and remediation resources based on how much risk each situation posed to human health, and would require the EPA Administrator to seek outside advice when risks of environmental hazards are assessed so as to ensure that EPA decisions are based on scientific data.

  The **Johnston amendment** to the EPA cabinet bill (S. 171), named for its sponsor, Sen. J. Bennett Johnston (D-La.), would require EPA to improve its discussion of human health risk assessments and include cost-benefit analyses in rulemakings. This amendment was added to the EPA Cabinet bill by a wide margin (95-3). A similar House amendment was introduced by Reps. John Mica (R-Fla.) and Karen Thurman (D-Fla.) but was pulled from consideration after a procedural vote in the House Rules Committee.

  S. 490, the Regulatory Flexibility Amendments Act of 1993, would reemphasize the need for federal agencies to comply with the Regulatory Flexibility Act of 1980 and also permit private enforcement of the Act's provisions.

  H.R. 830, the Regulatory Flexibility Amendments Act of 1993, and S. 165, an amendment to the National Competitiveness Act of 1993 (S. 4), would strengthen the Regulatory Flexibility Act of 1980, which requires regulatory agencies to consider the effects of their regulations on small businesses.

  H.R. 1088, the Small Business and Private Economic Sector Act is a companion to **S. 81.**

  H.R. 2910, the Risk Communication Act of 1993, would set out specific requirements for EPA risk assessments and require EPA to publish a plan to review and revise previous risk assessments.

  H.R. 3171, the Department of Agriculture Reorganization Act of 1994, would establish an Office of Environmental Risk Assessment that would be required

[54] (BNA 1994d, BN A 1994e)

to certify that the costs of Department of Agriculture environmental, health, and safety regulations were justified by the risks.

H.R. 3395, the Preparation of Risk Assessments in Connection with Federal Health and Safety or Environmental Regulations, would require federal health, safety, and environmental regulations to be supported by risk assessment, including comparative risk and cost analyses.

H.R. 4306, the Risk Assessment Improvement Act of 1994, would coordinate the scientific assessment of health risks within EPA and establish a pilot program to rank risks by severity.

The issue of "unfunded mandates" is also related to science policy. Risk assessments often form the basis of regulations, such as drinking water standards, that local governments must comply with. However, federal funding to comply with these standards is not generally provided.[55] In these cases, an unfunded mandate is said to exist. Unfunded environmental mandates are often criticized because local governments are compelled to devote their own limited resources to meeting federal requirements rather than responding to local needs and concerns. A seminal report on the impact of unfunded environmental mandates on nine Ohio cities estimated that compliance with federal environmental mandates would cost $2.8 billion (in 1992 dollars) during the period 1992-2001.[56] A survey of 314 cities estimated the cost of complying with unfunded federal mandates to be $54 billion for the years 1994-1998.[57] The CWA, Safe Drinking Water Act, and meeting solid waste disposal requirements were the most costly unfunded federal mandates. Meeting unfunded mandates has been estimated to consume approximately 12 percent of locally raised revenues.

Unfortunately, despite all of this proposed legislation and the good intentions of the sponsors, little has been proposed that has not been tried before. For example:

- **Mandatory cost-benefit analysis.** Former and current Executive Orders concerning regulatory review have required that federal agencies justify regulations with societal impacts of $100 million or more.[58]

---

[55] A high priority of the current Administration is to establish a State Revolving Fund through the reauthorization of the Safe Drinking Water Act. The fund would provide loans to local governments to help finance needed infrastructure for treatment and source protection.

[56] *Ohio Metropolitan Area Cost Report for Environmental Compliance* (September 15, 1992). Proposed legislation concerning unfunded mandates includes: S. 993 (Community Regulatory Relief Act), H.R. 140 (Federal Mandate Relief Act of 1993), S. 1604 (Small Governments Regulatory Improvement and Innovation Act of 1993), S. 1606 (Federal Mandates Funding Act of 1993), S. 1592 (Fiscal Accountability and Intergovernmental Reform Act), S. 1188 (Federal Mandate Relief Act of 1993), S. 648 (The Federal Mandates Relief Act), and S. 563 (CBO Analysis of Federal Mandates on State and Local Governments).

[57] (U.S. Conference of Mayors 1993)

[58] *See* nn.10 and 32.

- **Scientific review**. For example, EPA's SAB is a group of recognized. independent scientists who review many major EPA risk assessments. Other federal agencies have analogous review bodies.
- **Risk prioritization**. EPA, through the SAB, has already completed a project to examine the feasibility of prioritizing risks.[59]
- **Disclosure. For example:** (1) OSHA is required by law to support its regulations by "substantial evidence in the record";[60] and (2) EPA policy guidance, consisting of previously issued risk assessment, exposure, and risk characterization guidelines, already requires EPA staff to discuss fully their risk assessments.

Moreover, it is not clear that legislation of this genre could achieve the goals that the sponsors envision. First, the courts have had their hands full with citizen lawsuits to compel EPA to comply with other statutory mandates as simple and clear-cut as meeting deadlines for promulgating regulations.[61] Second, with the exception of H.R. 4306, none of the proposed legislation provides compliance or enforcement mechanisms, and nothing would ensure that EPA adhered to the spirit of the legislative mandate. The following items illustrate why a compliance or enforcement mechanism is essential.

- The standard of review under the Administrative Procedures Act[62] is "arbitrary and capricious."[63] A thorough discussion of this standard is beyond the scope of this report, but it has not proven to be a rigorous standard. As long as an agency decision is rational or reasonable, and is on the record, the decision will likely survive challenge under the arbitrary and capricious standard.[64]
- The Supreme Court's decision in *Chevron U.S.A., Inc. v. Natural Resources Defense Council* indicates that courts will defer to agency discretion where legislation is silent.[65]

---

[59] (SAB 1991)

[60] *See* Chapter 10, nn. 9-12.

[61] For example, the Bull Run Coalition was forced to sue EPA for failure to promulgate drinking water standards by June 19, 1988, as required in the 1986 amendments to the Safe Drinking Water *Act. Bull Run Coalition v. EPA.* D.C. Oregon, No. 88-6097-E (BNA 1988). The Bull Run Coalition also sued EPA for failure to promulgate other drinking water standards by the requisite deadline (BNA 1990).

[62] 5 U.S.C. §§551. This statute generally governs regulatory agency rulemakings.

[63] 5 U.S.C. §706(2)(A).

[64] See (Administrative Conference of the U.S. 1991, 323-333).

[65] 467 U.S. 837 (1984). In a unanimous opinion, the Court stated that "[j]udges are not experts in the field, and are not part of either political branch of government. Courts must, in some cases, reconcile competing political interests, but not on the basis of the judges' personal policy preferences. In contrast, an agency to which Congress has delegated policymaking responsibilities may, within the limits of that delegation,

It is difficult to imagine legislation that is sufficiently detailed to address the area of risk assessment comprehensively. As EPA recognized in the 1976 Interim Guidelines for Carcinogen Risk Assessment:

> *Expert scientific judgments in the areas of toxicology, pathology, biometry, and epidemiology are required to resolve uncertainties about the quality, adequacy, and interpretation of experimental and epidemiology data to be used [in] risk assessment.*[66]

As long as "expert scientific judgments" are required, there will be no simple legislative language which will improve regulatory risk assessment without also having the unintended and undesirable effect of freezing the practice of regulatory risk assessments in its current form.

The remainder of this report explores the impact of science policy on risk assessment. Chapter 3 discusses the most common and fundamental science policy issues and decisions in quantitative carcinogenic risk assessment. These science policy decisions are referred to as "default assumptions." Chapter 4 explores alternatives to the default assumptions. Chapters 5 through 12 discuss the role of science policy in risk assessment and risk management in the context of specific past and current regulatory actions. Finally, Chapter 13 presents the conclusions and recommendations of the project.

REFERENCES

ADMINISTRATIVE CONFERENCE OF THE UNITED STATES. 1991. *A Guide to Federal Agency Rulemaking. U.S. Government Printing Office, Washington, D.C.*

AFL-CIO v. OSHA, 965 F.2d 962 (11th Cir. 1992) (Air Contaminants).

BUREAU OF NATIONAL AFFAIRS (BNA). 1994a. *Daily Environment Report No. 38, A-8 (February 28, 1994).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1994b. *Daily Environment Report No. 157, A-1 (August 19, 1994).*

---

properly rely upon the incumbent administration's views of wise policy to inform its judgments. While agencies are not directly accountable to the people, the Chief Executive is, and it is entirely appropriate for this political branch of the Government to make such policy choices—resolving the competing interests which Congress itself either inadvertently did not resolve, or intentionally left to be resolved by the agency charged with the administration of the statute in light of everyday administration's views of wise policy to inform its judgments. While agencies are not directly accountable to the people, the Chief Executive is, and it is entirely appropriate for this political branch of the Government to make such policy choices—resolving the competing interests which Congress itself either inadvertently did not resolve, or intentionally left to be resolved by the agency charged with the administration of the statute in light of everyday realities. When a challenge to an agency construction of a statutory provision, fairly conceptualized, really centers on the wisdom of the agency's policy, rather than whether it is a reasonable choice within a gap left open by Congress, the challenge must fall. In such a case, federal judges—who have no constituency—have a duty to respect legitimate choices made by those who do."

[66] (EPA 1976, 21404)

BUREAU OF NATIONAL AFFAIRS (BNA). 1994c. *Daily Environment Report No. 157, A-1 (August 17, 1994).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1994d. *Daily Environment Report No. 91, B1 (May 13, 1994).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1994e. *Daily Environment Report No. 188, A-3 (September 30, 1994).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1994f. Daily Environment Report No. 85, A-5 (May 5, 1994).

BUREAU OF NATIONAL AFFAIRS (BNA). 1992. *Environment Reporter 23:655 (June 12, 1992).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1990. *Environment Reporter 21:476 (July 13, 1990).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1988. *Environment Reporter 19:1148 (October 7, 1988).*

BUREAU OF NATIONAL AFFAIRS (BNA). 1986. *Environment Reporter 16:2236 (April 18, 1986).*

Chevron U.S.A., Inc. v. Natural Resources Defense Council, 467 U.S. 837 (1984).

Corrosion Proof Fittings v. Environmental Protection Agency, 947 F.2d 1201 (5th Cir. 1991) (Corrosion Proof Fittings).

COUNCIL ON ENVIRONMENTAL QUALITY (CEQ). 1989. *Risk Analysis: A Guide to Principles and Methods for Analyzing Health and Environmental Risks. Washington, D.C.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS). 1993. Draft revised "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food." Fed. Reg. 58:16536.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994. Memorandum from Robert Sussman, Chair, Science Policy Council, and Lynn Goldman, Vice-Chair, Science Policy Council, to Carol M. Browner, Administrator: *Priorities for the Science Policy Council (May 26, 1994).*
ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993a. Memorandum from Carol M. Browner, Administrator, to Assistant Administrators, Associate Administrators, and Regional Administrators*: Creation of a Science Policy* Council (December 22, 1993).

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993b. Radiation Site Cleanup Regulations*. Fed. Reg. 58:54474-01.*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992a. Memorandum from F. Henry Habicht, Deputy Administrator, to Assistant Administrators and Regional Administrators: *Guidance on Risk Characterization for Risk Managers and Risk Assessors (February 26, 1992).*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992b. Exposure assessment guidelines. *Fed. Reg. 57:22888.*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991. *Fed. Reg. 56:63798.*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986. Interim procedures and guidelines for health risk assessments of suspected carcinogens*. Fed. Reg. 51:33992.*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1976. Interim procedures and guidelines for health risk and economic impacts of suspected carcinogens*. Fed. Reg. 41:21402-21405.*

EXECUTIVE OFFICE OF THE PRESIDENT. 1993a. Executive Order 12866: Regulatory planning and review. *Fed. Reg. 58:51735.*

EXECUTIVE OFFICE OF THE PRESIDENT. 1993b. Executive Order 12881: Establishment of the National Science and Technology Council. *Fed. Reg. 58:62491.*

EXECUTIVE OFFICE OF THE PRESIDENT. 1985. Executive Order 12498: Regulatory planning process*. Fed. Reg. 50:1036.*

EXECUTIVE OFFICE OF THE PRESIDENT. 1981. Executive Order 12291: Federal regulation. *Fed. Reg. 46:13193.*

FEDERAL FOCUS, INC. 1991*. Toward Common Measures: Recommendations for a Presidential Executive Order on Environmental Risk Assessment and Risk Management Policy. Washington, D.C.: Federal Focus, Inc.*

Industrial Union Dept., AFL-CIO v. American Petroleum Institute, 448 U.S. 607 (1980) {Benzene).

NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS (NCRP). 1993. Limitation of exposure to ionizing radiation. Report No. 116. Bethesda, Md.

NATIONAL RESEARCH COUNCIL (NRC) Committee on Risk Assessment of Hazardous Air Pollutants. *1994. Science and Judgment in Risk Assessment (Prepublication Copy). Washington, D.C.: National Academy Press (CAPRA Report).*

NATIONAL RESEARCH COUNCIL (NRC) Committee on Risk Assessment Methodology. *1993. Issues in Risk Assessment. Washington, D.C.: National Academy Press {CRAM Report).*

NATIONAL RESEARCH COUNCIL (NRC). 1991*. Environmental Epidemiology: Public Health and Hazardous Wastes. Washington, D.C.: National Academy Press.*

NATIONAL RESEARCH COUNCIL (NRC) Committee on the Institutional Means for Assessment of Risks to Public Health. 1983*. Risk Assessment in the Federal Government: Managing the Process. Washington, D.C.: National Academy Press (Red Book).*

Natural Resource Defense Council v. EPA, 824 F.2d 1146 (en banc) (D.C. Cir. 1987) (Vinyl Chloride).

OFFICE OF MANAGEMENT AND BUDGET (OMB). 1992. *Regulatory Program of the United States Government. (April I, 1991-March 31, 1992)*. Executive Office of the President, Washington, D.C.

OFFICE OF SCIENCE TECHNOLOGY AND POLICY (OSTP). 1985. Chemical carcinogens: A review of the science and its associated principles. *Fed. Reg. 50:10372-10442.*

OFFICE OF TECHNOLOGY ASSESSMENT (OTA). 1981. Technologies for Assessing Carcinogenic Risks from the Environment. Washington, D.C.

SCIENCE ADVISORY BOARD (SAB). 1991. *Reducing Risk: Setting Priorities and Strategies for Environmental Protection* (SAB-EC-90-021, September 20, 1990). Environmental Protection Agency, Washington, D.C.

SEILER, F.A., and J.L. ALVAREZ. 1994. Definition of a minimum significant risk. (Submitted for publication in *Technology,* published by the Franklin Institute, Philadelphia, Penn.).

U.S. CONFERENCE OF MAYORS. 1993. *Impact of Unfunded Federal Mandates on U.S. Cities: A 314-City Survey.* U.S. Conference of Mayors, Washington, D.C.

3
BASIC SCIENCE POLICY ISSUES AND DEFAULT ASSUMPTIONS

Despite years of research and study, considerable uncertainty and a lack of specific knowledge pervade the risk assessment process. These uncertainties give rise to questions, but the resulting questions frequently cannot practically be answered by science. In its 1983 landmark report on risk assessment, the Red Book,[1] the NRC identified more than fifty science policy questions that arise in risk assessment (e.g., How should experimental animal data be used when the exposure routes in experimental animals and humans are different?). Each of these questions represents an instance in which science alone cannot provide the answers. In these cases, a science policy decision is required.

In this chapter, ten major science policy issue areas in risk assessment are identified and discussed. The individual discussions illustrate the relationship between the science policy questions identified in the *Red Book*[2] and the major issue areas. Each of these major science policy issue areas is generally addressed by a default assumption in the risk assessment process (*see* Table 3-1). Default assumptions, the linchpins of the U.S. regulatory carcinogen risk assessment process, may be based in science, but they result from science policy decisions. Default assumptions are necessary to bridge uncertainty, variability, and gaps in scientific knowledge and therefore allow the risk assessor to continue the risk assessment. The origin and justification of each of the ten major default assumptions are discussed in this chapter.

Default assumptions affect regulatory risk assessments because of their frequent occurrence and conservative nature. Consequently, the choice, justification, and use of default assumptions has come under increased scrutiny. Evolving science and new data now indicate that many of the default assumptions may be incorrect or inappropriate in several specific cases. Default assumptions remain largely in place eleven years after publication of the Red Book and continue to drive the regulatory risk assessment process. Regulatory agencies such as the Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) have high thresholds for the quality and quantity of data required to justify departure from a default assumption. Additionally, there is major institutional hesitance to redo an assessment if good data become available late in the regulatory process. Thus, default assumptions may be

[1] (National Research Council [NRC] 1983)

[2] The *Red Book* (NRC 1983, 28) refers to gaps and uncertainties in scientific knowledge as *components* and to assumptions as *inference options.*

rigidly applied by a regulatory agency even if data indicate that the default assumption may be wrong.

Table 3-1. Major Default Assumptions in Cancer Risk Assessment

1. A substance that is carcinogenic in animals is also a human carcinogen.

2. When both benign and malignant tumors are observed in animals, their combined incidence is indicative of carcinogenic potential in humans.

3. In the presence of positive cancer incidence data, nonpositive data are not indicative of safety and are not used in quantitative risk assessment.

4. Carcinogenic effects observed at the maximum tolerated dose in animal bioassays are predictive of effects in humans at much lower doses.

5. The animal species exhibiting the greatest carcinogenic sensitivity is the most appropriate species on which to base estimates of human cancer risk.

6. Differences between species in mechanisms of carcinogenicity are not taken into account when extrapolating data from one species to another.

7. A carcinogen by one route of exposure is a carcinogen by any other route of exposure.

8. There is no nonzero threshold dose below which an increased risk of carcinogenic effects will not occur.

9. The dose-response curve is linear at low doses.

10. Chosen values for exposure variables are upper-bound point estimates which, when taken together, result in realistic upper-bound exposure estimates.

The ten science policy issues and associated default assumptions discussed in this chapter were selected because of the relative frequency with which they occur in typical regulatory risk assessments. The default assumptions discussed in this chapter (and listed in Table 3-1) are phrased generally and are not meant to be representative of all regulatory risk assessments. In fact, default assumptions are frequently not used when specific data or information are available, and exceptions to each of the default assumptions are known to exist (*see* Chapter 4). The purpose of this chapter is to describe generally the assumptions that are most often made to bridge gaps in scientific data and knowledge when no information is available. This is the essence of a "default" assumption. The case studies prepared for and presented in subsequent chapters of this report include several additional science policy issues and illustrate numerous instances in which default assumptions were not used in particular regulatory risk assessments.

I. Use of Animal Data to Predict Human Risk

As elucidated in the *Red Book,*[3] the first step in a risk assessment is hazard identification. This step involves determining if exposure to a substance can increase the incidence of adverse health effects or accelerate death. Data concerning health effects in humans are frequently not available, so toxicologists have developed testing protocols to determine the potential health effects in animals. However, relying on animal data raises several science policy questions. Consider the relevant science policy questions regarding the predictive value and evaluation of animal studies for use in human cancer risk assessment raised in the *Red Book*:

> *What degree of confirmation of positive results in animal studies should be necessary? Is a positive result from a single study sufficient, or should positive results from two or more animal studies be required? Should negative results be disregarded or given less weight?*
>
> *Should an animal study be weighted according to its quality and statistical power?*
>
> *What statistical significance should be required for results on an animal study to be considered positive?*
>
> *What is the overall weight of the evidence of carcinogenicity?*

Using animal studies to predict potential cancer risks in humans involves considerable uncertainty. Therefore, determining the relevance of animal data for quantitative human cancer risk assessment requires a science policy decision:

- ***Science policy issue.*** In the absence of adequate human data, what is the relevance of animal bioassay data to the process of estimating human risk?
- ***Default science policy decision.*** A substance that is carcinogenic to animals is also a human carcinogen.

Ideally, hazard identification should be based on epidemiologic studies or other human health effects data that are representative of realistic exposures to the substance in question. However, it is seldom possible to rely on or develop new human data because:

- Human data are often not available, or readily or ethically obtainable;
- Available epidemiologic data may not be of sufficient quality because, for example, of small sample size, biased sampling, or failure or inability to control for confounding risk factors;
- Available human data tend to be limited to studies of highly exposed workers; and

[3] (NRC 1983, 19)

- Epidemiologic studies are insufficiently sensitive to detect small increases in risk.[4]

To compensate for the absence of adequate human hazard or health effects data,[5] risk assessors use data from long-term tests on live animals in order to predict human risk. A substantial body of data suggests that many animal carcinogens may also be human carcinogens. Therefore, this default assumption enjoys wide acceptance among decision makers and is viewed as necessary and justifiable by most objective scientists in industry and academia.[6] Because of the lack of human data for most chemicals of concern, the International Agency for Research on Cancer (IARC) adopted this default assumption as a "pragmatic" decision.[7] This assumption is essential to the current regulatory risk assessment process because there is no alternative which will allow risk assessors to estimate quantitatively human risk in the absence of human data. In fact, the "most compelling argument in favor of this use of animal tests is the lack of any better system for risk evaluation."[8]

This default assumption is supported by the fact that, with the exception of **arsenic and environmental tobacco smoke,** all known human carcinogens[9] have also been reported to be carcinogenic in at least one animal study conducted in accordance with accepted scientific research standards. For further support, a study compared carcinogenic potency estimates for twenty-three chemicals showing strong evidence of carcinogenicity in humans or animals and for which suitable data for quantitative comparisons were available, and found that the potency estimates were generally comparable, although outliers were observed.[10]

---

[4] For example, a study with a cohort of 1,000-5,000 subjects cannot detect an increased risk below 5 or 10 percent. At the 95 percent confidence level, a nonpositive study with 1,000 cases is compatible with a 20 percent increase in risk (Buffler 1989, 37).

[5] In addition to the subjective nature of science policy decisions, there is an additional layer of subjectivity in risk assessment. Determining what constitutes "adequate" data is not an entirely objective decision, nor can it be. Rarely are there complete data which would be considered probative of the health effects of a chemical, its potency, or real levels of exposure and absorption. For example, the lack of exposure data and reliance on "surrogates" for exposure data were the primary considerations in the judgment that the epidemiologic data concerning diesel emissions and lung cancer were inadequate to classify diesel emissions as a known human carcinogen. However, the absence of direct exposure measurements and consequential use of surrogate exposure measures, such as being married to a smoker, was not viewed as a deficiency **in the judgment that environmental** tobacco smoke is a known human carcinogen. See (Environmental Protection Agency [EPA] 1990, 1-20; EPA 1992a).

[6] (Office of Science and Technology Policy [OSTP] 1985)

[7] (Ashby, et al. 1990, 271)

[8] (McGarity 1979)

[9] As classified by EPA's carcinogen classification system.

[10] (Allen, Crump, and Shipp 1988)

Using animal data to predict potential human risks has been criticized because it might lead to too many "false-positive"[11] designations of substances as human carcinogens. A review of animal bioassay conducted by the National Toxicology Program (NTP) showed that one-half of the chemicals tested produced positive responses in either rats or mice, but that the responses in rats and mice were consistent only 70 percent of the time. Assuming a similar sensitivity and selectivity for rodent bioassays in predicting human risks, it has been suggested that relying on rodent bioassays will falsely identify nine agents as human carcinogens for every human carcinogen that is missed.[12] In other words, false positives would outweigh false negatives by nine to one. Whether this represents a reasonable position from the public health perspective is a matter of policy, not science.

A single animal bioassay indicating a carcinogenic response in a single sex/species combination does not necessarily imply that the substance of concern will be considered a human carcinogen. Results from animal bioassays and human studies, when available, are evaluated in a "weight-of-evidence" determination of the likelihood that a chemical is a human carcinogen. The EPA guidelines for making weight-of-evidence determinations are contained in the *Guidelines for Carcinogen Risk Assessment.*[13] The guidelines are a policy document that describes how EPA risk assessors should address issues of scientific uncertainty, such as how to evaluate the likelihood that an animal carcinogen may also be a human carcinogen.

The first step in a weight-of-evidence determination is to evaluate the quality of each study and determine whether it constitutes evidence of a potential carcinogenic effect. Table 3-2 illustrates the criteria by which animal and human studies are judged. Application of these criteria requires interpretation and evaluation of the available data. Judgment calls are an integral part of the process because of the uncertain nature of much of the information. Experts in toxicology and carcinogenesis bring their professional knowledge to bear on these evaluations. Although based in scientific traditions, evaluating the quality of evidence provided by each study is a matter of both scientific judgment and science policy.

The second step is to consider and evaluate both the animal and human evidence, together with any supporting evidence, such as mutagenicity data and knowledge of toxicologic effects. The substance of concern can then be classified as to its potential human carcinogenicity based on this evaluation. The following categories of carcinogens are identified in the EPA classification scheme: [14]

---

[11] A false positive occurs when a test appears to detect a response that is actually absent. A. false negative, on the other hand, occurs when a test fails to detect a response that is actually present.

[12] (Lave et al. 1988, 631)

[13]

[14]

- **Group A** Human carcinogen;
- **Group B** Probable human carcinogen (This group is divided into Groups B1 and B2, based on the weight of the evidence from human epidemiologic studies);
- **Group C** Possible human carcinogen;
- **Group D** Not classifiable as to human carcinogenicity; and
- **Group E** Evidence of noncarcinogenicity for humans.

Table 3*2. Criteria by Which Animal and Human Studies Are Judged for Evidence of Carcinogenicity[15]

Level of Evidence	Human Study	Animal Study
Sufficient	Data indicate a causal relationship between agent and cancer.	Data indicate increase in malignant or combined malignant and benign tumors in (a) multiple species, (b) multiple studies, or (c) to an unusual degree in one study.
Limited	Data indicate a causal relationship is credible, but alternative explanations cannot be ruled out.	Data suggest a carcinogenic effect but are limited because (a) criteria for "sufficient" evidence are not met, (b) the studies are lacking in quality, or (c) only benign tumors are increased.
Inadequate	Too few data or studies of inadequate quality to demonstrate a causal relationship.	Major qualitative or quantitative limitations in the studies preclude demonstration of a carcinogenic effect.
No data	No data are available	No data are available.
No evidence	No association between exposure and increased risk of cancer is found.	No increased incidence in at least two studies in different species.

EPA suggested a matrix linking the evaluation of the weight of evidence from animal and human studies and the associated group classification. This classification scheme,

[15] Adapted from (EPA 1986, 33999).

which EPA asserts is not to be applied "rigidly or mechanically,"[16] is summarized in Table 3-3. As with the initial weight-of-evidence determination, the classification of a chemical as to its potential human carcinogenicity is a matter of both science and judgment.

Table 3-3. Categorization of Carcinogens Based on Weight-of-Evidence Determination of Animal and Human Data[17]

Human Evidence	Animal Evidence				
	Sufficient	**Limited**	**Inadequate**	**No data**	**No evidence**
Sufficient Limited	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No data	B2	C	D	D	E
No evidence	B2	C	D	D	E

EPA is currently in the process of revising its *Guidelines for Carcinogen Risk Assessment.* Part of this effort focuses on revising the means by which weight-of- evidence determinations are made.[18] The revision effort has been under way for some time and remains controversial, so it is not certain that the recently released draft revised guidelines will be formally adopted soon.[19]

II. Combining Benign and Malignant Tumors

Animals administered substances in bioassays may develop both malignant (cancerous) and benign (noncancerous) tumors. Deciding how to categorize and count tumors observed in animal bioassays for risk assessment purposes can be crucial given that the tumor count is a determinative factor in characterizing a bioassay as "positive" or "nonpositive."[20] Positive results indicate that the substance is associated with an increased incidence of cancer, whereas nonpositive results indicate that the substance is not associated with an increased incidence of cancer. The *Red Book* discussed the relevance of benign tumors and the appropriate grouping of tumors for statistical purposes in human cancer risk assessment in the following questions:

---

[16] (EPA 1986, 33996)

[17] Adapted from Table 1 (EPA 1986, 34000).

[18] (EPA 1992b)

[19] EPA hosted a workshop to discuss the most recent draft of the revised risk assessment guidelines on September 13 and 14, 1994.

[20] *Nonpositive* data are commonly referred to as negative data. We have attempted to avoid the term negative because it may incorrectly imply that a study reports a healthy effect from exposure.

Should benign and malignant lesions observed in animals be counted equally?

Into what categories should tumors observed in animals be grouped for statistical purposes?

Should only increases in the numbers of tumors in animals be considered, or should a decrease in the latent period for tumor occurrence also be used as evidence of carcinogenicity?

Should a dose-related increase in tumors observed in animals be discounted when the tumors in question have high or extremely variable spontaneous rates?

Because of limitations in understanding the relationship between benign and malignant tumors, determining the relevance of benign tumors in animals to human cancer risk assessment requires a science policy decision:

- **Science policy issue.** Is the occurrence of benign tumors in experimental animals relevant to estimating human cancer risk?
- **Default science policy decision**. Benign tumors are combined with malignant tumors in animals to establish carcinogenic potential in humans.

Thus, the default assumption is to count both benign and malignant tumors as indicators of potential carcinogenicity in humans. The total number of animals exhibiting tumors, whether malignant or not, is used to characterize the response observed in the animal bioassay and to estimate potential human cancer risk. According to EPA guidelines, benign and malignant tumors should be combined unless the observed benign tumors are not thought to progress to the observed malignancies.[21] In contrast, the Office of Science and Technology Policy (OSTP) reverses the burden of proof and recommends that benign and malignant tumors be combined only when it is scientifically defensible to do so.[22]

More has recently been learned about the potential for progression to cancer of some benign precancerous cell growths. These findings call into question the validity of combining benign and malignant tumors for risk assessment purposes. Based on these findings, some existing risk estimates have been questioned. For example:

- Certain pre- or nonneoplastic lesions in rat livers were reported not to progress to cancer and were deemed irrelevant for estimating human cancer

[21] (EPA 1986, 33999)

[22] (OSTP 1985, 10376)

risk.[23] Using revised criteria for classifying these lesions, certain dioxin-induced tumors were judged not to be precancerous. The resulting revised count of cancerous tumors allowed a cancer potency estimate that is sixteen times lower than the current EPA estimate.[24]

- Certain adenomas observed in animals exposed to **di(2-ethylhexyl) adipate** and **di-isononylphthalate** are judged not to be indicative of potential carcinogenic activity in humans, and neither of these compounds is now regulated as a human carcinogen.[25]

III. Relevance of Nonpositive Data

Positive bioassay data indicate the presence of a carcinogenic effect, while nonpositive bioassay data do not. Frequently, risk assessors are faced with the existence of both positive data and nonpositive data and must therefore decide which data to use in quantitative risk assessment. The *Red Book* framed the topic in the context of the following questions:

> *What relative weights should be given to epidemiologic studies with differing results? For example, should positive results outweigh negative results if the studies that yield them are comparable? Should a study be weighted in accord with its statistical power?*
>
> *What degree of confirmation of positive results should be necessary? Is a positive result from a single animal study sufficient, or should positive results from two or more animal studies be required? Should negative results be disregarded or given less weight?*
>
> *How should different results of comparable short-term tests be weighted? Should positive results be accorded greater weight than negative results?*

---

[23] (Maronpot, et al. 1986)

[24] (Keenan, et al. 1991)

[25] For di (2-ethylhexyl) adipate, the combined carcinomas and adenomas were reported to be statistically significant in male and female rodents, but the carcinomas were significant only in female rodents, and the adenomas in male rodents were within the range of the historical controls. Adenomas are benign tumors which do not always progress to malignant carcinomas (Integrated Risk Information System [IRIS] 1994).

Determining whether to use positive and nonpositive data, if both exist, in quantitative cancer risk assessment requires a science policy decision:

- **Science policy issue**. When both positive and nonpositive cancer incidence data exist, should the nonpositive data be used for quantitative risk assessment purposes?
- **Default science policy decision.** In the presence of positive cancer incidence data, nonpositive data are not indicative of safety and are not used in quantitative risk assessment.

Contradictory data are generally addressed by assuming that positive data outweigh nonpositive data for purposes of quantitative risk assessment.[26] Nonpositive data are not included in the risk assessment once sufficient positive data have been identified and the substance of concern has been classified as to its potential human carcinogenicity (See section I of this chapter). Nonpositive epidemiologic studies also generally fail to outweigh positive animal bioassay data.[27] This default assumption arises from a lack of confidence in nonpositive data, which may either represent either a "true negative" or "false negative,"[28] and because there is no consensus on how to incorporate nonpositive studies into quantitative risk assessment.[29]

Because animal bioassays are frequently conducted in more than one species, mixed responses may be observed. Consider the following examples from bioassays conducted by the NTP:

- **Acetaminophen,** a widely consumed analgesic found in nonprescription pharmaceuticals was tested in a long-term rodent bioassay. Although no carcinogenic activity was reported among male and female mice or male rats, the most highly exposed female rats exhibited an increased incidence of a type of leukemia.[30]
- **Drinking water disinfectants (chlorine and chloramine)**. Studies of mice and rats exposed to chlorine and chloramine in de-ionized water reported no

[26] However, this is not necessarily the case when evaluating the qualitative weight of evidence for carcinogenicity. Under EPA guidelines for carcinogen risk assessment, "a positive carcinogenic response in one species/strain/sex is not generally negated by negative results in other species/strains/sex. Replicate negative studies that are essentially identical in all other respects to a positive study may indicate that the positive results are spurious" (EPA 1986, 33995).

[27] (OSTP 1985)

[28] (Interagency Regulatory Liaison Group [IRLG] 1979; Food and Drug Administration [FDA] 1971)

[29] "First, agencies lack guidelines on how to use negative findings and mechanistic data in classification decisions and modeling. Second, there is a lack of consensus in the scientific community on when positive animal data are not indicative of human risk, and when negative data and/or mechanistic data are sound enough to be used in risk assessment" (Center for Risk Analysis 1991, 14).

[30] (National Institute for Environmental Health Sciences [NIEHS] 1993, 271)

evidence of carcinogenic activity in male or female mice or male rats, but a slight increase in mononuclear leukemia was reported among female rats.[31]

- **Mixtures of aspirin, phenacetin, and caffeine.** Mixtures of aspirin, phenacetin, and caffeine are used in nonprescription analgesic preparations for the relief of headache, muscular aches and pains, arthritis, and other common afflictions. Although no carcinogenic activity was observed in male and female mice or male rats, female rats were observed to have an increased incidence of urinary tumors.[32]

For all of the examples above, the following question may be asked: How should the nonpositive results in male and female mice and male rats be weighed against the positive results in female rats? In each case, the answer to this question is a matter of science policy.

IV. Use of Maximum Tolerated Doses in Animal Studies

Most substances of concern to regulators pose such a small risk at common environmental doses that detecting these small risks with statistical significance through an animal bioassay would require thousands, even millions, of animals.[33] Thus, attempting to directly measure low risks in sufficiently large animal bioassay animals is both impractical and prohibitively expensive. However, practically sized animal bioassays are limited in sensitivity. To overcome these problems, testing at the maximum tolerated dose (MTD) was developed and has been a central feature of animal bioassays for some time. Determining the relevance of carcinogenic effects observed at the MTD to human risk at much lower doses requires a science policy decision:

- **Science policy issue**. What is the relevance of data from animal bioassays conducted with high or maximum tolerated dose protocols to estimating potential human risk?
- **Default science policy decision**. Carcinogenic effects observed at the MTD in animals are predictive of effects in humans at much lower doses.

[31] In female rats, the increased incidence was statistically significant at the mid-dose but not at the high-dose, and the incidence was not clearly dose related, leading NTP to regard the bioassay results as equivocal evidence of carcinogenicity in female rats (NIEHS 1993, 269-270).

[32] (NIEHS 1993, 43)

[33] For example, in order to be 95 percent certain of detecting an increased risk of 1 in 1 million (10'6), a study would entail exposing 3 million animals at the human exposure level and comparing the observed response to that seen in 3 million unexposed control animals (McGarity 1979, 734). In contrast, a typical animal bioassay using about 600 animals would almost certainly fail to detect risks of less than 5 in 1,000, which is 5,000 times greater than the traditional risk level of concern (Wilkinson 1987, 845).

This default assumption holds that extrapolation of responses seen in animals at the MTD to lower doses more typical of human exposures is valid.[34] In MTD testing, doses far in excess of potential human exposures are administered to animals in an attempt to "ensure an adequate power for the detection of carcinogenic activity."[35] MTD testing overcomes the inherent low statistical sensitivity of practically sized animal bioassays by maximizing the likelihood of detecting a carcinogenic response in the bioassay.

The validity of MTD testing is predicated on the theory that a single molecule of a carcinogen can induce cancer, so that response observed at the MTD can be extrapolated to the lower levels experienced by humans.[36] The MTD is likely to be anywhere from 10,000 to 100,000 times higher than the doses of interest in humans. Extrapolations over such a large range would not even be attempted in most areas of science, where extrapolation beyond the range of observable data is generally discouraged.[37]

The key to MTD testing is the definition of what actually constitutes an MTD. Designation of the maximum dose to be used in a bioassay has been called the most controversial issue in animal testing.[38] The MTD is defined as the highest dose that is not lethal to animals over a lifetime but that produces some toxic effects.[39] For example, generally no more than a 10 percent reduction in body weight is permitted. Current EPA protocols allow a greater incidence of some adverse effects than other agencies, resulting in a definition of an EPA MTD that may be greater than that of another agency, such as the Food and Drug Administration (FDA).

Critics of MTD testing contend that the MTD is often so high that the resulting toxicity and carcinogenicity are due to the magnitude of the dose rather than to the inherent toxicity of the substance being tested. The Red Book addressed the MTD controversy in the following science policy questions:

> *How should findings of tissue damage or other toxic effects be used in the interpretation of tumor data? Should evidence that tumors may have resulted from these effects be taken to mean that they would not be expected to occur at lower doses?*

EPA's *Guidelines for Carcinogen Risk Assessment state that* "Evidence indicating that high exposures alter tumor responses by indirect mechanisms that may be unrelated to

---

[34] The NRC's Committee on Risk Assessment Methodology has more recently addressed the definition of use of the MTD in animal bioassay (NRC 1993). See also (Rodricks 1992, 140—144) and (Office of Management and Budget [OMB] 1990, 18-19) for discussions of the MTD controversy.

[35] (EPA 1986, 33994-33995)

[36] (Ottoboni 1991, 96-99)

[37] (Wilkinson 1987, 846)

[38] (OSTP 1985)

[39] (Carr and Kolbye 1991, 78-79)

effects at lower exposures should be dealt with on an individual basis."[40] If gross toxicity is observed at the MTD, then any carcinogenic response observed may actually be a result of a toxic response seen only at the MTD. For example, massive cell death and gross toxicity occurring at the MTD could result in conditions that favor tumor development,[41] and carcinogenic responses observed under these conditions should be carefully reviewed for their relevance to potential human responses.[42] Although the guidelines call for evaluation of these types of data, carcinogenic effects observed in animals at the MTD are generally assumed to be predictive for humans. Consider the following examples of indirect mechanisms of carcinogenesis seen only at high doses:

- **Corticosteroids, estrogens**, and some **sulfonamide** compounds are associated with cancer at high doses. However, when the dose in a bioassay is reduced to a point where cell death does not occur, such as at one-half of the MTD, oftentimes no tumors are observed.[43]
- The presence of stones in rodent bladder tissue gives rise to conditions which allow normal bladder cells to transform to malignancies. Tumors arise when doses of an agent sufficiently high to cause stone formation are administered, but tumors are not observed at lower doses without stone formation. This body of research holds that "the action of any non-genotoxic agent that includes bladder tumor[s] in rodents in the presence of stone[s] is therefore most probably irrelevant to human carcinogen risk assessment."[44]

There are additional arguments that the use of MTDs in animal testing may not be appropriate. For example, the NTP Board of Scientific Counselors concluded that two-thirds of the compounds identified as carcinogens by the NTP would not have been so classified if the MTD had not been used in the bioassay. The NTP board identified the following assumptions implicit in extrapolation from the MTD as invalid:

- Pharmacokinetics (i.e., the absorption, distribution, metabolism, and elimination of a substance in the body) are not dose-dependent;
- Dose-response is linear at low doses;
- DNA repair is not dependent on dose;
- Response is not age-dependent; and
- Test doses need not bear a relationship to human exposures. The NTP board called for a thorough re-evaluation of both the criteria by which high doses

[40] (EPA 1986, 33995)

[41] (OMB 1990, 18)

[42] (EPA 1986, 33995)

[43] It should be noted, however, that this observation may be due to the problem of limited sensitivity of the bioassay because of the small number of animals used.

[44] (Rodricks 1992, 142)

> for testing are selected and the criteria used to extrapolate from high to low doses.[45]

Essentially, the problem of the MTD is one of balance: [46]

> *Is it sensible to attempt corrections for one source of error [the limited sensitivity of bioassays] ...by introducing another source of error—the MTD—which may distort through toxicity and perhaps tumor promotion our perception of a chemical's propensity to induce cancer?*

The MTD should maximize the chance of observing cancer without producing toxic effects that have no bearing on likely responses at expected exposures, but should not be so low that false-negative results might be obtained. The continuing controversy demonstrates that this issue is far from settled.

V. Relative Sensitivity of Humans and Animals

Sometimes animal bioassay data exist for more than one species. Usually, the data indicate that some species are more sensitive than other species to the substance tested. For example, a greater incidence of tumors at a given dose may be observed, or tumors may be observed at lower doses. The *Red Book* raised the following science policy questions with respect to the relative sensitivity of humans and animals:

> *If data are available on more than one nonhuman species or genetic strain, how should they be used? Should only data on the most sensitive species or strain be used to derive a dose-response function, or should the data be combined? If data on different species and strains are to be combined, how should this be accomplished?*

Thus, the question of determining which set of animal bioassay data to use for estimating human health risks requires a science policy decision:

- **Science policy issue.** Which animal species should be used to represent humans in terms of carcinogenic response?
- **Default science policy decision.** The animal species exhibiting the greatest carcinogenic sensitivity is the most appropriate species on which to base estimates of human cancer risk.

EPA guidance suggests that "data from a species that responds most like humans should be used."[47] However, it is not generally possible to determine which species' response most resembles the response in humans. Therefore, in the absence of specific data, in order to be protective, it is assumed that humans are at least as sensitive as the most

[45] (National Toxicology Program [NTP] 1992, 31723)

[46] (Carr and Kolbye 1991, 79)

[47] (EPA 1986, 33997)

sensitive animal species.[48] Thus, the response observed in the most sensitive species and sex is generally chosen for quantitative estimation of risk to humans.

Humans may reasonably be anticipated to be more susceptible to carcinogenic effects than other species. For example, consider the following factors which would tend to indicate that humans are indeed more susceptible to carcinogens than lab animals: [49]

- Humans live up to 35 times longer than mice, allowing much more time for tumor induction and expression.
- Human blood circulation is 20 times slower than in mice, thereby increasing residence time in tissues and plasma.
- Humans have 3,000 times more cells than mice.
- The probability that any one human cell will be hit by a carcinogen, at a constant level of exposure, is approximately 100,000 times higher than in mice.

Thus, there are biologically plausible reasons to believe that humans are more susceptible to carcinogens than laboratory animals. The only possible choice, so the assumption goes, is to use data from the animal species showing the most sensitive response.

Despite the theoretical justifications for this assumption, it is often criticized because it results in the dismissal of all but the most sensitive data set and because it leads to erratic results. For example, one study found that data from the bioassay showing the most sensitive animal response were approximately correct for predicting human risks of **benzidine, chlornaphazine**, and cigarette **smoking**. However, human risks were overstated by a factor of 10 for aflatoxin, 50 for **diethylstilbestrol**, and 500 for vinyl **chloride**.[50] Human data are usually not available, so it is not possible to compare the risk estimates derived from human and animal data.

VI. Relevance of Differences Between Humans and Animals

Although humans and the animals used in bioassays are biologically similar, considerable differences exist that may result in distinct responses to toxic chemicals. However, the role of these differences in determining species-specific responses to toxic or carcinogenic chemicals is rarely well understood. An additional source of uncertainty is encountered in trying to convert doses in experimental animals to "equivalent" doses in humans. The *Red Book* raised the following science policy questions concerning the evaluation and use of mechanistic data:

---

[48] (EPA 1986, 33997)

[49] (Saffiotti 1980, 1310) citing (NRC 1977).

[50] (NRC 1975)

> *How should evidence of different metabolic pathways or vastly different metabolic rates between animals and humans be factored into a risk assessment?*
>
> *How should information on comparative metabolic processes and rates in experimental animals and humans be used?*
>
> *What factor should be used for interspecies conversion of dose from animals to humans?*

As is evident from the questions above, determining how or whether to include species-specific factors in quantitative risk assessment requires a science policy decision:

- Science policy issue. When predicting human health risk on the basis of animal data, how should mechanistic variations between species be taken into account?
- Default science policy decision. Differences between species in mechanisms of carcinogenicity are not taken into account when extrapolating data from one species to another.

Although mechanistic data are not normally included in quantitative risk assessments, evidence is accumulating that species differences in mechanisms may be sufficient to preclude assuming that an animal carcinogen poses a cancer risk to humans. Unfortunately, mechanistic information is rarely available or is of limited use. Moreover, animal bioassays are generally not designed to develop mechanistic or pharmacokinetic data. Consequently, the default practice of not considering specific mechanistic information in risk assessments has been most often applied.

However, as mechanistic information is increasingly developed, its use in risk assessments is also increasing. For example, sometimes the mechanisms that give rise to observed carcinogenicity in a test species are not possible in humans. Examples of how the mechanism of carcinogenesis differs between animals and humans so that animal bioassay data may not be predictive of human risk include the following.

- Renal carcinogenicity in male rats is associated with exposure to **unleaded gasoline**.[51]
- **Butylated hydroxyanisole (BHA),** a food preservative, has been associated with tumors of the forestomach in rodents, an organ for which there is no equivalent in humans, but not in the esophagus, which is the most similar organ in humans.[52] Furthermore, food sits in rodent forestomachs for long periods of time, but passes rapidly through the human esophagus.[53]

---

[51] See Chapter 7, "Unleaded Gasoline."

[52] (Whysner 1993) See Chapter 11, "Toxics Release Inventory."

[53] "(Ashby, et al. 1990, 281)

- Certain liver-specific animal carcinogens induce peroxisome proliferation[54] in the liver (e.g., **2-diethylhexylphthalate, short-chain grade chlorinated paraffins, and trichloroethylene (TCE)).**[55] Although a link between peroxisome proliferation and cancer is not proven, it has been suggested that peroxisome proliferation increases the levels of reactive oxygen species that could damage DNA and other cellular molecules.[56]
- **Benzidine**, a known carcinogen in humans and in laboratory animals, is associated with bladder cancer in humans, liver cancer in rats, and bladder tumors in dogs. Research has determined that humans and dogs metabolize benzidine similarly, whereas rats have a different metabolic process. The differences in metabolism are most important because metabolites of benzidine, rather than benzidine itself, are the proximate cause of the observed tumors. Thus, "knowledge of metabolic differences helps explain the species' similarities and differences in tumor response."[57]

Because mechanistic information which would allow an explicit consideration of differences in sensitivity across species is generally unavailable, a generic approach for estimating equivalent doses in animals and humans is required. Current risk assessment practice is to use a "scaling factor" to scale doses used in animal bioassays to equivalent doses in humans. As such, the use of scaling factors represents the only attempt in current risk assessment methods to incorporate differences in sensitivity of different species. Scaling factors account for differences in sensitivity to the effects of substances and other agents between animals and humans resulting from differences in their relative sizes. For example, small animals have a higher metabolic rate than larger animals. These differences in metabolism would be expected to result in different

responses to chemicals at the same dose across species. Conversely, it is also expected that different doses could be associated with the same degree of response in different species.

A scaling factor must be employed because sufficient mechanistic data rarely exist to justify a direct dose conversion. EPA stated that "extrapolation on the basis of surface area is considered to be appropriate because certain pharmacological effects commonly scale according to surface area."[58] This approach is termed Surface Area Equivalence (SAE). SAE explains why metabolic activity (expressed on a per kilogram body weight basis) is much greater in small animals than in large animals. Under the assumption of

---

[54] *Peroxisome proliferation refers* to an increase in the number of peroxisomes, which are cell organelles that catalyze the production and breakdown of hydrogen peroxide.

[55] *See* (Steinberg and DeSesso 1993) on trichloroethylene; (ICI Chemicals 1994, 8-9), and Chapter 9, "Trichloroethylene."

[56] (EPA 1992c, VIM)

[57] (Rodricks 1992)

[58] (EPA 1986, 33998)

SAE, doses in animal species and humans are expressed in terms of milligram (mg) of substance per square meter (m^2) of body surface area. Equivalent doses in mg/m2 are then assumed to produce the same effects in all species.[59]

VII. Extrapolation Across Routes of Exposure

Frequently, animal bioassay data using the route of administration or exposure of interest in humans are not available. Under these circumstances, the applicability of the available data involving a different route of exposure must be determined. The *Red Book* raised the following science policy issues with respect to "route-to-route extrapolation":

> *How should experimental animal data be used when the exposure routes in experimental animals and humans are different?*
>
> *What is the significance of a positive finding in an epidemiologic study in which the route of exposure is different from that of a population at potential risk?*

Pressure to regulate often precludes delays associated with developing route-specific cancer data. Therefore, recognizing the time and expense involved in developing new data, a science policy decision is required:

- **Science policy issue.** Data indicate that ingestion of a substance may be associated with cancer. If inhalation exposures are of concern, what is the relevance of the ingestion data to the prediction of inhalation risk?
- **Default science policy decision**. A carcinogen by one route of exposure is a carcinogen by any other route of exposure.

In the absence of data to the contrary, it is generally assumed that a substance found to be carcinogenic in animals via one route of administration may be carcinogenic in humans via a different route of exposure.[60] This default assumption arose because injection, gavage, and other direct dosing techniques, which are more easily controlled and measured in the laboratory, are more commonly used in bioassays. The assumption is often justified on the basis that carcinogenicity is a systemic response which depends on the amount of chemical reaching the target organ rather than on the route of administration. EPA guidelines require that any route-to-route extrapolation "be consistent with the existing metabolic and pharmacokinetic information on the chemical" and that all "considerations used in making the route-to-route extrapolation ... be carefully explained."[61] However, when a quantified risk estimate is required but data for the desired route of exposure are lacking, route-to-route extrapolation is generally

---

[59] (Vocci and Farber 1988)

[60] A well-known exception to this default assumption is **cycasin**, a naturally occurring chemical that is transformed in the stomach to **methylazoxymethanol**, a potent genotoxic carcinogen. This substance is carcinogenic when ingested, but not by other exposure routes (Ashby et al. 1990, 280).

[61] (EPA 1986, 33997)

used. The alternative approach—not producing a risk estimate for the desired route of exposure—is also sometimes taken.[62]

"There is at this time no simple, direct and generally applicable way in which toxicity data derived from one route of exposure in animals can be used to assess the risks to humans from exposure by another route."[63] Rather, careful case-by-case consideration must be employed:

> *The highest degree of success in making a valid extrapolation is likely where information on the relationships between the doses administered and the amounts or concentrations arriving at the site of toxic action are known for both routes of administration and where adequate toxicological data are available for one of the routes.*[64]

Reliable route-to-route extrapolation is most likely for substances which, following absorption and distribution, do not require metabolic activation before acting at a single site to produce a single toxic effect. Thus, understanding the absorption, distribution, and metabolism of a substance is essential for reliable route-to-route extrapolation. For example, a substance absorbed orally passes directly to the liver, where it may be metabolically activated prior to distribution throughout the body; whereas the substance may be distributed in an unmetabolized form if inhaled.[65] If the metabolite is the

cause of the observed tumors, carcinogenic effects would not reasonably be expected from inhalation exposures.

Consider the following examples where the validity of route-to-route extrapolation would reasonably be questioned:

- **Selenium sulfide** is an active ingredient in dandruff shampoo. Oral administration of selenium sulfide by gavage resulted in positive results for male and female rats and female mice.[66] However, in humans the exposure route of concern is dermal. A bioassay of dermal exposure to prescription-strength selenium sulfide was negative.[67] What then is the significance to human risk of the oral versus the dermal administration studies?

---

[62] See Integrated Risk Information System (IRIS) chemical profiles, in which ingestion data for a chemical have been used to estimate an oral potency factor but have not been extrapolated across routes of exposure to estimate an inhalation potency factor.

[63] (Sharratt 1988, 407)

[64] (Sharratt 1988, 405)

[65] (Sharratt 1988, 401-102)

[66] (NIEHS 1993, 108-109)

[67] The study may have been limited by the relatively short lifespan of the particular strain of mice used (NIEHS 1993).

- EPA proposed to revoke the food additive regulation for the pesticide **ethylene oxide** primarily on the basis of a positive cancer animal bioassay in which ethylene oxide was administered via inhalation. Also cited was a study where administration of ethylene oxide by gavage was associated with tumors of the rodent forestomach, and subcutaneous injection in mice was associated with tumors at the site of injection.[68] How should the findings of the inhalation and injection studies be interpreted given that the general route of exposure to ethylene oxide is dietary?
- To develop information concerning potential human cancer risk from inhalation of **glass wool fibers**, animal bioassays have been conducted where glass wool fibers were injected, implanted, or otherwise artificially instilled in the respiratory tract of the laboratory animals. The animals did not actually inhale the glass wool fibers.[69] Given that animal bioassays and epidemiologic studies may not indicate that inhalation of glass wool fibers increases human cancer risk,[70] how should the positive findings from the implantation studies be interpreted with respect to inhalation risk in humans?[71]

Although frequently used, this default assumption is not applied without consideration and evaluation. For example, in the case of glass wool fibers, EPA has stated:

> *Positive results from studies using intrapleural or intraperitoneal injection/implantation method[s] in the absence of positive findings from inhalation experiments do not indicate that these fibers will produce tumors in man upon inhalation* [72]

Clearly, this demonstrates that EPA does not always assume that a carcinogen by one route is a carcinogen by any other route. Rather, this default assumption is applied generally only when it is defensible to do so, although there are sure to be questionable instances of its application.

VIII. Existence of Thresholds for Carcinogenicity

If a substance is a carcinogen at all levels of exposure, the substance is said to act on a no-threshold basis. The substance is said to act on a threshold basis if there are some levels of exposure which are not associated with carcinogenic activity. The absence or

---

[68] (EPA 1994, 33943)

[69] *See* (North American Insulation Manufacturers Association [NAIMA] 1994) citing *e.g.*, (Wagner et al. 1984; Mohr et al. 1984).

[70] *See* (NAIMA 1994, App. B).

[71] *See* Chapter 11, "Toxics Release Inventory."

[72] (NAIMA 1994, 9-10) citing (EPA 1988). This view was also espoused by the U.S. National Institute of Occupational Safety and Health (NIOSH), the World Health Organization, and the American Federation of Labor-Congress of Industrial Organizations (AFL-CIO).

existence of threshold levels of exposure for carcinogenesis is a major continuing controversy. The *Red Book* phrased this science policy issue in terms of dose-response models:

> *What dose-response models should be used to extrapolate from observed doses in humans to relevant doses?*

Questions about the shape of the dose-response curve and the possible existence of thresholds for carcinogens cannot be answered by science alone, but require a science policy decision:

- **Science policy issue**. The available data do not demonstrate the absence or existence of a threshold for carcinogenesis.
- **Default science policy decision**. There is no nonzero dose below which an increased risk of carcinogenic effects will not occur.

The no-threshold default assumption is based upon an analogy with radiation-induced cancer[73] and assumes there is no safe exposure. This assumption suggests that "exposure to even one molecule of a carcinogen is associated with a small but nonzero risk of tumor induction."[74] Thus, as Figure 3-1 indicates, the no-threshold dose-response curve is derived by constraining the dose-response relationship obtained from epidemiologic or animal bioassay data in the observable range to pass through the origin. Zero response is assumed to occur only at zero dose.

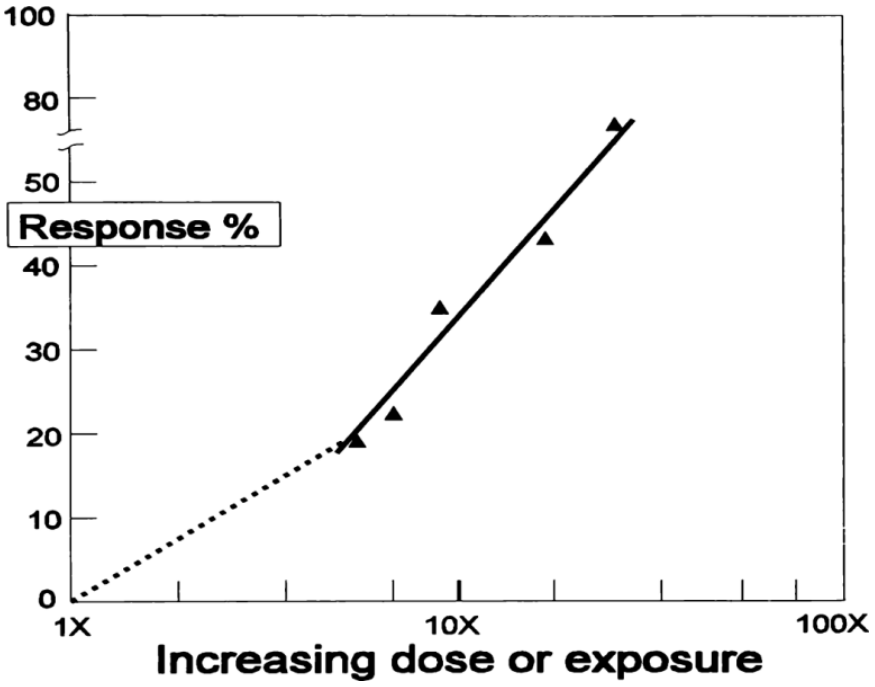

Figure 3-1. Extrapolation of dose-response curve showing extrapolation to zero—assumption of no-threshold.

[73] (Ottoboni 1991, 96-97)

[74] (NRC 1994)

Unfortunately, limitations in the ability of animal and epidemiologic studies to detect risks in the low-dose range (as discussed in Sections IV and IX of this chapter) mean that information concerning potential health effects at low or near-zero doses is rarely available. Thus, for all practical purposes,

> *... the presence or absence of threshold [for carcinogenesis] cannot be demonstrated experimentally.... Present experimental procedures and practices are not capable of providing experimental verification of [the existence of thresholds in carcinogenesis].*[75]

Human and animal data are not sufficient "to define the dose-incidence relationship in the low dose domain or to exclude the possibility of a threshold."[76] Thus, "... it is not possible to perform an animal bioassay experiment to establish [statistically] a threshold dose below which no toxic effect occurs." [77] Nor is it likely that a threshold dose could be detected in an epidemiologic study.

In other words, the existence of a threshold can neither be proved nor disproved using animal bioassay or epidemiologic data. Rather, the resolution of whether a threshold for carcinogenesis exists rests on theoretical arguments. Increased understanding of the mechanisms of carcinogenesis and the body's ability to resist the effects of carcinogens through DNA repair [78] has cast doubt on the assumption that all carcinogens act through a no-threshold mechanism. Major arguments supporting the possible existence of thresholds in carcinogenesis are summarized below.[79]

- Current understandings of carcinogenesis envision a multistage process that involves:
  - Exposure, absorption, distribution, activation, deactivation, and elimination of the chemical and products formed from it;
  - Interaction with receptors leading to molecularly transmittable products; and
  - Survival and proliferation of the transformed cells to produce cancer.

  Anything that limits or inhibits one of the stages above may constitute a threshold.

---

[75] (Purchase 1993)

[76] (Upton 1988, 865)

[77] (Gaylor 1987)

[78] Although DNA repair is known to occur in human cells, it alone cannot be said to prove the existence of a threshold for carcinogenesis because: DNA repair does not reduce DNA damage to zero; not all DNA repair systems are error-free; and variations in DNA repair efficiency occur among cells, tissues, strains, and species (OSTP 1985).

[79] (Fishbein 1980)

- Age, sex, nutrition, population density, hormonal state, or concomitant disease may affect response to carcinogens, allowing previously checked processes to proceed to cancer.
- Latency period increases as dose decreases; therefore, at low doses, a threshold may be implied because multiples of a lifetime would be required for the induction of cancer.
- If several transformed cells in close proximity are required to produce cancer (the multihit hypothesis), then reduced dose will markedly reduce the likelihood that cancer will be observed because the probability of a sufficient number of transformed cells in close proximity is greatly reduced.
- Some carcinogens produce cancer only at doses exceeding those that produce pathological responses.
- Evidence that carcinogenesis is subject to immunosurveillance, particularly cell- mediated immunity, is growing. Thus, even in cases where direct DNA damage might occur at very low doses, the combination of immunosurveillance and DNA repair could create a threshold for clinically observable pathology or nonlinearity in the dose-response curve at low doses.

Arguments that there is no threshold in carcinogenesis also exist. Major arguments against the existence of thresholds include: [80]

- Cancer is seen as an expression of a permanent, replicable defect resulting from amplification of a defect initiated in one cell by reaction of the agent with a critical receptor.
- The total cumulative dose of some carcinogens necessary for carcinogenesis is less than the single dose required to produce an equivalent response.
- Experiments on radiation-induced cancer have not statistically demonstrated a threshold.[81]

Thus, with so many arguments supporting both the existence and absence of thresholds in carcinogenesis, the issue of thresholds in carcinogenesis is quite complicated. Resolution of this issue is necessarily chemical-specific and dependent upon a thorough understanding of the mechanism of carcinogenicity. Unfortunately, this level of detail is not available for the vast majority of chemicals of concern.

[80] (Fishbein 1980)

[81] The National Research Council's BEIR V report stated that, with respect to low-dose radiation, the existence of a threshold cannot be proved or disproved (NRC 1990, 181).

IX. Extrapolation to Low Doses

The relationship between the observed health effects or responses and the associated doses is known as the "dose-response relationship" or "dose-response curve." For virtually all substances the shape dose-response relationship is unknown—and unknowable—at low doses (see Figure 3-2). Related science policy questions identified in the *Red Book* include:

> *What dose-response models should he used to extrapolate from observed doses in humans to relevant doses?*
>
> *Should dose-response relationships be extrapolated according to best estimates or according to upper confidence limits when using epidemiologic data?*
>
> *What mathematical models should be used to extrapolate from experimental animal doses to humans?*
>
> *Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits when using animal data? If the latter, what confidence limits should be used?*

The shape of the dose-response curve cannot be determined at low doses and is therefore termed "trans-scientific.[82]

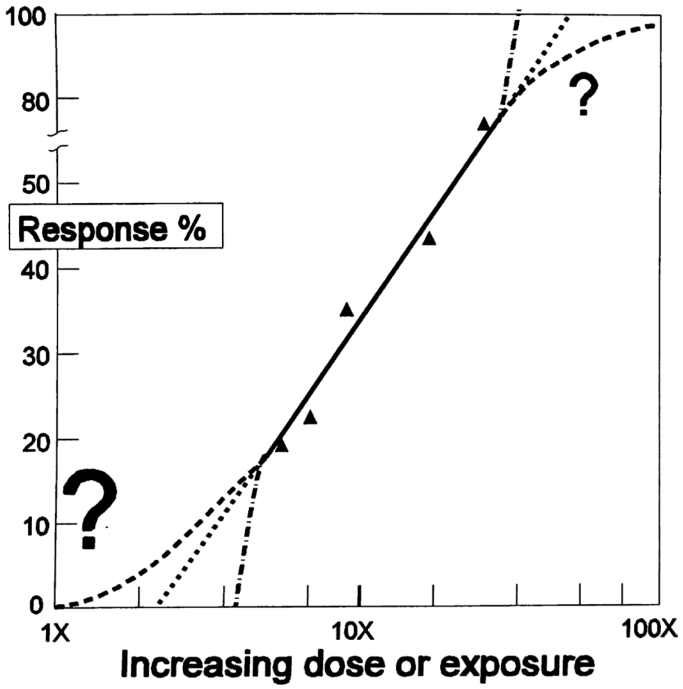

Figure 3-2. Dose-response curve indicating regions where shape of curve is unknown.

[82] (McGarity 1979, 733; Ottoboni 1991, 193-195)

In other words, science is simply inadequate to define the dose-response curve at low doses. Therefore, a science policy decision is required:

- **Science policy issue**. Data indicate a dose-response relationship at high doses, but few or no data concerning the dose-response relationship at lower levels exist.
- **Default science policy decision**. The dose-response relationship is linear at low doses.

The limitations of animal bioassay and epidemiologic studies are such that a response of less than 5 in 1,000 (0.5 percent) or 1 in 100 (1 percent) will not be observed through the data.[83] Due to this limited sensitivity, dose-response relationships in the low-dose range are practically unknowable, and the shape of the dose-response curve in the low-dose range must be assumed to facilitate quantitative risk assessment and to be protective of public health.

The assumption of low-dose linearity is quite controversial. It has been said that:

> *... the most contentious judgment in carcinogen risk assessment is how to extend the dose-response curve from the high doses to which animals are exposed in the laboratory to the lower doses to which humans are exposed in the environment.*[84]

The assumption of low-dose linearity does not imply that the dose-response curve is actually known, or even thought to be, linear at low doses. The assumption of low-dose linearity does not provide a "best estimate" of risk in the low-dose region; rather, it is generally used to provide an upper limit on risk estimates at low doses.[85] EPA supports the assumption of linearity because it:

> *... leads to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may be as low as zero,*[86]

Thus, use of a linearized dose-response curve is a bounding approximation which is not likely to underestimate risk at low doses.[87] EPA guidelines require that the range of

---

[83] (Wilkinson 1987, 845)

[84] (Wilkinson 1987, 845)

[85] (Gaylor 1987; EPA 1986, 33995)

[86] (EPA 1986, 33997-33998)

[87] The dose-response curve is commonly assumed to be concave upward in this region so that the low-dose linearity assumption effectively constitutes an upper bound of the risk at low doses. Nonetheless, some believe that the assumption has substantial scientific support in current data and biologic theory (NRC 1994).

risks defined by the upper-bound risk estimate based on linear extrapolation and the lower limit, which may be as low as zero, be explicitly stated. [88] Unfortunately, summary documents prepared for decision makers and the public rarely indicate the range of risk estimates or uncertainty associated with the estimates resulting from the linearity assumption.[89]

The default mathematical extrapolation model used by regulatory agencies is the linearized multistage (LMS) model.[90] The LMS model was first proposed as a simplification of the multistage model in 1957. In attempting to explain carcinogenesis, the multistage model assumes that a single cell can generate a tumor only after it has undergone a certain—but unspecified—number of changes that are maintained after cell division.[91] A cell can be transformed into a premalignant cell following chemical exposure, and the resulting premalignant cell proliferates at a constant rate, giving rise to a mass of exponentially growing preneoplastic cells. A preneoplastic cell can, in turn, be changed into a cancerous cell, which may then ultimately develop into a cancerous tumor.[92] although the LMS model is a simplification of the multistage model; it is essentially a curve-fitting procedure in which the dose-response curve is constrained to be linear at low doses. Risk estimates derived using the LMS model are upper-bound estimates of the linear portion of the curve.

The LMS model has been criticized for several significant deficiencies: [93]

- The linear dose-response relationship is not derived from a biological theory of carcinogenesis.
- The LMS model does not consider agent-induced stimulation of cell proliferation.
- It is difficult to incorporate data other than cancer bioassay data into the LMS procedure.
- The LMS model provides only point risk estimates that have limited practical use.
- Only two distinct rate-limiting steps have been demonstrated in carcinogenesis.
- The LMS model does not explain hereditary tumors.

Defenders of the LMS model claim that if exposure to an external agent increases the rate of processes that were already occurring at the cellular level within the body, then

---

[88] (EPA 1986, 33998)

[89] (Nichols and Zeckhauser 1986, 64)

[90] (EPA 1986, 33997)

[91] (Brown 1987; Armitage and Doll 1957)

[92] (Charnley and Thorslund 1988)

[93] Combined and summarized from (Thorslund, Brown, and Charnley 1987; Moolgavkar 1986).

the observed carcinogenic response will be linear at low doses using almost any extrapolation model.[94]

X. Use of Upper-Bound, Point Exposure Estimates

Exposure assessment is the step in risk assessment where the amount of a substance that comes into contact, or may come into contact, with the population of concern is determined or estimated. Frequently, adequate and reliable exposure data are not available, so exposures must be estimated. As evidenced by the numerous *Red Book* science policy questions below, a considerable portion of the debate surrounding risk assessment centers on how to estimate exposures:

> *How should one deal with different temporal exposure patterns in the study population and in the population for which risk estimates are required? For example, should one assume that lifetime risk is only a function of total dose, irrespective of whether the dose was received in early childhood or in old age? Should recent doses be weighted less than earlier doses?*
>
> *How should dietary habits and other variation in lifestyle, hobbies, and other human activity patterns be taken into account?*
>
> *For exposure variables, should point estimates or a distribution be used?*
>
> *For exposure concentrations, should point estimates or a distribution be used?*
>
> *How should one extrapolate exposures measurements from a small segment of a population to the entire population?*
>
> *How should exposures of special risk groups, such as pregnant women and young children, be estimated?*
>
> *What are the statistical uncertainties in estimating the extent of health effects? How are these uncertainties to be computed and presented?*
>
> *What are the biologic uncertainties in estimating the extent of health effects? What is their origin? How will they be estimated? What effect do they have on quantitative estimates? How will the uncertainties be described to agency decision-makers?*
>
> *Which dose-response assessments and exposure assessments should be used?*
>
> *Which population groups should be the primary targets for protection, and which provide the most meaningful expression of the health risk?*

[94] (Crump, Allen, and Shipp 1989)

> *How should one predict the dispersion of air pollutants into the atmosphere due to convection, wind currents, etc., or predict seepage rates of toxic chemicals into soils and groundwater?*

Considering the range of questions that must be answered when performing an exposure assessment, a general science policy decision is required:

- **Science policy issue.** If data on human exposure are unavailable for a particular substance or site, how can exposures be estimated for purposes of quantitative risk assessment?
- **Default science policy decision.** Chosen values for exposure variables are upper-bound point estimates which, when taken together, result in realistic upper-bound exposure estimates.

Exposure assessment is routinely the most resource-demanding phase of a complete risk assessment. Because much of the exposure assessment process relies on modeling and estimation techniques to overcome data gaps, exposure assessments are widely regarded as the "weakest link" in risk assessment. [95] Because of the tremendous variety in potential combinations of exposure variables and mathematical models, EPA has developed guidelines and default assumptions for exposure variables and exposure assessment methodology to promote consistency and comparability among exposure assessments.[96]

In addition to being concerned with the choice of values for individual exposure variables, this science policy issue concerns the general guiding principles used in directing risk assessors on what values to assume for exposure variables (i.e., who is exposed at what level, and who requires protection?). For example:

- When setting permit standards for a facility's air emissions, EPA generally performs a risk assessment for the hypothetical maximally exposed individual (MEI). The MEI is postulated to remain at the facility fenceline, downwind from the facility, twenty-four hours a day for seventy years. Although the MEI is not believed to exist, permits and regulations are nevertheless set as if the MEI were real. More likely estimates of exposures are rarely calculated and are considered even less often.[97] The MEI methodology has been shown to estimate the 99.99th percentile exposure of the most exposed person. [98] In other words, there is only a 0.01 percent chance that the maximally exposed individual's exposure is greater than that estimated using the MEI assumptions.

---

[95] **(OSTP 1985)**

[96] *See* (EPA 1992d; EPA 1992e; EPA 1991; EPA 1989).

[97] For more detailed discussion, see (NRC 1994, 3-3-3-4).

[98] (Hawkins 1991, 115)

- In the Superfund program, EPA guidance calls for a combination of exposure variables taken at average, 90th, and 95th percentile levels.[99] EPA states that these values, when combined in exposure estimates, will yield a reasonable maximum exposure (RME) estimate that is defined by EPA to be at about the 95th percentile level of exposure. However, simple statistics indicate that a combination of several upper-bound estimates does not result in an estimate of exposure at the 95th percentile. For example, combining three values at their 95th percentile results in a value that is at the 99.8th percentile.[100] Furthermore, the exposure values often specified by regulatory agencies for use in risk assessment often lie well beyond the 95th percentile value obtained from the best available data.[101] Clearly, the EPA approach to estimating an RME overestimates its intended 95th percentile exposures.[102]
- In the Superfund program, EPA guidance for estimating contaminant exposure concentrations calls for use of the upper 95th percentile confidence limit on the arithmetic average concentration. The average concentration is used because:[103]
  - Carcinogenic potency factors and noncarcinogenic reference doses are based on lifetime average exposures.
  - The average concentration is most representative of the concentration that would be contacted at a site over time.

  The upper confidence limit (UCL) on the mean is used because limited data may not accurately reflect the contaminant concentrations at a site. However, since environmental data are often log-normally distributed, this UCL often exceeds the maximum value, in which case EPA suggests using maximum contaminant concentrations. Use of maximum concentrations in such cases may be unreasonable and is not likely to be representative of potential exposures at a site. EPA, however, justifies this requirement on the basis that an estimated 95th percentile UCL on the mean that is greater than the highest detected concentration implies that the true mean may actually be greater than the highest detected concentration.104 This argument rests solely on the idea that limited sampling is unlikely to detect the full range of contaminant concentrations at a site.

---

[99] (EPA 1989)

[100] (Harris and Burmaster 1992)

[101] (Finley and Paustenbach 1994)

[102] For example, it has been calculated that the RME approach overestimates the true 95th percentile exposure by factors ranging from 10 to more than 1,000, depending on the sample size and the geometric standard deviation of the data. Further, fully 60 percent of EPA-derived RME estimates overestimate the 95th percentile exposure by more than one order of magnitude (Donahoe, Foster, and Chrostowski 1990).

[103] (EPA 1992e)

[104] (EPA 1992f)

A major criticism of the point-estimate approach is that the practice of using only upper-bound estimates for exposure variables disregards a tremendous amount of information and results in a single estimate of exposure and risk that conveys a false sense of precision.[105] Further disadvantages of single-point exposure and risk assessments are that uncertainty and variability are not readily quantified, and an indication of the range of possible exposures and risks is not available. Uncertainty analysis has lately come to be viewed as an essential and necessaiy component of meaningful risk assessments.[106] The shortcomings of the traditional point estimate approach are becoming more widely acknowledged:

> *Single-value risk estimates ...do not provide an indication of the degree of uncertainty associated with the estimate ... [and] do not convey the conservative nature of some risk estimates.*[107]

Six potential pitfalls of exposure assessment, as currently practiced, have been identified: [108]

1. Emphasis on the MEI is misplaced, and results of such analyses are prone to misinterpretation and misrepresentation.
2. The repeated use of conservative default assumptions results in exposure estimates that overstate likely exposures.
3. Inaccurate exposure estimates may result from improper use and statistical evaluation of environmental data.
4. Environmental fate and transport of chemicals are often not considered in exposure assessments.
5. Exposure assumptions and model estimates are often not validated using real data.
6. Indirect pathways of exposure are often not included in exposure assessments.

Clearly, based on these potential pitfalls, the practice of exposure assessment is much in need of improvement. Documents such as EPA's 1992 Guidelines for Exposure Assessment, [109]will usher in a new era of exposure assessment that may move toward more reasonable and accurate exposure characterization.

---

[105] (Hembra 1993)

[106] (NRC 1994; Carnegie Commission 1993)

[107] (Carnegie Commission 1993, 87)

[108] (Keenan, Finley, and Price 1994)

[109] (EPA 1992d)

Conclusions

Science policy decisions are made to bridge gaps in data and scientific knowledge. Default assumptions are made:

- When there is no or insufficient scientific basis to distinguish among plausible alternatives; and
- To standardize and facilitate regulatory risk assessment.

Default assumptions are perceived—and criticized—by some as being conservative. There are others who criticize them for insufficient protectiveness. The selection of default assumptions generally is driven by the policy decision to avoid underestimating potential risks. Given the frequent use of quantitative risk assessment in health and environmental regulation, for any individual science policy issue, use of a default assumption may be the most practical option for getting the work done. Departures from default assumptions have been rare in the past, but alternative assumptions have been adopted in limited cases. Attempts to depart from default assumptions in future risk assessments will invite increased scrutiny, which could cause regulators to shy away from consideration of alternatives.

Continued reliance on default assumptions can be problematic in two events:

- Multiple conservative science policy decisions, known as "compounded conservatism," may result in inconsistent or unduly biased decisions; and
- Whether or not compounded conservatism results, regulatory decision makers and the public are often unaware of:
  - The gaps and uncertainties in scientific knowledge and data used in calculating a risk assessment;
  - The policy-based default assumptions that are used to bridge these gaps and uncertainties; and
  - The extent to which default assumptions may determine the outcome of the risk assessment.

This chapter has discussed ten major default assumptions individually and has not addressed the impact of several defaults in the aggregate. To illustrate the potential impact of compounded conservatism, consider the following example. [110] In a risk assessment for tetrachloroethylene (PCE), the cumulative impact of three science policy decisions was investigated. The three steps in estimating the risk associated with exposure to PCE were: (1) the form of the dose-response model (linear or nonlinear); (2) the scaling factor applied in extrapolation from animals to humans (surface area or body weight equivalence); and (3) the species used for extrapolation (mouse or rat, where mice were the more sensitive species). Risk estimates were made using the eight

[110] See (Nichols and Zeckhauser 1986, 64-65) citing (Campbell et al. 1982).

possible combinations of the three assumptions above. The high estimate was obtained using all default assumptions: a linear, surface-area-based extrapolation of the mouse data. The low estimate was obtained using alternatives to the default assumptions: a nonlinear, weight-based extrapolation of the rat data. The high estimate was 35,000 times greater than the low estimate.

The example above illustrates how multiple conservative assumptions can dramatically influence the risk assessment. Furthermore, in the example above, the high estimate was obtained when the typical default assumptions were used. Although current scientific knowledge cannot determine which set of assumptions is correct, the fact that such a wide range of estimates is possible provides fuel for critics of current risk assessment methodologies. To the degree that alternatives can be identified and justified, even though in many cases science alone will not be adequate to do so, the debate and controversy regarding default assumptions in risk assessment will continue.

From the discussion in this chapter, it is evident that science is unlikely ever to answer certain "trans-scientific" questions (*e.g.,* what is the shape of the dose-response curve at low doses? Do thresholds for carcinogens exist?). Therefore, policy-based default Assumptions will always be necessary in risk assessment. However, continued reliance on default assumptions in all cases represents an unacceptable stagnation of science. Recent research suggests that alternatives to the default assumptions are plausible, and the policy basis for the trans-scientific issues is being questioned. The next chapter discusses alternatives to default assumptions and provides examples of where they have been or might be used in regulatory risk assessments. The remaining hurdle is for EPA to specify a mechanism by which alternatives may be evaluated and subsequently incorporated in risk assessments if judged to be acceptable and appropriate.

REFERENCES

ALLEN, B.C., K.S. CRUMP, and A.M. SHIPP. 1988. Correlation between carcinogenic potency of chemicals in animals and humans. *Risk Analysis 8(4):531-544.*

ARMITAGE, P., and R. DOLL. 1957. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. *Br. J. Cancer 11:161-169*.

ASHBY, J., N.G. DOERRER, and F.G. FLAMM. 1990. A scheme for classifying carcinogens. *Regul. Toxicol. Pharmacol. 12:270—295.*

BROWN, C.C. 1987. Approaches to intraspecies dose extrapolation. Chapter 10 in R.G. Tardiff and J.V. Rodricks (eds.), Toxic Substances and Human Risk. New York: Plenum Press.

BUFFLER, P.A. 1989. The evaluation of negative epidemiologic studies: The importance of all available evidence in risk characterization. *Regul. Toxicol. Pharmacol. 9:34—43.*

CAMPBELL, G.L., D. COHAN, and D.W. NORTH. 1982. *The Application of Decision Analysis to Toxic Substances*: *Proposed Methodology and Two Case Studies*. Office of Pesticides and Toxic Substances, Environmental Protection Agency, Washington, D.C.

CARNEGIE COMMISSION ON SCIENCE, TECHNOLOGY and GOVERNMENT. 1993. *Risk and the Environment: Improving Regulatory Decision Making*. New York: Carnegie Corporation.

CARR, C.J., and A.C. KOLBYE, Jr., 1991. A critique of the use of the maximum tolerated dose in bioassay to assess cancer risks from chemicals. *Regul. Toxicol. Pharmacol. 14:78-87.*

CENTER FOR RISK ANALYSIS. 1991. OMB v. Agencies, Highlights of workshop discussion, comments of Dr. Gary Flamm. Boston, Mass.: Harvard School of Public Health.

CHARNLEY, G., and T.W. THORSLUND. 1988. Biologically-based models to predict cancer risk. Chapter 8 in C.C. Travis (ed.), *Carcinogen Risk Assessment.* New York: Plenum Press.

CRUMP, K.S., B.C. ALLEN, and A.M. SHIPP. 1989. Choice of dose measure for extrapolating carcinogenic risks from animals to humans: An empirical investigation of 23 chemicals. *Health Physics 57(Suppl. l):387-393.*

DONAHOE, S., S. FOSTER, and P. CHROSTOWSKI. 1990. Estimation of exposure and risk for superfund baseline risk assessments. Prepared for Waste Management, Inc. Clement International Corporation, Fairfax, Va.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994. Pesticides; Proposed rule revoking certain food additive regulations. *Fed. Reg. 59:33941.*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992a. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders.* Offices of Research and Development and Air and Radiation, Washington, D.C. EPA/600/6-90/006F.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992b. *Working Paper for Considering Draft Revisions to the U.S. EPA Guidelines for Cancer Risk (Review Draft)*. Office of Research and Development, Washington, D.C. EPA/600/AP-92/003.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992c. *Drinking Water Criteria document for Di(2-ethylhexyl)adipate (Final)*. Office of Water, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992d. Guidelines for exposure assessment (Notice*). Fed. Reg*. 57(104):22888-22938.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992e. Memorandum from F. Henry Habicht, Deputy Administrator, to Assistant Administrators and Regional Administrators: *Guidance on Risk Characterization for Risk Managers and Risk Assessors (February 26, 1992).*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992f. *Supplemental Guidance to RAGS: Calculating the Concentration Term. Office of Solid Waste and Emergency Response, Washington, D.C. (OSWER Directive 9285.7-08, PB92-963373).*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991. *Human Health Evaluation Manual, Supplemental Guidance: Standard Default Exposure Factors. Office of Solid Waste and Emergency Response, Washington, D.C. (OSWER Directive 9285.6-03).*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1990*. Health Assessment Document for Diesel Emissions. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-90/057a.*

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1989. *Risk Assessment Guidance for Superfund: Volume I—Human Health Evaluation Manual (Part A) (Interim Final)*.Office of Emergency and Remedial Response, Washington, D.C. EPA/540/1-89/002.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1988. *Health Hazard Assessment of Nonasbestos Fibers. Washington*, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986. Guidelines for carcinogen risk assessment. *Fed. Reg*. 51(185):33992-34003.

FINLEY, B., and D. PAUSTENBACH. 1994. The benefits of probabilistic exposure assessment: Three case studies involving contaminated air, water, and soil. Risk Analysis 14(1):53—73.

FISHBEIN, L. 1980. Overview of some aspects of quantitative risk assessment. *J. Toxicol. Environ. Health 6:1275-1296.*

FOOD AND DRUG ADMINISTRATION (FDA), Advisory Committee on Protocols for Safety Evaluation. 1971. Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides. *Toxicol. Appl. Pharmacol*. 20:419-438.

GAYLOR, D.W. 1987. Statistical interpretation of toxicity data. Chapter 5 in R.G. Tardiff and J.V. Rodricks (eds.), *Toxic Substances and Human Risk.* New York: Plenum Press.

GRAHAM, J.D., and D.W. DOCKERY. 1994. Rethinking particle pollution and the Clean Air *Act. Risk in Perspective 2(2): 1-2.*

HARRIS, R.H., and D.E. BURMASTER. 1992. Restoring science to superfund risk assessment. *Toxics Law Reporter (March 25, 1992): 1318-1323.*

HAWKINS, N.C. 1991. Conservatism in maximally exposed individual (MEI) predictive exposure assessments: A first-cut analysis. *Regul. Toxicol. Pharmacol.* 14:107-117.

HEMBRA, R.L. 1993. Statement before the Senate Subcommittee on Superfund, Recycling, and Solid Waste Management (9/30/93). General Accounting Office, Washington, D.C.

ICI CHEMICALS AND POLYMERS, LTD. 1994. EPA Docket Control #OPPTS-400082. Washington, D.C. (April 1994).

INTEGRATED RISK INFORMATION SYSTEM (IRIS). 1994. Chemical Profile: Di(2-ethylhexyl)adipate. Environmental Criteria and Assessment Office, Environmental Protection Agency, Cincinnati, Ohio.

INTERAGENCY REGULATORY LIAISON GROUP (IRLG) Work Group on Risk Assessment. 1979. Scientific bases for identification of potential carcinogens and estimation of risks. J. Natl. Cancer Inst. 63:241-268.

KEENAN, R.E., B.L. FINLEY, and P.S. PRICE. 1994. Exposure assessment: Then, now, and quantum leaps in the future. Risk Analysis 14(3):225-230.

KEENAN, R.E., D.J. PAUSTENBACH, R.J. WENNING, and A.H. PARSONS. 1991. Pathology re-evaluation of the Kociba et al. (1978) bioassay of 2,3,7,8-TCDD: Implications for risk

assessment. J. Toxicol. Environ. Health 34:279-296.

LAVE, L.B., F.K. ENNEVER, H.S. ROSENKRANZ, and G.S. OMENN. 1988. Information value of the rodent bioassay. Nature 336:631-633.

MARONPOT, R.R., C.A. MONTGOMERY, Jr, G.A. BOORMAN, and E.E. McCONNELL. 1986. National Toxicology Program nomenclature for hepatoproliferative lesion of rat. Toxicol. Pathol. 14(2):263-273.

McGARITY, T.O. 1979. Substantive and procedural discretion in administrative resolution of science policy questions: Regulating carcinogens in EPA and OSHA. Georgetown Law J.

67:729-809.

MOHR, U., et al. 1984. Morphological aspects of mesotheliomas after intratracheal instillations of fibrous dusts in Syrian golden hamsters. Exp. Path. 26:179-83.

MOOLGAVKAR, S.H. 1986. Carcinogenesis modeling: From molecular biology to epidemiology. Ann. Rev. Pub. Health 7:151—169.

NATIONAL INSTITUTE FOR ENVIRONMENTAL HEALTH SCIENCES (NIEHS). 1993. Compendium of abstracts from long-term cancer studies reported by the National Toxicology Program from 1976 to 1992. Environ. Health Persp. 101(Suppl. 1).

NATIONAL RESEARCH COUNCIL (NRC), Committee on Risk Assessment of Hazardous Air Pollutants. 1994. Science and Judgment in Risk Assessment. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on Risk Assessment Management (CRAM). 1993. Use of the maximum tolerated dose in animal bioassay for carcinogenicity. In Issues in Risk Assessment. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on the Biological Effects of Ionizing Radiations. 1990. Health Effects of Exposure to Low Levels of Ionizing Radiation. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on the Institutional Means for Assessment of Risks to Public Health. 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Safe Drinking Water Committee. 1977. Drinking Water and Health. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Environmental Studies Board. 1975. Carcinogenesis in man and laboratory animals. In Pest Control: An Assessment of Present and Alternative

Technologies, Volume I, Contemporary Pest Control Practices and Prospects. Washington, D.C.: National Academy Press.

NATIONAL TOXICOLOGY PROGRAM (NTP), Board of Scientific Counselors. 1992. National Toxicology Program (NTP), Final report of the Advisory Review by the NTP Board of Scientific Counselors (Request for comments). 57 FR 31721.

NICHOLS, A.L., and R.J. ZECKHAUSER. 1986. The dangers of caution: Conservatism in

assessment and the mismanagement of risk. Advances in Applied Micro-Economics 4:55-82.

NORTH AMERICAN INSULATION MANUFACTURERS ASSOCIATION (NAIMA). 1994. Comments on EPA's proposed addition of Glass, Rock, and Slag Wool Fibers to the Toxics Release Inventory. U.S. Environmental Protection Agency Docket No. OPPTS-400082. Washington, D.C.

OFFICE OF MANAGEMENT AND BUDGET (OMB). 1990. Regulatory Program of the United States Government (April 1, 1990-March 31, 1991). Executive Office of the President, Washington D.C.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP). 1985. Chemical carcinogens: Review of the science and its associated principles. Fed. Reg. 50:10372-10442.

OTTOBONI, M.A. 1991. The Dose Makes the Poison—A Plain-Language Guide to Toxicology (Second edition). New York: Van Nostrand Reinhold.

PURCHASE, I.F.H. 1993. Thresholds are deceptive—Let's be honest! AIHC Journal 1(3): 12-13, 16.

RODRICKS, J.V. 1992. Calculated Risks—The Toxicity and Human Health Risks of Chemicals in Our Environment. Cambridge, England: Cambridge University Press.

ROSENTHAL, A., G.M. GRAY, and J.D. GRAHAM. 1992. Legislating acceptable cancer risk from exposure to toxic chemicals. Ecology Law Quarterly 19:269-362.

SAFFIOTTI, U. 1980. The problem of extrapolating from observed carcinogenic effects to estimates of risk for exposed populations. J. Toxicol. Environ. Health 6:1309-1326.

SHARRATT, M. 1988. Assessing risks from data on other exposure routes—Possibilities and limitations of using toxicity data derived from one exposure route in assessing risks from other exposure routes. Regul. Toxicol. Pharmacol. 8:399-407.

STEINBERG, A.D., and J.M. DeSESSO. 1993. Have animal data been used inappropriately to estimate risks to humans from environmental trichloroethylene? Regul. Toxicol. Pharmacol. 18:137-153.

THORSLUND, T.W., C.C. BROWN, and G. CHARNLEY. 1987. Biologically motivated cancer risk models. Risk Analysis 7(1): 109-119.

UPTON, A.C. 1988. Are there thresholds for carcinogenesis? The thorny problem of low-level exposure. Annals N.Y. Acad. Sci. 534:863-884.

VOCCI, F., and T. FARBER. 1988. Extrapolation of animal toxicity data to man. Regul. Toxicol. Pharmacol. 8:389-398.

WAGNER, J.C., et al. 1984. Animal experiments with MMM(V)F effects of inhalation and intrapleural inoculation in rats. In Biological Effects of Man-Made Mineral Fibers, Vol. 2. Proceedings of a WHO/IARC Conference, Copenhagen, Denmark.

WILKINSON, C.F. 1987. Being more realistic about chemical carcinogenesis. Environ. Sci. Technol. 21(9):843-847.

WHYSNER, J. 1993. Mechanism-based cancer risk assessment of butylated hydroxyanisole. In G.M. Williams (ed.), Antioxidants Chemical, Physiological, Nutritional and Toxicological Aspects. Princeton, N.J.: Princeton Scientific Publishing Company, 283-293.

4
ALTERNATIVE ASSUMPTIONS TO THE BASIC SCIENCE POLICY ISSUES

The basic science policy issues and default assumptions in quantitative risk assessment were introduced in Chapter 3. This chapter examines alternatives to the default assumptions. It offers perspective on the suitability, scientific credibility, and practicality of the defaults and potential alternatives for quantitative risk assessment. Most of the discussions rely on specific examples taken from the published literature. The chapter does not discuss possible alternatives comprehensively or exhaustively, nor does it portray specific alternatives as superior or inferior to the default assumptions. Inclusion of an alternative in this chapter is not meant to imply that that alternative is or ever could be feasible in all circumstances.

I. Use of Animal Data to Predict Human Risk

As discussed in Chapter 3, data indicating that a chemical is carcinogenic in animals are assumed to be predictive of potential carcinogenic activity in humans. This default assumption remains a key issue in risk assessment, but resolution is unlikely in the near future. The available animal data are evaluated to determine the likelihood that the substance of concern is a human carcinogen.[1] This issue continues to be controversial and difficult because of the practical limitations on the available alternatives. Viable alternatives to relying on the default assumption include the following:

- **Generate new human data.** Human data adequate for quantitative risk assessment are preferable to animal bioassay data for use in human quantitative risk assessment. However, the generation of new human data may not be practical because:

5. ►► Human studies involve legal and ethical considerations.
6. ►► Human populations suitable for study may not be readily available.
7. ►► Human studies may take too long to complete because of the long latency period for most cancers.

- **Determine suitability of extrapolation on a case-by-case basis.** It may be worthwhile in some cases to conduct research into mechanisms of

[1] The Environmental Protection Agency (EPA) uses the Guidelines for Cancer Risk Assessment in making these determinations. See (EPA 1986a).

carcinogenicity and/or toxicity in order to determine the suitability of the default assumption. In those cases where research indicates that responses in animals are not predictive of potential responses in humans, animal to human extrapolation would not be used to develop quantitative risk estimates. [2] Use of this alternative may be limited by the constraints on time and resources available for research.

- **Forgo quantitative risk assessment**. In some circumstances, it may be better to provide decision makers and the public with a qualitative description of risk rather than a quantitative estimate. A qualitative risk assessment would be especially useful when the available data suggest increased risks but are insufficient for quantitative risk assessment. A qualitative risk assessment provides an indication of the circumstances under which increased risks are anticipated, but does not establish a numerical estimate of risk. Although much environmental regulation is justified on the basis of numerical risk estimates, no regulatory agency is currently compelled by law to conduct a quantitative risk assessment.[3]

Because of the practical limitations on generating new human data and forgoing quantitative risk assessment, departure from this default assumption likely will depend on case-by-case research.

II. Combining Benign and Malignant Tumors

In estimating potential carcinogenic risks to humans, the incidence of benign and malignant tumors is generally combined. This practice is based on the default assumption that benign tumors can progress to malignancy and are therefore indicative of potential cancer risks. Alternatives to combining benign and malignant tumors include:

- **Combine only when scientifically defensible**. The Principles of Carcinogen Risk Assessment published by the Office of Science and Technology Policy (OSTP) in 1985 indicate that benign and malignant tumors should be combined only when the observed benign tumors are believed to progress to the observed malignant tumors.[4] Under Environmental Protection Agency (EPA) guidelines, however, combining benign and malignant tumors is always considered to be "scientifically defensible" unless it can be shown that the combination is not biologically justified.[5] Thus, the OSTP and EPA approaches differ in the burden of proof.

---

[2] See Chapter 7, "Unleaded Gasoline."

[3] See Chapter 2, n. 9, 23.

[4] (OSTP 1985)

[5] (EPA 1986a, 33994)

- **Conduct research on a case-by-case basis.** Distinguishing which benign tumors are likely to progress to malignant tumors can be attempted on a case- by-case basis.[6] However, such research: (1) is likely to be expensive and time-consuming, and may be limited in impact to the specific substance studied; (2) will be worthwhile in a limited number of cases where the potential costs of regulation justify such expenditures.
- **Present the results of quantitative risk assessment with and without inclusion of benign tumors.** This alternative would provide the decision maker and the public with a range of risk estimates. The uncertainty associated with combining and distinguishing benign and malignant tumors could then be factored into the risk assessment.

Given the resources and time generally required to conduct scientific research, the more practical alternative would be to present a range of risk estimates based on reasonable combinations of benign and malignant tumors. This practice is sometimes performed in regulatoiy risk assessment documents.

III. Relevance of Nonpositive Data

Because of the limited sensitivity of animal bioassays and epidemiologic studies, nonpositive data are not generally assumed to be indicative of safety. Weight-of-evidence carcinogenicity classifications are made on the basis of the positive data alone. Nonpositive data may be considered relevant only when the nonpositive data clearly outweigh the positive data.[7] Once considered in the weight-of-evidence determination, however, nonpositive data are disregarded and are not generally used in quantitative risk assessment. Alternatives to not incorporating nonpositive data in quantitative risk assessment include:

- **Implement criteria for adequacy of nonpositive data.** Although no amount of nonpositive data will constitute evidence of safety with absolute certainty, there are probably some amount and quality of nonpositive data which would be sufficient to establish a significant likelihood of safety. Criteria for establishing the requisite amount and quality of nonpositive data could be developed and implemented. For example, the National Research Council (NRC) suggested that:

  > *Compounds found to be negative in a standard set (two species and both sexes) of bioassays conducted at the MTD can be designated as noncarcinogens with a relatively high degree of confidence.8*

[6] See examples discussed in Section II of Chapter 3.

[7] (EPA 1986a, 33995)

[8] (National Research Council (NRC) 1993a)

The Carnegie Commission has recommended that all regulatory agencies develop inventories of risk information pertinent to each agency's mission. These inventories should include both positive and nonpositive data. However, the commission noted that "Journals—and investigators—sometimes reject negative findings as uninteresting. As a result, reliable evidence that suggests that a substance does not cause a hazard often may be unpublished and otherwise unavailable."[9] Citing agency needs to reflect statutory preferences and other mission-specific concerns, the commission deferred to agency risk managers the task of defining an algorithm for how nonpositive information should be used.

- **Use nonpositive data to establish a "ceiling" of risk**. While nonpositive data cannot be used to establish safety with absolute certainty, they may be used to set upper limits on the risk that could have been detected.[10] EPA suggests that nonpositive epidemiologic studies be used to define upper limits of possible risks, [11] which may then be compared to risks estimated from animal data. Examples of where this approach has been applied include the *Health Assessment Document* for **trichloroethylene** [12] and a risk assessment for **benzene** in the Netherlands. [13]
- **Include all data in quantitative risk assessment.** Implementation of this alternative could be difficult and is open to criticism. For example, consider the hypothetical animal bioassay results and the associated risks extrapolated to humans in Table 4•1.

---

[9] (Carnegie Commission 1993, 85)

[10] (Interagency Regulatory Liaison Group 1979)

[11] (EPA 1986a, 33996)

[12] EPA's Carcinogen Assessment Group (CAG) uses nonpositive epidemiologic studies to derive upper-limit risk estimates as a check against the estimates derived from positive animal studies. In the case of trichloroethylene (TCE), nonpositive epidemiologic data resulted in an upper limit risk estimate of 1.7x1 O'5 associated with lifetime inhalation of 1 pg/m3 of TCE. The risk estimate obtained using positive animal data was about ten times lower. Therefore, EPA concluded that there was not evidence that TCE is a less potent carcinogen in humans than in animals (EPA 1985, 8126-8-131).

[13] The approach taken for benzene by The Health Council of the Netherlands is an interesting example. Epidemiological studies of workers exposed to less than 10 ppm benzene have consistently failed to demonstrate an effect, whereas workers exposed to more than 200 ppm clearly demonstrate an increased risk of leukemia. From the positive findings at 200 ppm, an exposure of 0.65 pg/m3 was associated with a risk of 1 in 1 million (10‘6). Using the combined nonpositive studies, the upper limit of the relative risk was linearly extrapolated downward, resulting in an exposure level of 1.4 pg/m3 at a risk of 10'6. Thus, a conservative, upper-limit risk estimate based on nonpositive data is twice as high as the "best" estimate using positive data. For comparison, in the United States, a benzene exposure level of 0.1 μg/m^3 is associated with 10^{-6} risk (Swaen 1988).

Table 4-1. Hypothetical Animal Bioassay Results and Extrapolation to Human Risk [14]

Test Group	Tumor Incidence	Human Risk*
Male Mice	50/100	$Lx10^{-3}$
Female Mice	10/100	$2x10^{-4}$
Male Rats	5/100	$Lx10^{-4}$
Female Rats	1/100 (not significant)	0

*Assumes linear extrapolation to human exposures 500 times lower than bioassay exposures.

> Following current EPA policy,[15] the human risk estimate would be based on the observed response in male mice (the most sensitive test group) and reported as a plausible upper-bound risk estimate of 1.16x1 $O^{-3.16}$ Using the most sensitive test group for extrapolation to humans provides a 25 percent chance of being "correct" and a 75 percent chance of being "conservative." Incorporating all of the positive and nonpositive data by averaging the results from all four sex/species combinations produces a risk estimate of 3.3x1 O^{-4}. However, this average risk estimate has no scientific basis and little chance of being correct, but is less conservative.[17]

Averaging risk estimates is a mathematical exercise and is without scientific basis.[18] Despite the criticisms cited above, EPA sometimes uses arithmetic or geometric means of several risk estimates derived from separate sex/species data sets.[19] However, EPA does not generally use nonpositive studies in computing these average risk estimates. Other approaches, such as pooling results from several individual studies, are typically

[14] Adapted from (Finkel 1994). Note that other science policy issues, such as the relevance of animal data to predicting potential human risks and linear extrapolation, are also involved in this hypothetical example.

[15] (EPA 1986, 33997)

[16] Assuming a normal distribution of potencies in mice, the range of risk estimates would be a bell-shaped curve with a mean of lxlO'3, a lower-bound of 8.4x1 O'4, and an upper-bound of $1.16xl0^{-3.}$

[17] (Finkel 1994)

[18] For purposes of this chapter and unless otherwise noted, the term "average" is generic in nature and represents some measure of central tendency such as a weighted average, arithmetic mean, or geometric mean.

[19] see, for example, Integrated Risk Information System (IRIS) Chemical Profiles for **carbon tetrachloride, dichlorvos, methylene chloride, and DDT.**

limited to positive studies, but may reduce the uncertainty associated with extrapolating from only one data set.[20]

IV. Use of Maximum Tolerated Doses in Animal Studies

Use of maximum tolerated doses (MTDs) in animal bioassays has been criticized for many reasons. The most frequent criticism is that carcinogenic effects observed at the MTD are at least as likely to be a response to the magnitude of the test dose rather than an indication of the substance's inherent carcinogenicity. Nevertheless, use of MTD testing remains an accepted procedure in regulatory risk assessments. The following alternatives to MTD testing—and the attendant default assumption that data from such testing are predictive of human risk—were presented by the National Research Council (NRC):[21]

- **Redesign the bioassay.** Bioassay doses could be determined as follows:
  - When human exposures are within one or two orders of magnitude of the animal MTD, use the MTD in the bioassay; and
  - when human exposures are more than one or two orders of magnitude lower than the animal MTD, use a fraction of the MTD (e.gMTD/3) as the highest dose and additional doses spaced geometrically down from the high dose.

This alternative incorporates information on expected exposures into animal bioassays, but could result in reduced bioassay sensitivity at lower doses.

- **Base the highest dose tested on preliminary mechanistic studies.** Before initiating a bioassay, preliminary studies could be conducted to obtain mechanistic and dose-response information. This information would then be evaluated to assist in the determination of the highest dose to be tested. This approach would replace the MTD with the minimally toxic dose (minTD) or the highest subtoxic dose (HSTD).[22] This approach would be expected to produce carcinogenic responses in animals that are more qualitatively and quantitatively similar to expected low-dose responses in humans than would MTD testing. However, bioassay sensitivity would likely be reduced.
- **Develop a systematic program for identifying human carcinogens which involves, but does not necessarily depend upon, the results of MTD testing.** In such a program, MTD testing would be conducted after an indication that a substance merits examination. The MTD bioassay would be

[20] See (Velazquez et al. 1994).

[21] See (NRC 1993a).

[22] The minTD or HSTD should not result in shortened lifespans, weight loss, or demonstrable organ or tissue toxicity, which usually indicates disruption of cell and tissue function and structure (Carr and Kolbye 1991, 80).

followed by tests to determine the mechanism of carcinogenicity and pharmacokinetic parameters. This information would be used to determine if the observed response in animals at the MTD is the result of inherent toxicity or a response to the magnitude of the dose. Although this alternative could provide improved information for quantitative risk assessment, it may be impractical to test many substances. However, the National Institute of Environmental Health Sciences (NIEHS) has begun just such a research effort.[23]

The alternatives above may be criticized because elimination of the MTD would decrease the probability of observing a carcinogenic response in any reasonably sized bioassay. However, if gross toxic effects occurring only at the MTD are responsible for the observed carcinogenicity in a bioassay, then it is doubtful that the observed response has any real meaning to potential human risks. Resolution of the issue of MTD testing will require balance as scientists try simultaneously to reduce spurious observations of cancer and maintain sufficient sensitivity to detect actual carcinogenic responses.

V. Relative Sensitivity of Humans and Animals

When faced with a choice of animal data to use for human cancer risk assessment, risk assessors generally choose the data set from the sex and species showing the most dramatic response. Alternatives to using this default assumption include:

- **Use the most relevant animal species**. EPA guidelines call for use of data from the animal species that responds most like humans, but it is generally not possible to make this determination.[24] it could be argued, however, that larger mammals would be expected to respond more like humans. For example, where bioassays of adequate quality of rats and dogs are available, uncertainty in the extrapolation could be reduced by selecting the dog bioassay for extrapolation if dogs are determined to be physiologically more similar to humans than rats. Due to expense and animal rights concerns, however, data from larger species are likely to remain scarce.
- **Combine bioassays of different species**. Where it is not possible to determine which species most closely resemble humans, it may be appropriate to combine or pool the bioassay data from various species and strains. One type of pooling, known as "meta-analysis," will tend to average the results of the bioassays on a weighted basis. However, there would be no scientific validity to the pooling itself. Human response is not likely to be truly reflected by a combination of rat, mouse, and dog responses. Additionally, combining different bioassays may introduce new uncertainties

[23] National Institute of Environmental Health Sciences (NIEHS) 1994)

[24] (EPA 1986a, 33997)

into the extrapolation as adjustments for differences among species are made before pooling the data.

The alternatives above may not be practical for cancer risk assessment because studies using higher-order mammals are likely to be prohibitively expensive.

VI. Relevance of Differences Between Humans and Animals

Differences between animals and humans in absorption, distribution, metabolism, and elimination (ADME) of substances and in mechanisms of carcinogenesis are rarely well understood. Therefore, such differences are rarely incorporated in risk assessments. Recently, however, advances in science have resulted in improved understanding of ADME and possible mechanisms of carcinogenesis. Potential alternatives to the default assumption that are based on these recent scientific advances include:

- **Develop mechanistic data**. According to the National Toxicology Program's (NTP) Board of Scientific Counselors, rational risk assessment requires "mechanism-of-action-oriented research." The NTP board found that the NTP:

  > *... places too much emphasis on testing per se, and not enough emphasis on providing the mechanistic insight required for a realistic interpretation of the significance of the testing results with regard to human health.... Studies directed towards discerning the mechanism(s) of action of the chemical of interest need to be incorporated into, and juxtaposed with, the bioassay in order to place its results in proper perspective.*[25]

Because bioassays are not generally designed for or suited to developing mechanistic or pharmacokinetic data, such data can only be developed through additional studies.[26] The NTP board, as well as the NRC, suggested that mechanism and pharmacokinetic studies be conducted prior to bioassays. Mechanistic information has been used in the past to show that several compounds which cause certain kidney tumors only in male rats do not pose a cancer risk to humans.[27]

- **Develop physiologically based pharmacokinetic models.** The incorporation of data from ADME studies into physiologically based pharmacokinetic (PBPK) models represents a tremendous opportunity to improve the interpretation of animal bioassays. PBPK models, which are a series of inter-related mathematical equations that describe tissues in the body, air and blood flows through them, and rates of processes occurring in

[25] (National Toxicology Program [NTP] 1992)

[26] For example, mitotic division rates are not determined during bioassays, but this information is very useful in characterizing the capacity of a chemical to promote tumors (Wilson 1989). See also discussion of the two-stage model of carcinogenesis in Section IX below.

[27] *See* Chapter 7, "Unleaded Gasoline."

them, can provide a physiological basis for extrapolating exposures and risks between species and across routes of exposure. The primary parameters required for a PBPK model are the size of tissues and tissue groups, air and blood flows, partition coefficients, and metabolic constants. PBPK models can address such phenomena as repeated exposure, enzyme induction and inhibition, physiologic change with age, and various interactions.[28] PBPK models have been developed and applied to a variety of chemicals, including **trichloroethylene (TCE), tetrachloroethylene (PCE), and methylene chloride,** and have been used by EPA to reduce previous risk estimates for methylene chloride.[29] Unfortunately, the data necessary to estimate these parameters are not generally available for environmental contaminants because of the high cost of studies and relative shortage of experienced toxicologists.[30]

- **Use biologically based dose-response models**. A biologically based dose-response model for cancer is derived from a direct understanding of the biological processes underlying carcinogenesis. Producing the most accurate risk estimates:

  ... is only possible with biologically-based models that will explicitly allow the incorporation of the wealth of data that is becoming available from studies on the biochemistry and molecular biology of carcinogenesis.[31]

The scientific bases underlying biologically based dose-response models for carcinogenesis are discussed in Section IX below.

- Use scaling factors. Scaling factors are routinely used to convert the doses used in animal bioassays to "equivalent" doses in humans that are expected to produce the same response. Three scaling factor approaches have been developed and used: 32
  - **Body mass equivalence (BME)** assumes that an equivalent dose per unit of body weight (e.g., five milligrams per kilogram of body weight) will have the same effect in all species.
  - **Equal proportions assumes** that chemicals in equal proportions (e.g., five parts per million in food or air) will have similar effects in all species.

[28] (Watanabe, Schumann and Reitz 1988)

[29] See discussion in Section IX.

[30] (Sharratt 1988)

[31] (Frederick and Wilson 1991)

[32] (Vocci and Farber 1988)

- **Body surface area equivalence (SAE)** assumes that the equivalent dose per square meter of body surface area (e.g, five milligrams per square meter) will produce the same effects in all species.

Equivalent doses and risks can vary by a factor of up to thirty-five depending on the scaling factor used.[33] Compared to risk estimates obtained using SAE scaling, extrapolation on the basis of BME reduces estimated risks to humans by a factor of six when using rat data and fourteen when using mouse data.[34] SAE scaling, which gives the most conservative results, is favored by EPA.

EPA, the Food and Drug Administration (FDA), and the Consumer Product Safety Commission (CPSC) have been discussing adoption of a common scaling factor.[35] EPA and CPSC favor SAE scaling, [36]but FDA favors BME. BME and SAE scaling factors can be expressed as a ratio of milligrams of chemical to kilograms of body weight (mg/kg) raised to some exponent. The exponent is 1 for BME [$(mg/kg)^1$] and 2/3 for SAE [$(mg/kg)^{2/3}$]. Based on a best fit of experimental scientific data, a middle approach using an exponent of 3/4 [$(mg/kg)^{3/4}$] was proposed in 1992 for use by all three agencies, but has not yet been formally adopted.

With the exception of scaling factors, which are used routinely, the alternatives above are likely to be impractical in many cases. Expenditures for developing mechanistic and pharmacokinetic data are likely to be high and will be undertaken only when sufficient justification exists. Further, models must be developed and their results must then be accepted by the scientific community, which occurs only over time. However, current research indicates that advances in our understanding of the mechanisms of carcinogenesis are possible. Incorporation of these advances in regulatory risk assessments will encourage further work in this area, which could ultimately revolutionize our understanding of cancer and carcinogenesis.

VII. Extrapolation Across Routes of Exposure

Frequently, data from an animal bioassay using the route of administration or exposure that is of interest for humans are not available. The default assumption of route-to-route extrapolation is made because animal bioassays cannot always be designed to mimic human routes of exposure.[37] Alternatives to the default assumption include:

---

[33] (NRC 1983)

[34] (Office of Science and Technology Policy [OSTP] 1985)

[35] (EPA 1992a)

[36] EPA uses BME scaling for noncarcinogens and SAE scaling for carcinogens. This apparent discrepancy may be explained by the use of an uncertainty factor of ten in all noncarcinogenic risk assessments to extrapolate exposures from animals to humans.

[37] For example, because laboratory animals are reluctant to inhale cigarette smoke, the data concerning carcinogenicity of cigarette smoke have been collected from animal bioassays involving intrapulmonary implants and skin-painting of cigarette smoke condensate (EPA 1992b).

- **Perform studies employing the relevant route of exposure**. If time and resources are available, new studies employing the relevant route of exposure can be performed. Route-specific information has been used in risk assessments in the past. Examples include:[38]
  - **Asbestos.** Inhalation risk estimates are based on studies of workers exposed to asbestos via inhalation, while ingestion risk estimates are based on rat bioassays where the rats were administered asbestos in drinking water by gavage.
  - **Arsenic.** Inhalation risk estimates are derived from studies of smelter worker populations, while ingestion risk estimates are based on studies of human populations consuming drinking water with high arsenic concentrations. Animal bioassays concerning the carcinogenicity of arsenic are inconsistent and inconclusive.
- Develop PBPK models. PBPK models 39can provide a physiological basis for extrapolating from one route of exposure to another. Unfortunately, the data necessary to estimate these parameters are not generally available for Environmental contaminants because of the high cost of the necessary studies and relative shortage of experienced toxicologists.[40]

The ability to extrapolate toxicity from the route of administration in animal bioassays to the routes of interest in humans likely will vary from substance to substance. Thus, a regulatory agency should carefully evaluate available data to determine whether route-to-route extrapolation is likely to produce believable results before attempting the extrapolation.

VIII. Existence of Thresholds for Carcinogenicity

It is typically assumed that substances cause cancer through a nonthreshold mechanism. In other words, exposure to any amount of a substance, even one molecule, is associated with a small, but nonzero, increase in risk. Alternatives to employing this default assumption include:

- **Distinguish genotoxic from nongenotoxic carcinogens.** Genotoxic carcinogens are thought to act directly on the genetic material of a cell. Nongenotoxic carcinogens are thought to induce cancer through other mechanisms. Genotoxic and nongenotoxic carcinogens are generally regulated differently in Europe, where only genotoxic compounds are assumed to exert some carcinogenic effect at any dose, and nongenotoxic compounds are regulated according to a threshold model.

---

[38] From chemical profiles on the EPA Integrated Risk Information System (IRIS).

[39] See discussion in Section VI of this chapter.

[40] (Sharratt 1988)

A proposed classification scheme, which considers genotoxicity and the existence of cell proliferation upon exposure, predicts whether thresholds of carcinogenicity may exist. The following categories have been proposed: [41]

- **Genotoxic compounds**. Existence of a threshold is unlikely (**2-acety laminofluorene, diethylnitrosamine, and dimethylnitrosamine).**
- **Nongenotoxic compounds that induce cell proliferation through Interaction with a specific cell receptor**. Existence of a threshold is questionable **(phorbol Sters, dioxins, and hormones).**
- **Nongenotoxic compounds that induce cell proliferation through an indirect mechanism.**[42] Existence of a threshold is likely because carcinogenic response is usually related to toxicity and cell regeneration **(sodium saccharin, antioxidants, liver toxins**, and **kidney toxins)**.[43]

EPA attempted to distinguish genotoxic and nongenotoxic carcinogens in 1983. The proposed approach was to place nongenotoxic carcinogens in a lower regulatory risk category than genotoxic carcinogens. The proposal was greeted with such strong protest and dissent that it was dropped.[44] Nevertheless:

> *[t]he scientific facts in support of mechanistically distinct types of carcinogens have increased greatly over the last 10 years and the concept has steadily achieved acceptance, although some remain unconvinced. Yet, the alternative to differentiating carcinogens according to their intrinsic properties is to maintain the assumptions of 40 years ago that all carcinogens are basically alike. This assumption allows simplistic approaches to risk assessment, but does not accommodate current scientific knowledge, and also is a poor if not erroneous basis for public health protection and effective cancer prevention.45*

The tide is changing, however, and regulatory agencies are beginning to include current scientific thinking in their risk assessment methodologies.

- Distinguish threshold/nonthreshold suspect carcinogens on a case-by-case basis. Examples of work being done in the field of identifying thresholds for specific suspect carcinogens include:

---

41 (Cohen and Ellwein 1990)

42 Indirect mechanisms for inducing cell proliferation include a mitogenic stimulus, regeneration resulting from toxicity, and interruption of physiological processes.

43 "If a chemical is nonmutagenic and its carcinogenicity is due to cell proliferation that results from near-toxic doses, one might commonly expect a virtual threshold in the dose-response" (Ames and Gold 1990).

44 (Marshall 1983; Wilkinson 1987, 845)

45 (Williams and Weisburger 1992, 132)

- ❖ TCE. Based on review of epidemiologic studies, mechanism of carcinogenicity studies, etc., it has been suggested that a threshold model of carcinogenicity may be more appropriate for TCE.46
- ❖ Dioxin. Recognized as a suspect nongenotoxic carcinogen, 47acceptable daily intakes for dioxin are one to three orders of magnitude higher in Europe, where nonthreshold models are employed, than in the United States, where nonthreshold models are used.48
- ❖ Arsenic. Arsenic is thought to effect genes that control cell proliferation and differentiation, recombination, and other effects on DNA. It has been suggested that all arsenical diseases, including cancer, are governed by threshold mechanisms, and there exists a consensus that intakes of up to 400 pg/day of arsenic are safe.49

- ➢ **Use the same approach for noncarcinogens and carcinogens**. Consistent with toxicological principles, most noncarcinogens are thought to act on a threshold basis. These thresholds are established by identifying no observed adverse effect levels[50] (NOAELs) in an animal species. Uncertainty factors are then applied to the NOAEL to estimate a level of exposure in humans that is not anticipated to result in adverse effects. This approach could easily be applied to carcinogens which are thought to act on a threshold basis.

Because thresholds are likely to remain undetectable using current animal bioassay protocols, detailed research on biological mechanisms will be required to establish the existence of thresholds. Determining the existence of thresholds from human data has been judged to be virtually impossible because of individual variation and because humans experience so many confounding factors.[51] The identification of a threshold will likely rely not on the ability to find a dose at which risk is nonexistent, but rather on compelling chemical-specific mechanistic arguments developed from a high-quality database.

---

46 (Steinberg and DeSesso 1993) *See* Chapter 9, "Trichloroethylene."

47 (Gough 1988)

48 The range of virtually safe doses in Europe is 1 to 10 picograms/kilogram/day (pg/kg/d). Estimated virtually safe doses in the United States, i.e., a dose associated with an increase in risk of 1 in 1 million, range from 0.006 pg/kg/d at EPA, to 0.057 pg/kg/d at FDA and from 0.028 to1.2 pg/kg/d at the Centers for Disease Control (CDC).

49 (Stohrer 1991)

50 A no observed adverse effect level is defined as the highest experimental dose at which no "adverse" effect is observed. What is considered to be an adverse effect is a subjective determination which may vary between risk assessors and risk assessments.

51 (Interagency Regulatory Liaison Group [IRLG] 1979)

IX. Extrapolation to Low Doses

Because the shape of the dose-response curve in the low-dose region cannot be determined, it is generally assumed to be linear in order to calculate a protective risk estimate. Alternatives to the default use of the linearized multistage model (LMS) include:

- **Use other mathematical extrapolation models**. Alternative mathematical extrapolation models to the LMS model exist, including: probit,[52] log-normal probit,[53] log-logistic,[54] one-hit,[55] gamma multihit,[56] Weibull[57] and time-to-Tumor[58] models. Table 4-2 illustrates that the most frequently used dose-response models predict similar curves in the range of observable responses. Table 4-3 illustrates, however, that the extrapolation models diverge markedly at low doses. Although "[different extrapolation models ... may fit the observed data reasonably well ... [they] may lead to large differences in the projected risk at low doses."[59] Thus, justification for using one extrapolation model over the others is not generally possible because "[g]oodness-of- fit to the experimental observations is not an effective means of discriminating among [extrapolation] models."[60] Use of the LMS model is justified on a policy basis because it is less likely to underpredict cancer risks at low doses.[61]
- **Use different types of models.** Other model types include biologically based models, PBPK models, and benchmark dose models.
  - **Biologically based cancer models**. In 1981, a biologically based, two- stage model for carcinogenesis was developed (see Figure 4-1).[62] The advantage of using the two-stage model in regulatory risk assessment stems from its

[52] *See* (Hartung 1987).

[53] *See* (Mantel and Bryan 1961; Mantel et al. 1975).

[54] *See* (Berkson 1944).

[55] *See* (Brown 1987; Hoel et al. 1975; and van Ryzin 1980).

[56] *See* (Rai and van Ryzin 1979)

[57] *See* (Nordling 1953; Fisher and Holloman 1951).

[58] *See* (Thorslund, Brown, and Chamley 1987; OSTP 1985).

[59] (EPA 1986b)

[60] (OSTP 1985) In his testimony before the U.S. House Subcommittee on Transportation and Hazardous Materials on November 17, 1993, Dr. James Wilson, of Monsanto Company, stated that none of the available dose-response extrapolation models can really be tested and that they are all based on limited science; i.e., they are mathematical expressions with limited biological bases. Thus, Wilson said, no extrapolation model is more relevant/correct/appropriate than any other. Wilson asserted that the LMS model is most often used because it tends to give the most conservative estimate of risk.

[61] (EPA 1986a, 33997)

[62] (Moolgavkar and Knudson 1981)

basis in biology.[63] The model assumes that two critical and inheritable cellular changes are all that is necessary to produce a malignant cell, which can then progress to a full tumor.

Table 4-2. Comparison of Dose-Response Relationships over the Range of Observable Response Rates[64]

Dose Level	Percent responders, by model		
	Log-normal	Log-logistic	One-hit
16	98	96	100
8	93	92	99
4	84	84	94
2	69	70	75
1	50	50	50
1/2	31	30	29
1/4	16	16	16
1/8	7	8	8
1/16	2	4	4

Table 4-3. Extrapolation of Dose-Response Relationships to Low Dose Levels Using Different Extrapolation Models[65]

Dose Level	Percent Responders, by Model				
	One-hit	Multistage	Log-logistic	Multihit	Log-normal
0.01	0.7	0.3	0.4	0.14	0.05
0.001	0.07	0.03	0.026	0.00014	0.00035
0.0001	0.007	0.003	0.0016	0.0000015	0.0000001

[63] 63The two-stage model can explain numerous phenomena in carcinogenesis that the LMS model cannot, including: genetic predisposition to cancer; patterns in childhood cancer rates; hormonally influenced changes in breast cancer rates; changes in respiratory cancer rates associated with variable smoking patterns; the fact that for many human carcinomas, the age-specific incidence rates increase roughly with the fourth to the seventh power of age; and the results of initiation-promotion experiments for multiple agents (Chamley and Thorslund 1988). The two-stage model may also explain the following phenomena: tumor rates at high experimental doses are often lower than at lower doses, even when adjustments for differential mortality are made; exposure to several carcinogens can result in antagonistic additive, multiplicative, or supermultiplicative joint tumor rate responses; these joint responses appear to be dose-dependent; and transformed cell masses that may be tumor precursors will sometimes regress and disappear after exposure is ceased (Thorslund, Brown, and Chamley 1987).

[64] Adapted from (Food and Drug Administration (FDA) 1971).

[65] (Brown 1987)

The two-stage model has been applied to many sets of data, including lung cancer and smoking, and breast cancer in relation **to hormones, radiation**, and **heredity**. This model can take into account physiological factors, such as whether agents affect transition rates or the kinetics of tissue growth, etc.[66] The NRC Committee on Risk Assessment Methodology (CRAM) reviewed efforts to apply a two- stage model of carcinogenesis to various chemicals and encouraged further testing and development of this model.[67] Unfortunately, current bioassay protocols do not provide sufficient or appropriate information to use the two-stage model. Further mechanism and cellular-level studies at low doses will be required for each substance in order to exploit the two-stage model to its full potential.[68] Nevertheless, this model has been called "the foundation upon which future cancer risk estimates will be based."[69]

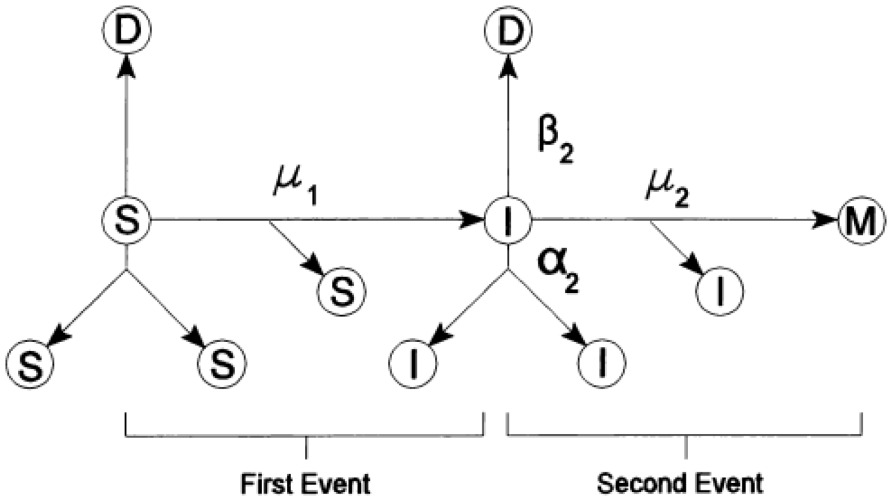

Figure 4-1. Two-stage model for carcinogenesis. S = normal stem cell, I = intermediate (one-hit) cell, D = differentiated (or dead) cell, M = malignant cell; μI = rate at which first event occurs, μ2 = rate at which second event occurs, α2=rate of division of intermediate cells, β2 = rate of differentiation and death of intermediate cells. In a small time interval, a given stem cell (S) may divide with a certain probability to give rise to two daughter cells (S), or it may differentiate (or die) (D) and thus leave the pool of susceptible cells, or it may divide (with a small probability) into two cells, one of which is normal (S) ana the other of which has suffered the first event to become an intermediate cell (1). The intermediate cell may in turn give rise to two intermediate daughters (I); die or differentiate (D); or give rise (with a small probability) to one intermediate cell (I) and one malignant cell (M). Source: Moolgavkar 1986.

- **PBPK models.** PBPK models describe the distribution and biotransformation of chemicals and provide estimates of doses delivered to target tissues.[70] Accordingly, PBPK modeling requires a detailed study

[66] (Moolgavkar and Knudson 1981)

[67] (NRC 1993b, 215-216)

[68] (Wilson 1989)

[69] (Paustenbach 1989)

[70] (Bois, Zeise, and Tozer 1990)

of the ADME of substances in the body. Such data, however, are not generally collected during animal bioassays. Although an increased emphasis on PBPK modeling has occurred over the last few years, it was estimated in 1988 that ADME data had not been used in setting 90 percent of exposure standards.[71] Nonetheless, PBPK modeling is "considered likely to move quantitative risk assessment and low-dose extrapolation models to the next level of refinement."[72] Attempts at PBPK modeling for quantitative risk assessment purposes are discussed below.

TCE. The amount of TCE metabolized in humans from drinking water contaminated at 32 parts per billion (ppb) was demonstrated to be five orders of magnitude lower than metabolized levels observed in rats inhaling TCE at 500 parts per million (ppm). Assuming similar metabolic pathways in rats and humans, the data imply that ingestion of drinking water contaminated with TCE at 32 ppb does not increase human cancer risk because the higher rat exposures were not associated with increased cancer incidence.[73]

PCE. It was demonstrated that the dose delivered to the liver did not vary linearly with the dose administered through the lungs. The implication of this result is that cancer risk from PCE will not increase linearly with administered dose at low doses.[74]

Methylene chloride. ADME data from humans, rats, mice, and hamsters were used to develop a PBPK model for methylene chloride, a suspected lung and liver carcinogen. Use of the PBPK model resulted in an estimated combined risk of lung and liver cancer for methylene chloride which was 110 times lower than that originally derived by EPA.[75] EPA subsequently accepted a revision of the PBPK model results and reduced its estimated virtually safe dose (VSD) at a risk of 10^{-6} by a factor of about nine.[76] A subsequent examination of the PBPK model, in which uncertainty and intraindividual variability were included in the analysis, however, indicated that the model indicated a greater than 5 percent chance that the VSD should have been revised upward.[77]

---

[71] (Watanabe, Schumann, and Reitz 1988)

[72] (Paustenbach 1989)

[73] (Koizumi 1989)

[74] (Travis, White and Arms 1989)

[75] (Reitz et al. 1989)

[76] (EPA 1987)

[77] (Portier and Kaplan 1989)

Uncertainty analysis can be applied to PBPK models.[78] Uncertainty analysis in PBPK modeling incorporates ranges of likely values for individual parameters and provides probability distributions of chemical concentrations in target organs rather than single-point estimates. Resulting probability distributions can be combined with a Monte Carlo simulation of exposures.[79] This approach would ultimately result in a probabilistic description of the risk associated with exposure that incorporates—rather than arbitrarily assumes away—uncertainty in input parameters and provides an indication of the range of uncertainty in the risk estimates.

- **Benchmark Dose.** The benchmark dose (BMD) method is a statistical approach used to estimate a theoretical NOAEL from one or more animal studies of sufficient quality and statistical power. The BMD approach takes into account the observed dose-response data and uses information from all studies. Although currently proposed only for use in noncancer risk assessment, the BMD could allow consistent evaluation of carcinogens and noncarcinogens. As with the standard NOAEL approach, uncertainty factors are applied. However, the BMD is potentially less arbitrarily conservative than the standard NOAEL approach.[80]

- **Use ranges and distributions of carcinogenic potency estimates**. Three variations of this alternative exist:

  - **Range of potency estimates from one model**. Central, low, and high estimates of carcinogenic potency from one extrapolation model derived from one data set may be used. For example, instead of relying only on the upper-bound estimate from the LMS model, six different risk estimates using the LMS model could be made:

    1. Constrained maximum likelihood of the cancer potency factor (the model is constrained to be linear and positive at low doses);

    2. Unconstrained maximum likelihood of the cancer potency factor; and

    3-6. The 95th percentile upper confidence limit and 95th percentile lower confidence limit, with and without the linear constraint.

    A range of estimates would "provide data that assist in judging the biological relevance of the model and the values it generates."[81]

---

[78] (Farrar et al. 1989)

[79] *See* Section X in this chapter.

[80] (American Industrial Health Council (AIHC) 1993, 14—16)

[81] (AIHC 1983) cited in (Paustenbach 1989).

- **Distribution of potency estimates from one model**. A probability distribution (*see* Figure 4-2) of the carcinogenic potency for dioxin was produced with the LMS model.[82] The potency estimates range from zero to approximately 13,000 (mg/kg/d) $^{-1}$ The 95th percentile value of 9,700 (mg/kg/d)'1 is about 16 times lower than the current EPA estimate.

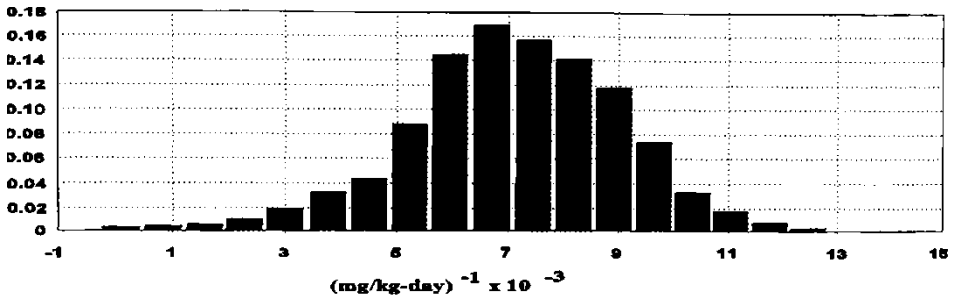

Figure 4-2. Probability distribution for the cancer potency factor for 2, 3, 7, 8-TCDD using the linearized multistage model and histopathological reevaluation of cancer bioassay data. Source: Copeland et al.1993

- **Potency estimates from different models**. This approach uses several different models to estimate risks followed by an examination of all results.[83] If the results are within an order of magnitude, then the assessor has demonstrated that the choice of extrapolation model did not dramatically affect the risk assessment. The various extrapolation models produce wide-ranging risk estimates at low doses, however, so this approach is not likely to be successful. Moreover, this approach may present regulators with unwieldy ranges of risk estimates.[84]

- **Overall probability distribution of potency estimates.** This variation uses all available studies to produce an overall probability distribution of the carcinogenic potency based on one model. In the case of **chloroform,** this approach would yield a cancer potency factor 22 percent lower than the current EPA estimate. Inclusion of nonpositive studies likely would lower the potency estimate even further.[85]

A variety of alternatives for the LMS model exists. Although all alternatives may offer improved risk estimates, each does so at a price. Each of the alternatives above requires additional data, and additional resources would be necessary to produce the data. In fact, no matter how much research money is directed toward determining the shape of the dose-response curve, it is unlikely that the true shape in the low-dose region will

[82] (Copeland et al. 1993)

[83] (Swaen 1988)

[84] For example, when the FDA was evaluating potential risks to humans ingesting 0.12 grams per day of saccharin, a variety of extrapolation models and scaling factor approaches were used. Lifetime risk estimates ranged from 0.001 to 5,200 additional cases of bladder cancer per million people exposed. FDA eventually chose a linearized model, which predicted risks of up to 1,200 per million (Klapp 1992).

[85] (Integrated Risk Information System [IRIS] 1993)

ever be determined. Therefore, science policy will always be a factor in low-dose extrapolation.

X. Use of Upper-Bound, Point Exposure Estimates

The use of upper-bound point estimates for exposure variables in an exposure assessment, particularly in combination with the other default assumptions, virtually assures that risks will not be underestimated. However, exposure and risk assessments have come under criticism because the degree to which likely risks are overstated is unknown. Alternatives to the use of default values for variables in exposure assessments include:

- **Use actual exposure data.** Although logistically difficult and resourceintensive, the need to estimate exposures can be eliminated if exposures can be directly measured. Exposure measurements may take the form of:
  - Outfitting exposed persons with monitoring devices (radiation detector badges, personal air monitors);
  - Measuring levels of a substance in the tissues or body fluids of exposed persons (lead in blood, dioxin in body fat or blood); and
  - Measuring levels of a biomarker for the substance of concern in the body fluids of exposed persons (cotinine, the metabolite of nicotine, in the saliva, blood, and urine of smokers; cholinesterase inhibition from exposure to **carbamate** and **organophosphate pesticides)**.

  In the case of permitting a new facility or assessing future risks, however, exposures cannot be measured and must be estimated. Although research on exposure measurement methods is being conducted, exposure measurement will never fully replace exposure assessment. Consequently, considerable attention must be devoted to improving exposure assessment methods.
- **Use reasonable, mean, or median values for all exposure variables.** The cumulative impact of using upper-bound point estimates is illustrated for **polychlorinated biphenyls (PCBs)** in Table 4-4.[86] In this case, the worst-case risk estimate is 150 million times greater than one using more reasonable alternative exposure assumptions. Using mean or median values for exposure variables does not guarantee that a mean or median estimate will result. This is true for the same reason that combining 95th percentile values does not result in an overall 95th percentile estimate. Furthermore, relying on a single-point estimate eliminates a great deal of information regarding the range of possible and/or likely exposures and risks.

[86] (Maxim 1989)

- **Use low, central, and high exposure variable values to estimate low, central, and high exposures**. This approach may provide an improved "picture" of the range of likely exposures, but does not indicate the relative frequency with which they might occur. EPA's recently revised Guidelines for Exposure Assessment[87] suggest that two exposure estimates be made: (1) a central tendency estimate, such as the mean, median, or both, and (2) a high-end estimate. The high-end estimate should represent an exposure greater than the 90th percentile, but below the maximum possible. This approach has been followed in a recent EPA proposed rulemaking.[88]
- **Use probability distributions of exposure variables**. Statistical techniques, such as Monte Carlo analysis, can be used with probability distributions of exposure variables to provide a complete picture of the range and frequency of likely exposures and risks. The case studies below illustrate the utility of Monte Carlo probabilistic techniques and compare the upper-bound risk estimates obtained using point and probabilistic methods.

Table 4-4. Comparison of Worst-Case and Reasonable Alternative Values for Exposure Assessment Variables[89]

Variable	Worst-Case	Alternative	Remarks
PCB soil concentration	2,000 ppm	100 ppm	2,000 ppm was a hotconcentration spot; 90% of area had concentrations less than 100 ppm
Surface soil depletion	None	2-year half-life	Depletion by photolysis and volatilization likely
Fraction absorbed	1.0	0.2	1.0 is likely to be high; 0.2 is a better estimate
Age-specific ingestion rates (mg/day)			Worst case values are Reported; easonable are more consistent with literature and EPA guidance
0-1	5,000	50	
1-2	5,000	100	
2-6	10,000	100	
6-11	1,000	50	
11-18	1,000	0	
18-70	100	0	
Body weight	Comparable	Comparable	

[87] (EPA 1992c)

[88] (EPA 1994)

[89] Adapted from (Maxim 1989).

Carcinogenic Potency/g for 70 kg on slope factor of adult	$2.34x10^{-3}$	$1.5x10^{-5}$	Worst case is based on slope factor of 4.34 $(mg/kg/d)^{-1}$; alternative is from an OTA report
Estimated lifetime risk	$5.4x10^{-1}$	$3.7x10^{-9}$	

- Case Study 1. The protectiveness of drinking water standards was evaluated for PCE, chloroform, bromoform, and vinyl chloride by calculating exposures and risks at maximum allowable levels of contamination. These risk estimates are compared to the EPA risk assessment in Table 4-5. Note that only the 95th percentile estimate for chloroform exceeded the EPA point estimate.[90]
- **Case Study 2.** California's risk assessment methodology was compared with a probabilistic assessment of exposure to **dioxins** and **furans** emitted from an incinerator stack. In the probabilistic assessment, the 50th and 95th percentile risk estimates were $1.6x10^{-8}$ and $8.7x10^{-8}$, respectively. The California point estimate, 1.5x1 O^{-5}, is about 170 times higher than the 95th percentile estimate.[91]

Table 4-5. Comparison of Probabilistic and Point Estimates of Risk for Drinking Water Contaminants at Their MCLs[92]

Contaminant	50th percentile Probabilistic Risk	95th percentile Probabilistic Risk	EPA Point Risk Estimate
Tetrachloroethylene	$6.8x10^{-7}$	$4.9x10^{-6}$	$7.3x10^{-6}$
Chloroform	$9.4x10^{-6}$	$1.4X10^{-4}$	$1.7 *0^{-5}$
Bromoform	$2.3x10^{-6}$	$1.6x10^{-5}$	$2.3x10^{-5}$
Vinyl chloride	$4.6x10^{-6}$	$2.9x10^{-5}$	$5.4x10^{-5}$

- Case Study 3. A multiple pathway exposure assessment to dioxin was used to determine cleanup standards. Considering exposures to contaminated soils, cleanup levels protective of 95 percent of the population at a risk level of 10- 5 were estimated to be approximately 10 ppb and 50 ppb for residential and industrial exposures, respectively. These levels are

[90] (Finley and Paustenbach 1994)

[91] (Finley and Paustenbach 1994)

[92] Adapted from (Finley and Paustenbach 1994).

compared to usual residential and industrial soil cleanup levels of 1 ppb to 20 ppb, and up to 1,000 ppb, respectively.[93]

Several probabilistic exposure and risk assessments have been published recently, including the Following: [94]

- A Monte Carlo approach was employed to estimate risks associated with exposure to dioxin at a former wood treatment facility. Using appropriate distributions for exposure variables, the Monte Carlo simulation demonstrated that the risks predicted by the traditional Superfund approach overstated the 95th percentile exposures by a factor of approximately seventy.[95]
- The Hazardous Waste Cleanup Project (HWCP) examined the impact of compound conservative exposure assumptions in exposure and risk assessments performed for Superfund sites.[96] HWCP used Monte Carlo techniques to estimate exposures at a hypothetical site via several exposure pathways and compared the resulting 95th percentile exposure with that estimated according to the EPA Superfund guidance. As shown in Table 4-6, the default exposure variables resulted in exposure estimates two to sixty times greater than the estimates obtained using Monte Carlo methods.

Table 4-6. Comparison of EPA Default and Monte Carlo Exposure Estimates for Four Exposure Pathways [97]

Exposure Pathway	Monte Carlo 95th Percentile Exposure (mg/kg/day)	EPA Default Value Exposure (mg/kg/day)	Ratio of EPA to Monte Carlo 95th Percentile Exposures
Ingestion of water	$1.3x10^{-2}$	$2.9x10^{-2}$	2.2
Ingestion of soil	$2.4X10^{-6}$	$3.5x10^{-5}$	14.6
Ingestion of food	$3.3x10^{-4}$	$3.6x10^{-3}$	10.9
Dermal contact	$1.2x10^{-7}$	$6.7x10^{-6}$	55.8

[93] (Finley and Paustenbach 1994)

[94] In addition to the examples cited in the text, the reader is referred to the following publications on probabilistic risk assessment: (Eschenroeder and Faeder 1988; Finley, Scott, and Paustenbach 1993; McKone and Bogen 1992; Thompson, Burmaster, and Crouch 1992)

[95] (Copeland et al. 1993)

[96] (Hazardous Waste Cleanup Project (HWCP) 1993)

[97] Adapted from (HWCP 1993).

- The Superfund method has been found to estimate exposures 10 to 1,000 times higher than the 95th percentile exposure using Monte Carlo simulation.[98] Even with 5,000 environmental samples, the Superfund methodology consistently overestimated the 95th percentile exposure calculated using a probabilistic approach.

The results from a probabilistic exposure assessment can provide decision makers and the public with more and better information. Consider the following characterizations of risk for a point estimate and probabilistic assessment: [99]

- **Point estimate** "The potential increased cancer risk associated with DDT in river sediments is unlikely to exceed lxlO^{-6} for most people."
- **Probabilistic assessment** "The plausible increased cancer risks at the 50th, 95th, and 99th percentiles of the exposed population are lxlO^{-8}, 5x1 O^{-7}, and lxlO^{-6}, respectively. A sensitivity analysis indicates that the critical exposure variables, such as the concentration of DDT in the edible portion of smallmouth bass, are based on high quality, reliable data; therefore, our confidence in the risk estimates is high. Our analysis also indicates that 90 percent of the increased cancer risk would be eliminated if there were a ban on catching carp or catfish from the river."

The comparative advantages and disadvantages of the point and probabilistic alternatives to estimating exposures are more fully illustrated in Table 4-7.

Probabilistic exposure assessments have been touted as the answer to the dual problems of compound conservatism and false precision in risk assessments. However, there are obstacles to including probabilistic methods in risk assessment. First, the need for well-characterized probability distributions for exposure variables is of paramount importance to the eventual standardization and acceptance of probabilistic exposure assessments. Although sufficient data are claimed to exist to designate standard probability distributions for all exposure variables, probability distributions for a number of exposure variables must still be developed. [100]

---

[98] (Donahoe, Foster, and Chrostowski 1990a)

[99] (Donahoe, Foster, and Chrostowski 1990a)

[100] Examples include: chemical-specific dermal permeability coefficients, chemical-specific cancer potency factors, chemical-specific oral bioavailabilities for ingested soil, inputs to fate and transport models, adult soil ingestion rates, and interior surface dermal contact rates (Finley and Paustenbach 1994).

Table 4-7. Advantages and Disadvantages of Using Point and Probabilistic Estimates in Risk Assessments[101]

Advantages	Disadvantages
Point Estimates	
Simple, accessible Readily accepted by regulators Can provide a "bounding estimate"	Repeated use of conservative point estimates tends to overestimate actual Readily accepted by regulators exposure significantly Sensitivity or uncertainty analyses usually not very meaningful, especially when comparing different point estimates
Probabilistic Assessments	
Provides more meaningful information to risk managers and public Avoids disputes over best point estimate Risk estimates are associated with a quantitative measure of uncertainty Eliminates creeping conservatism Allows for quantitative evaluation of conservatism in point estimate approach Sensitivity analysis more meaningful Facilitates comparison of competing risks	More complicated and time consuming More difficult to conduct quality assurance of the calculations Current regulatory guidelines do not encourage its use

Second, regulators have been hesitant to include such analyses in risk assessments because the required ranges and distributions of data are often not available and regulatory agency staff are not trained to conduct and evaluate such analyses.[102] Nonetheless, probabilistic methods have recently been used by regulators to some extent.[103]

[101] Adapted from (Finley and Paustenbach 1994).

[102] (Donahoe, Foster, and Chrostowski 1990a; Hembra 1993)

[103] For example, in a Hazardous Waste Management System rulemaking, EPA used Monte Carlo modeling in the Composite Model for Landfills (EPACML) to estimate probability distributions of dilution/attenuation factors (DAFs) for chemicals leaching from wastes and migrating to ground water. A probability density function (PDF) of DAFs was obtained using the EPACML and the 95th percentile value of the DAF taken from this PDF. Monte Carlo techniques were also used to support a hazardous waste

Exposure concentrations must often be estimated because the data are unavailable. Current guidance and regulations call for upper-bound estimates of exposure concentrations. In Superfund, exposure concentration is estimated as the upper 95th percentile confidence limit on the arithmetic mean.[104] In the case of air emissions, the maximally exposed individual (MEI) is assumed to be exposed to the maximum annual average contaminant concentration for a lifetime.[105] These assumptions clearly represent conservative defaults. Alternative methods of estimating exposure concentrations have been proposed, including:

- **Use the average of each contaminant concentration derived from point concentration measurements.** The alternative assumes that a "random walk" over a site over time would result in an exposure concentration that is approximated by the average concentration of the contaminants. This approach represents an increase in realism compared to the 95th upper confidence limit (UCL) on the mean that is currently used.
- Use the expected value of each concentration derived from point concentration measurements. Expected values may not be the same as average values because the probability that each is correct is factored in.106
- **Use computer-generated mean concentrations (or higher levels).** The computer-based mathematical approach known as "kriging" uses the spacial distribution of contaminants and more accurately characterizes the levels present. The strength of kriging is that a map of concentrations is generated so that essentially an infinite number of point estimates of concentrations exists, which provide a more realistic representation of the pattern of contamination across a site. An illustration of this approach for estimating representative **PCE** exposure concentrations in groundwater is illustrated in Table 4-8.

delisting petition (EPA 1991). EPA has also used Monte Carlo simulation to calculate dilution attenuation factors for constituents leaching from landfills in a previous rulemaking (EPA 1990).

[104] (EPA 1989)

[105] (Hawkins 1991, 109)

[106] (Nichols and Zeckhauser 1986, 72)

Table 4-8. Comparison of Estimated Exposure Point Concentrations of Tetrachloroethylene (PCE) [107]					
Data Used	**Concentration (μg/L)**				
	Average	**UCL on Average**	**90th Percentile**	**Maximum**	**RME Cone.**
Raw data	143	15,934	174	1,625	1,625
Kriged data, 40-yard grid	37.8	86.0	57.8	969	86.0
Kriged data, 120-yard grid	11.8	22.9	20.6	79.9	22.9

Following EPA Superfund guidance for generating RME estimates, exposure concentrations are calculated as the 95th percentile UCL on the arithmetic mean. When, as in the case above, the UCL on the mean exceeds the maximum value in the data set, the maximum value is used as the representative exposure concentration. Thus:

- Using point estimates, the RME concentration would be assumed to be 1,625 μg/L;
- When kriging is done, the UCL on the mean would be calculated to be 86 pg/L using a 40-yard grid and 22.9 μg/L using an 120-yard grid.

  The RME exposure point concentration for PCE is overestimated by a factor of nineteen to seventy-one at this site.

- **Use the frequency distribution of contaminant concentrations derived from the point data.** This alternative would more closely reflect reality, but suffers from the limitation of relying only on point estimates.
- **Use estimated concentration frequency distributions obtained using kriging.** Assuming that the available data are accurate and representative, this approach would be closest to reality.

It is clear that there are a number of alternative approaches to the default used of upper- bound point exposure estimates. Efforts to produce more realistic and representative estimates of exposure will require more data and resources.

Use of probability distributions requires more skill, judgment, and knowledge than plugging predetermined values for exposure variables into standard equations. The use of probabilistic methods does not necessarily guarantee better risk assessment results, but it can facilitate a more thorough evaluation of likely exposures and risks.

[107] (Donahoe, Foster, and Chrostowski 1990b)

Future Direction

As the previous discussion demonstrates, alternatives to the default assumptions are indeed available in many cases. However, the assumption-by-assumption approach to examining default assumptions used in exposure and risk assessments makes it impossible to predict or appreciate the impact of each individual assumption on the final assessments. Each default assumption in and of itself may seem reasonable, but when all are lumped together, it is difficult to determine exactly how much and where the resulting compounded conservatism has obscured an estimate of the actual risk.[108]

A novel approach has been developed by the American Industrial Health Council (AIHC). The Comprehensive Methodology[109] shows promise as a way to incorporate uncertainty and policy judgments into regulatory risk assessments directly. The Comprehensive Methodology represents a potential paradigm shift away from the reliance on default assumptions to one in which all information available on a particular chemical or substance is explicitly incorporated in developing probabilistic distributions of risk estimates. At the very least, this approach represents a change from the *status quo*, which relies on arbitrary and insupportable choices among default assumptions.

The Comprehensive Methodology is designed to provide a probability distribution of carcinogenic risks under specific exposure scenarios. It is based on the premise that all potentially relevant data should be considered. In contrast, "risk assessors and managers currently give dominant weight to a cancer potency assessment method that censors data and takes little account of toxicological and epidemiological judgment."[110] The Comprehensive Methodology relies on expert judgment to deviate from default assumptions. The experts are called upon to assign weights, or probabilities, to the various options rather than choose a single option at each decision point. For example, it may be assumed that there is a 75 percent chance that a chemical is a human carcinogen and a 25 percent chance that it is not. These weights are then used in a probability tree that describes the options at each decision point. Finally, a probabilistic risk assessment is produced.

The Comprehensive Methodology has been used to assess risks of inhalation exposure to formaldehyde.[111] The probability tree for the formaldehyde risk assessment included the options at six levels listed in Table 4-9. The numbers in parentheses indicate the subjective probabilities that were assigned to each option.

---

[108] Assuming, of course, that the "actual risk" could be determined.

[109] (Graham 1992)

[110] (Graham 1992, 3)

[111] (Evans et al. 1994)

Table 4-9. Simplified Probability Tree for Formaldehyde Risk Assessment Using Comprehensive Methodology [112]

Level One - Human carcinogenic hazard ➢ Formaldehyde is a human carcinogen (0.8) ➢ Formaldehyde is not a human carcinogen (0.2)
Level Two - Mechanism of action ➢ Cell proliferation, but not genotoxicity involved in carcinogenesis (0.8) ➢ Genotoxicity, but not cell proliferation involved in carcinogenesis (0.005) ➢ Both cell proliferation and genotoxicity involved in carcinogenesis (0.195)
Level Three - Dose scale ➢ Dose should be expressed in terms of exposure concentration (0.1) ➢ Dose should be expressed in terms of intake (0.3) ➢ Dose should be expressed in terms of binding of formaldehyde to DNA (0.6)
Level Four - Dose-response model[a] ➢ Threshold: probit model ➢ Sublinear: multistage model ➢ Sublinear with low-dose linearity: Multistage, linear below 1 ppm exposure ➢ Linear: One-hit model
Level Five - Experimental data set ➢ Use malignant tumors only (0.8) ➢ Use malignant and benign tumors (0.2)
Level Six - Interspecies scaling factor[b] ➢ Body mass equivalence ➢ Intermediate approach (mg/kg) 3/4 ➢ Surface area equivalence

[112] Adapted from (Evans et al. 1994).

[a] Relative probabilities were estimated using a bootstrapping procedure which considered how well the data fit each model. Probabilities were also modified when dependence on probabilities in other levels was expected.

[b] Relative probabilities were not specified.

Risks for the 432 different combinations of the options in the probability tree were calculated, and a single probability distribution was produced. A probability distribution gives the decision maker information about the magnitude and the likelihood that various risk estimates are correct. The Comprehensive Methodology has been used to generate two formaldehyde risk assessments—one involving ambient exposures and the other involving workplace exposures. The probability distribution of the national annual increased incidence of cancer attributed to lifetime inhalation of 2.28 ppb formaldehyde, the average outdoor air concentration, is displayed in Figure 4-3.

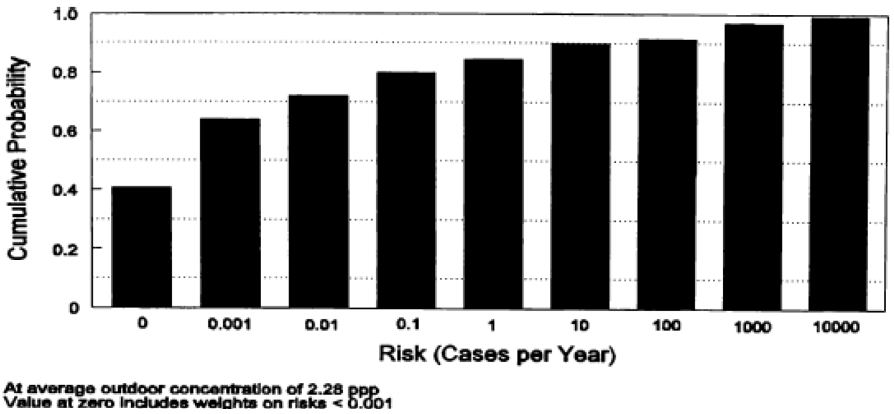

Figure 4-3. Cancer risk from ambient formaldehyde. Nationwide incidence attributable to exposure. Source: Evans et al. 1994.

The EPA published an upper-bound estimate of 124 cancers per year, which corresponds to the 94.22nd percentile on the probability distribution obtained using the Comprehensive Methodology. For comparison, the Comprehensive Methodology estimates a 95th percentile incidence of 220 cancers annually. Note, however, that Figure 4-3 indicates an 85 percent probability that the national annual cancer incidence attributable to inhalation of ambient formaldehyde is less than one. Figure 4-4 depicts the probability distribution of the additional risk faced by a worker exposed to 0.75ppm formaldehyde, the occupational standard, during a forty-year working lifetime. As seen in Figure 4-4, using the Comprehensive Methodology, there is an 80 percent probability that the risk faced by such a worker is less than $1x10^{-6}$. Summary statistics for both risk assessments are summarized in Tables 4-10 and 4·11.

With the results from the Comprehensive Methodology, a regulatory decision maker is presented with a description of the range of possible risks as well as some indication of how likely each estimate is correct. The decision maker can purposefully select a degree of conservatism that is appropriate in the particular rulemaking context.

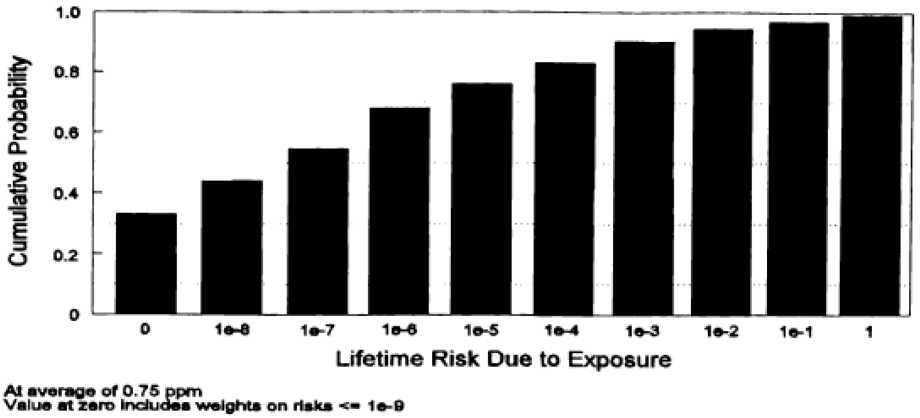

Figure 4-4. Cancer risk from workplace formaldehyde. Lifetime risk to exposed worker. Source: Evans et al. 1994.

Table 4-10. Nationwide Annual Cancer Incidence Attributable to Exposure to 2.28 ppb of Formaldehyde (Summary Statistics) [113]	
Percentile	**Cancer Incidence**
Minimum	0
Median (50th percentile)	0.00000009
EPA upper-bound	124
95th percentile	220
Mean	280
Maximum	11000

Table 4-11. Lifetime Added Risk for a Worker Exposed to 0.75 ppm of Formaldehyde[114]	
Percentile	**Added Risk**
Minimum	0
Median (50th percentile)	0.00000004
95th percentile	0.003
Mean	0.004
Maximum	0.13

[113] **Adapted from (Evans et al. 1994).**

[114] Adapted from (Evans et al. 1994).

Although this method relies on subjective scientific judgment in deriving probabilistic weights among the options, the same might be said for the current risk assessment approach, which also relies on judgments. Thus, the subjective judgments required in the Comprehensive Methodology do not represent a relative disadvantage over the *status quo*[115]

Conclusions

As this chapter has illustrated, alternatives to the default assumptions discussed in Chapter 3 are indeed available in many cases. However, in most cases, justification of these alternatives relies on chemical- and/or species-specific data and arguments. Consequently, it is unlikely that any default assumptions will be completely replaced. A justifiable alternative may be identified for a class of chemicals, but at present there is no universally justifiable and acceptable alternative to any of the default assumptions. Replacement of default assumptions will occur only after sufficient research and data have indicated that an alternative is more likely to be correct than the default. The alternative must also still be protective of public health. Thus, in the near future, research on alternatives will be limited in impact and are likely to result only in incremental changes in the risk assessment process.

Research, however, cannot resolve all of the science policy issues in risk assessment. Certain science policy questions cannot be practically or ethically solved with science. These issues include the shape of the dose-response curve in the low-dose region and the existence or absence of thresholds. Issues such as these generally will remain in the province of science policy. For this category of questions, the default assumptions are likely to remain in place, except in specific limited circumstances. This is due in part to the need for regulatory agencies to be protective of public health and in part to a recognition that science will never be able to answer all of the questions that we can put to it.

The Comprehensive Methodology developed by AIHC represents a potential revolution in the way risk assessments are conducted. Some believe this methodology, if combined with PBPK models and distributional exposure assessments, could be a dramatic improvement upon current risk assessment methods. Full and complete incorporation of all uncertainty and variability would be achieved, and exposures and risks would be expressed in terms of probabilistic distributions. Regulatory decision makers would be presented with complete probabilistic descriptions of the ranges of expected exposures and risks, rather than point estimates. Probabilistic distributions would enable decision makers to consider the likelihood that various exposure and risk estimates will occur and determine explicitly the appropriate degree of conservatism in regulations. This would allow for a degree of separation of risk assessment and risk management, as advocated in the NRC *Red Book* that cannot currently be achieved.

---

[115] (Evans et al. 1994, 31)

Such a change in environmental regulatory decision making within federal agencies will require a commitment to the need for such a change as well as a commitment to funding the required research. If regulatory agencies indicate a willingness to evaluate and incorporate alternatives to default assumptions in regulatory risk assessments, the regulated community will have an incentive to conduct the necessary research. In the end, all parties are likely to benefit, as knowledge of mechanisms of carcinogenesis and understanding of the hazards posed by environmental contaminants is increased.

REFERENCES

AMERICAN INDUSTRIAL HEALTH COUNCIL (AIHC). 1993. Evaluating the benchmark dose methodology: AIHC/EPA workshop. AIHC Journal 1(3): 10—11, 14-16.

AMERICAN INDUSTRIAL HEALTH COUNCIL (AIHC). 1983. Significant Developments Regarding Government Cancer Risk Assessment Methodology. American Industrial Health Council, Washington, D.C.

AMES, B.N., and L.S. GOLD. 1990. Chemical carcinogens: Too many rodent carcinogens. Proc. Natl. Acad. Sci. USA 87:7772-7776.

BERKSON, J. 1944. Application of the logistic function to bio-assay. J. Amer. Stat. Assoc. 39:357-365.

BOIS, F.Y., L. ZEISE, and T.H. TOZER. 1990. Precision and sensitivity of pharmacokinetic models for cancer risk assessment: Tetrachloroethylene in mice, rats, and humans. Toxicol. Appl. Pharmacol. 102:300-315.

BROWN, C.C. 1987. Approaches to intraspecies dose extrapolation. Chapter 10 in Tardifif, R.G., and Rodricks, J.V. (eds.), Toxic Substances and Human Risk. New York: Plenum Press.

CARNEGIE COMMISSION ON SCIENCE, TECHNOLOGY and GOVERNMENT. 1993. Risk and the Environment: Improving Regulatory Decision Making. Carnegie Corporation, New York.

CARR, C.J., and A.C. KOLBYE, Jr. 1991. A critique of the use of the maximum tolerated dose in bioassays to assess cancer risks from chemicals. Regul. Toxicol. Pharmacol. 14:78-87.

CHARNLEY, G., and T.W. THORSLUND. 1988. Biologically based models to predict cancer risk. Chapter 8 in C.C. Travis (ed.), Carcinogen Risk Assessment. New York: Plenum Press.

COHEN, S.M., and L.B. ELLWEIN. 1990. Cell proliferation in carcinogenesis. Science 249:1007-1011.

COPELAND, T.L., D.J. PAUSTENBACH, M.A. HARRIS, and J. OTANI. 1993. Comparing the results of a Monte Carlo analysis with EPA's reasonable maximum exposure individual (RMEI): A case study of a former wood treatment site. Reg. Toxicol. Pharm. 18:275-312.

DONAHOE, S., S. FOSTER, and P. CHROSTOWSKI. 1990a. Estimation of Exposure and Risk for Superfund Baseline Risk Assessments. Prepared for Waste Management, Inc. Clement International Corporation, Fairfax, Va.

DONAHOE, S., S. FOSTER, and P. CHROSTOWSKI. 1990b. Estimation of Exposure Point Concentrations for Superfund Baseline Risk Assessments. Prepared for Waste Management, Inc. Clement International Corporation, Fairfax, Va.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994. Hazardous waste management system; Carbamate production identification and listing of hazardous waste; and CERCLA hazardous

substance designation and reportable quantities (Notice of proposed rulemaking). Fed. Reg. 59(40):9808-9870.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992a. Draft report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg3/4/d. Fed. Reg. 57(109):24152-24173.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992b. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. Offices of Research and Development, and Air and Radiation, Washington, D.C. 4-25-26. EPA/600/6-90/006F.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992c. Guidelines for exposure assessment (Notice). Fed. Reg. 57(104):22888-22938.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991. Hazardous waste management system: Identification and listing of hazardous waste; final exclusion. Fed. Reg.

56(250):67197-67206.

ALTERNATIVE ASSUMPTIONS 1 0 1

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1990. Hazardous waste management

system; Identification and listing of hazardous waste; Toxicity characteristic revisions. Fed. Reg. 55(61):11798-11862.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1989. Risk Assessment Guidance for

Superfund: Volume I—Human Health Evaluation Manual (Part A) (Interim Final). Office of Emergency and Remedial Response, Washington, D.C. EPA/540/1 -89/002.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1987. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Dichloride): Pharmacokinetics,

Mechanism of Action, and Epidemiology (External Review Draft). Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-87/030A.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986a. Guidelines for carcinogen risk

assessment. Fed. Reg. 51(185):33992-34003.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986b. Guidelines for estimating exposures. Fed. Reg. 51(185):34042-34054.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985. Health Assessment Document for Trichloroethylene (Final Report). Office of Health and Environmental Assessment, Washington, D.C.

ESCHENROEDER, A.Q., and E.J. FAEDER. 1988. A Monte Carlo analysis of health risks from PCB-contaminated mineral oil transformer fires. Risk Analysis 8:291-299.

EVANS, J.S., J.D. GRAHAM, G.M. GRAY, and R.L. SIELKEN. 1994. A distributional approach to characterizing low-dose cancer risk. Risk Analysis 14(l):25-34.

FARRAR, D., B. ALLEN, K. CRUMP, and A. SHIPP. 1989. Evaluation of uncertainty in input parameters to pharmacokinetic models and the resulting uncertainty in output. Toxicology Letters 49:371-385.

FINKEL, A.M. 1994. Some Small Steps for Congress, Some Giant Leaps—Backwards—for Risk Assessment? Testimony before the House Subcommittees on Environment, Energy and Natural Resources and on Legislation and National Security (February 1, 1994).

FINLEY, B.L., and D. PAUSTENBACH. 1994. The benefits of probabilistic exposure assessment: Three case studies involving contaminated air, water, and soil. Risk Analysis 14(l):53-73.

FINLEY, B.L., P. SCOTT, and D.J. PAUSTENBACH. 1993. Evaluating the adequacy of maximum contaminant levels as health-protective clean-up goals: An analysis based on Monte Carlo

techniques. Reg. Toxicol. Pharm. 18:438—455.

FISHER, J.C., and J.H. HOLLOMAN. 1951. A new hypothesis for the origin of cancer foci. Cancer 4:916-918.

FOOD AND DRUG ADMINISTRATION (FDA), Advisory Committee on Protocols for Safety Evaluation. 1971. Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides. Toxicol. Appl. Pharmacol. 20:419—438.

10 2 CHOICES IN RISK ASSESSMENT

FREDERICK, C.B., and A.G.E. WILSON. 1991. Comments on incorporating mechanistic data into quantitative risk assessment. Risk Analysis 11(4):581—582.

GOUGH, M. 1988. Science policy choices and the estimation of cancer risk associated with exposure to TCDD. Risk Analysis 8(3):337-342.

GRAHAM, J.D. 1992. Developing realistic estimates of risk—Comprehensive methodology. American Industrial Health Council Quarterly (Spring/Summer):l-4.

HARTUNG, R. 1987. Dose-response relationships. Chapter 3 in R.G. Tardiff and J.V. Rodricks (eds.), Toxic Substances and Human Risk. New York: Plenum Press.

HAWKINS, N.C. 1991. Conservatism in maximally exposed individual (MEI) predictive exposure assessments: A first-cut analysis. Regul. Toxicol. Pharmacol. 14:107-117.

HAZARDOUS WASTE CLEANUP PROJECT (HWCP). 1993. Exaggerating Risk: How EPA's Risk Assessments Distort the Facts at Superfund Sites Throughout the United States. Hazardous Waste Cleanup Project, do Morgan, Lewis & Bockius, Washington, D.C.

HEMBRA, R.L. 1993. Statement before the Senate Subcommittee on Superfund, Recycling, and Solid Waste Management (9/30/93). General Accounting Office, Washington, D.C.

HOEL, D.G., D.W. GAYLOR, R.L. KIRCHSTEIN, U. SAFFIOTTI, and M.A. SCHNEIDERMAN. 1975. Estimation of risks of irreversible, delayed toxicity. J. Toxicol. Environ. Health 1:133-151.

INTEGRATED RISK INFORMATION SYSTEM (IRIS). 1993. Integrated Risk Information Chemical Profdes, Updated 01/01/93. Environmental Criteria and Assessment Office, Environmental Protection Agency (EPA), Cincinnati, Ohio.

INTERAGENCY REGULATORY LIAISON GROUP (IRLG), Work Group on Risk Assessment. 1979. Scientific bases for identification of potential carcinogens and estimation of risks. J. Natl. Cancer Inst. 63:241—268.

KLAPP, M.G. 1992. Bargaining with Uncertainty: Decision-Making in Public Health,

Technological Safety, and Environmental Quality. Westport, Conn.: Auburn House.

KOIZUMI, A. 1989. Potential of physiologically based pharmacokinetics to amalgamate kinetic data of trichloroethylene and tetrachloroethylene obtained in rats and man. Br. J. Ind. Med. 46:239-249.

MANTEL, N,, N.R. BOHIDAR, C.C. BROWN, J.L. CIMINERA, and J.W. TUKEY. 1975. An improved Mantel-Bryan procedure for “safety” testing of carcinogens. Cancer Research 33:865-872.

MANTEL, N., and W.R. BRYAN. 1961. "Safety" testing of carcinogenic agents. J. Natl. Cancer Inst. 27(2):455-470.

MARSHALL, E. 1983. Revisions in cancer policy. Science 220:36-37.

MAXIM, L.D. 1989. Problems associated with the use of conservative assumptions in exposure and risk analysis. Chapter 14 in D.J. Paustenbach (ed.), The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

McKONE, T.E., and K.T. BOGEN. 1992. Uncertainties in health risk assessment: An integrated case study based on tetrachloroethylene in groundwater. Reg. Toxicol Pharm. 15:86-103.

MOOLGAVKAR, S.H., and A.G. KNUDSON, Jr. 1981. Mutation and cancer: A model for human carcinogenesis. J. Natl Cancer Inst. 66:1037-1052.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS). 1994. NIEHS—Vision for the Future. Research Triangle Park, N.C.

NATIONAL RESEARCH COUNCIL (NRC), Committee on Risk Assessment Methodology (CRAM). 1993a. Use of the maximum tolerated dose in animal bioassays for carcinogenicity. In Issues in Risk Assessment. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on Risk Assessment Methodology (CRAM). 1993b. The two-stage model of carcinogenesis. In Issues in Risk Assessment. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on the Institutional Means for Assessment of Risks to Public Health. 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, D.C.: National Academy Press.

NATIONAL TOXICOLOGY PROGRAM (NTP), Board of Scientific Counselors. 1992. National Toxicology Program (NTP), Final report of the Advisory Review by the NTP Board of Scientific Counselors (Request for comments). Fed. Reg. 57:31721-31730.

NICHOLS, A.L., and R.J. ZECKHAUSER. 1986. The dangers of caution: Conservatism in

assessment and the mismanagement of risk. Advances in Applied Micro-Economics 4:55-82.

NORDLING, C.O. 1953. A new theory on the cancer industry mechanism. Br. J. Cancer 7:68-72.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP). 1985. Chemical carcinogens: Review of the science and its associated principles. Fed. Reg. 50:10372-10442.

PAUSTENBACH, D.J. 1989. A survey of risk assessment. Chapter 1 in D.J. Paustenbach (ed.), The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

PORTIER, C.J., and N.L. KAPLAN. 1989. Variability of safe dose estimates when using complicated models of the carcinogenic process—A case study: Methylene chloride. Fund. Appl. Toxicol 13:533-544.

RAI, K., and J. VAN RYZIN. 1979. Risk assessment of toxic environmental substances using a generalized multi-hit dose response model. In N. Breslow and A. Whittemore (eds.), Energy and Health. Philadelphia: Society for Industrial and Applied Mathematics, 99-117.

REITZ, R.H., F.A. SMITH, M.E. ANDERSEN, H.J. CLEWELL, III, and M.L. GARGAS. 1989. Use of physiological pharmacokinetics in cancer risk assessments: A study of methylene chloride. Chapter 5 in D.J. Paustenbach (ed.), The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

SHARRATT, M. 1988. Assessing risks from data on other exposure routes—Possibilities and limitations of using toxicity data derived from one exposure route in assessing risks from other exposure routes. Reg. Toxicol. Pharm. 8:399-407.

STOHRER, G. 1991. Arsenic: Opportunity for risk assessment (Review article). Arch. Toxicol. 65:525-531.

STEINBERG, A.D., and J.M. DeSESSO. 1993. Have animal data been used inappropriately to estimate risks to humans from environmental trichloroethylene? Reg. Toxicol. Pharm. 18:137-153.

SWAEN, G.M.H. 1988. The use of epidemiological data in risk assessment. Regul. Toxicol. Pharmacol. 8:422—430.

THOMPSON, K.M., D.E. BURMASTER, and E. CROUCH. 1992. Monte Carlo techniques for quantitation uncertainty analysis in public health risk assessments. Risk Analysis 12:53-63.

THORSLUND, T.W., C.C. BROWN, and G. CHARNLEY. 1987. Biologically motivated cancer risk models. Risk Analysis 7(1): 109-119.

TRAVIS, C.C., R.K. WHITE, and A.D. ARMS. 1989. A physiologically based pharmacokinetic approach for assessing the cancer risk of tetrachloroethylene. Chapter 23 in D.J. Paustenbach (ed.), The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

VAN RYZIN, J. 1980. Quantitative risk assessment. J. Occup. Med. 22(5):321-326.

VELAZQUEZ, S.F., P.M. McGINNIS, S.T. VATER, W.S. STITELER, L.A. KNAUF, and R.S. SCHOENY. 1994. Combination of cancer data in quantitative risk assessments: Case study using bromodichloromethane. Risk Analysis 14(3):285-291.

VOCCI, F., and T. FARBER. 1988. Extrapolation of animal toxicity data to man. Reg. Toxicol. Pharm. 8:389-398.

WATANABE, P.G., A.M. SCHUMANN, and R.H. REITZ. 1988. Toxicokinetics in the evaluation of toxicity data. Reg. Toxicol. Pharm. 8:408—413.

WILKINSON, C.F. 1987. Being more realistic about chemical carcinogenesis. Environ. Sci. Technol. 21(9):843-847.

WILLIAMS, G.M., and J.H. WEISBURGER. 1992. Chemical carcinogenesis. Chapter 5 in M.O. Amdur, J. Doull, and C.D. Klaassen (eds.), Casarett and Doull's Toxicology: The Basic Science of Poisons (Fourth edition). New York: Pergamon Press.

WILSON, J.D. 1989. Assessment of low-exposure risk from carcinogens: Implications of the Knudson-Moolgavkar two-critical mutation theory. In Biologically Based Models for Cancer Risk Assessment. New York: Pergamon Press.

5
FLUORIDE IN DRINKING WATER

Introduction

Fluoride has been added to drinking water as a public health measure to reduce the incidence of dental caries[1] for more than fifty years. Nevertheless, communities have debated the relative benefits of reduced dental caries and improved oral health versus the potential risks of adverse health effects on teeth and bones. The public health community has long held that the benefits of fluoridation far outweigh any potential risks. Potential long-term health effects, however, are poorly understood.

Recent animal studies indicate equivocal evidence of increased cancer risk associated with fluoridated drinking water. Epidemiologic studies have not established an association between fluoride and bone cancer risk in humans. The major science policy issue considered in this case study is the evaluation of fluoride as to its potential to cause cancer in humans. Two reviews of the available animal and human data were conducted recently by the U.S. Department of Health and Human Services (DHHS) and the National Research Council (NRC). Both of these reviews concluded that there was no evidence that fluoride is a human carcinogen. Based on the conclusions of these reviews, the Environmental Protection Agency (EPA) announced in late 1993 that existing fluoride drinking water standards would remain in place.

Science Policy Issue Addressed in this Case Study
➢ Relevance of carcinogenic responses observed in animals to predicting potential risks in humans.

Fluoride[2] has been routinely added to public drinking water since 1945, when Grand Rapids, Michigan, was the first community to do so.[3] The decision to fluoridate drinking

[1] Dental caries are commonly referred to as cavities.

[2] Fluoride is added to drinking water in the form of sodium fluoride (NaF), hydrofluorosilicic acid (H2SiF6), or sodium silicofluoride (Na_2SiF_6). Most of the fluoride used in drinking water is a byproduct of phosphate fertilizer production (Hileman 1988, 39).

[3] (Hileman 1988, 26)

water continues to be made at the local level.[4] Fluoridation of drinking water enjoys wide support in the United States and has been endorsed by the American Medical Association (AMA), the American Dental Association (ADA), the U.S. Public Health Service (PHS) and every Surgeon General since the early 1950s.[5] Currently, an estimated 50 percent of the U.S. population consumes drinking water that is artificially fluoridated.

Fluoridation of drinking water is currently regarded as the most cost-effective method of reducing dental caries,[6] especially because it can provide the greatest benefit to those least able to afford or seek preventive and restorative dentistry. Furthermore, reduction in dental caries reduces dental disease, tooth loss, time away from work or school, and anesthesia-related risks associated with dental treatment.[7]

In the 1930s, H. Trendley Dean, a dental surgeon with the PHS, demonstrated that the incidence of mottled teeth (**i.e**., dental fluorosis) was increased in communities with higher naturally occurring fluoride concentrations in drinking water.[8] Dental fluorosis, which is caused by excess fluoride reaching developing teeth, is characterized by increased porosity of the tooth enamel that can lead to pitting and staining.[9] Dental fluorosis can range from very mild, which is barely visible, to severe, which features pronounced discoloration and pitting.[10] Although dental fluorosis can be severe, it is generally regarded as a cosmetic rather than adverse health effect.[11] Dean concluded that a fluoride concentration of 1 milligram per liter (mg/L) was the threshold of dental fluorosis, at which 10 to 12 percent of exposed children would exhibit very mild dental fluorosis.[12] Dental fluorosis demonstrates a clear dose-response relationship, with increasing prevalence and severity observed at higher concentrations. Figure 5-1 illustrates the relationship between fluoride concentrations and dental fluorosis.

Dean and his co-workers also discovered that the incidence of dental caries was decreased in communities with higher fluoride concentrations. The incidence of dental caries dropped markedly as fluoride concentrations increased to about 1 mg/L. above 2 mg/L fluoride, further reductions in caries were not observed. Figure 5-1 illustrates the effect of increasing fluoride concentration on the incidence of dental caries.

---

[4] Voter referenda are often used to determine if local water supplies should be fluoridated. Only eight states require fluoridation statewide (Hileman 1988, 29).

[5] (Hileman 1988, 28)

[6] The weighted average annual cost of fluoridation is estimated to be $0.51 per person (Department of Health and Human Services [DHHS] 1991, 35).

[7] (DHHS 1991, ES-3)

[8] (National Research Council (NRC) 1993, 45; DHHS 1991, 50; Hileman 1988, 28)

[9] (NRC 1993, 22)

[10] (NRC 1993, 32-34)

[11] (Environmental Protection Agency [EPA] 1993, 68827)

[12] (NRC 1993, 35)

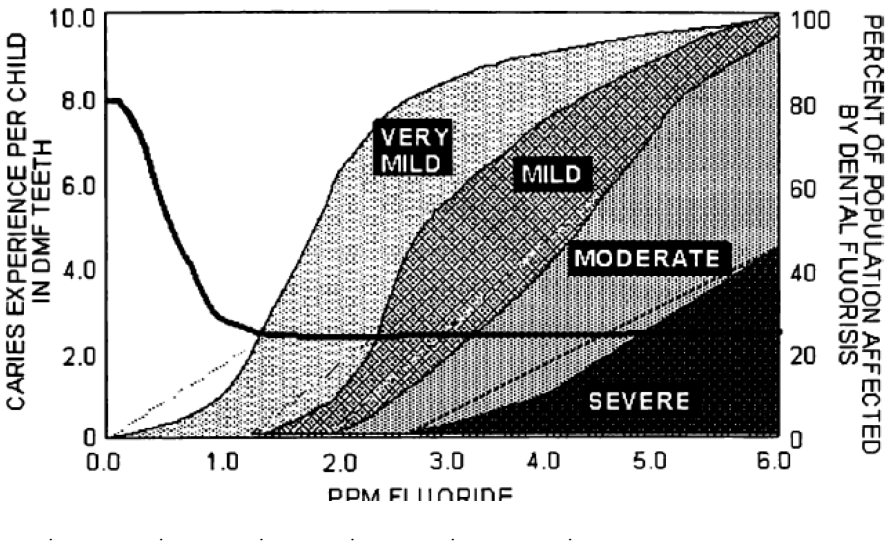

Figure 5-1. Dental canes and dental fluorosis in relation to fluoride in public water supplies. Source: DHHS 1991

Based on the data available to him, Dean suggested that a fluoride concentration of 1 mg/L prevented dental caries and minimized the occurrence of dental fluorosis.[13] In 1943, the PHS identified 1 mg/L fluoride as the optimal level for drinking water fluoridation.[14] Thus, since the beginning, fluoridation of drinking water has been a matter of balancing the benefits of improved dental and oral health versus the potential for discoloration of the teeth.

Fluoride Drinking Water Regulations

In 1962, the PHS established an optimal range of fluoride concentrations in drinking water of 0.7 to 1.2 mg/L, depending on the mean temperature of the locality.[15] The optimal range, based on the pioneering work of Dean, was designed to limit dental fluorosis to no more than 10 percent of the population and to maximize the prevention of dental caries.[16]

In 1975, the Safe Drinking Water Act (SDWA) transferred the responsibility of regulating contaminants in drinking water to EPA. Previously, this function had been performed by the PHS. SDWA requires EPA to establish standards for contaminants in drinking water that may cause adverse effects on the health of persons and that are known or anticipated to occur in public water systems. Fluoridation of drinking water

---

[13] (NRC 1993, 29; DHHS 1991, 50)

[14] (Hileman 1988, 28)

[15] (U.S. Public Health Service [PHS] 1962) The temperature dependence of the recommended optimal fluoride levels reflects a desire to account for increased water consumption in warmer climates. *See* Table 21 (NRC 1993, 30) for an illustration of the temperature dependence of the optimal fluoride concentration.

[16] (NRC 1993, 5)

represents a special case because it is both naturally occurring and is artificially added. Communities with naturally occurring fluoride are required to remove fluoride concentrations in excess of levels established under the SDWA. Communities using artificial fluoridation may not exceed the levels established under the SDWA.

EPA standards for fluoride in drinking water have changed over time. In 1976, EPA established a Maximum Contaminant Level (MCL)[17] for fluoride in drinking water at 1.4 to 2.4 mg/L (*i.e.,* twice the optimal level established by the PHS).[18] In 1985, the Maximum Contaminant Level Goal (MCLG) for fluoride was promulgated at 4 mg/L.[19] The MCLG was established with an adequate margin of safety below the no observed adverse effect level (NOAEL) for crippling skeletal fluorosis of 10 mg/L in humans.[20] In 1986, the MCL for fluoride was also set at 4 mg/L.[21] A secondary MCL (SMCL), which is an unenforceable standard established to improve aesthetic qualities of water and to protect the public welfare,[22] was set at 2 mg/L to protect against objectionable dental fluorosis. The incidence of moderate and severe fluorosis was believed to affect a significant portion of the population at levels above 2 mg/L.[23] Based on the current standards, communities with naturally occurring fluoride are likely to reduce fluoride concentrations to between 2 and 4 mg/L, and communities with artificial fluoridation are unlikely to add fluoride to levels exceeding 2 mg/L. In most cases, communities are likely to try to achieve the optimal fluoride concentration.

Health Concerns Regarding Fluoridation of Drinking Water

Despite the potential for reductions in tooth decay, fluoridation of drinking water has been—and remains—controversial. Perceptions and judgments regarding the fluoridation of public water supplies tend to be strongly polarized. For example, fluoridation has been called "an extremely important public health measure" but has also been criticized because it "amounts to mass medication to control a disease which

---

[17] EPA drinking water standards consists of Maximum Contaminant Levels (MCLs) and Maximum Contaminant Level Goals (MCLGs). MCLGs are set at levels at which no known or anticipated health effects occur and are not legally enforceable. EPA policy is to set MCLGs for known and probable carcinogens at zero. Legally enforceable MCLs are then set as close as feasible to the MCLG. *Feasible* is defined to be the "use of the best technology, treatment techniques, and other means which ... are available (taking cost into consideration)" (EPA 1993, 68826). Thus, MCLGs are based primarily on health effects, whereas MCLs include a consideration of technological feasibility and cost.

[18] (EPA 1985, IX-25)

[19] *See* 50 FR 47142. The MCLG (which at that time was referred to as a Recommended Maximum Contaminant Level, RMCL) was challenged in court by the Natural Resources Defence Council (NRDC), but was upheld by the U.S. Court of Appeals for the D.C. Circuit *in NRDC v. EPA, 812 F.2d 721 (D.C. Cir. 1987) (EPA 1993, 68826).*

[20] (EPA 1985, IX-39). Note that less severe cases of skeletal fluorosis or fluoride-induced changes in bone were not identified by EPA as health effects worth protecting against (Hileman 1988, 38).

[21] See 51 FR 11396.

[22] (EPA 1993, 68826)

[23] (EPA 1985, IX-38)

is neither life threatening nor grossly debilitating."[24] Opponents of fluoridation often stress the ethical issues involved in imposing medication on the public.[25] The controversy continues largely because the evidence regarding the benefits of fluoridation is inconsistent and our understanding of potential long-term health effects is limited.

The role of fluoridated drinking water in reducing dental caries is not well understood. Early studies in the fluoridated communities of Grand Rapids, Michigan; Newburgh, New York; Evanston, Illinois; and Brantford, Ontario, Canada, indicated reductions in dental caries ranging from 50 to 65 percent. Other studies have indicated smaller reductions in the incidence of dental caries. Recent studies show rates of tooth decay to have decreased by about the same amount in fluoridated and unfluoridated communities over the last forty years.[26] Furthermore, the incidence of dental fluorosis is increasing, even in areas where water is not fluoridated.[27] Both the increased incidence of dental fluorosis and reductions in dental caries have been attributed to the greater exposures to fluoride resulting from the availability of fluoride-containing toothpaste and dental products, and to naturally occurring fluoride in foods and beverages. Improved oral hygiene and changes in nutrition have also been cited as contributors to the observed reduction in tooth decay.[28] Changes in fluoride exposure patterns suggest that drinking water is not the primary source of fluoride for most people today.

Exposure to high levels of fluoride is associated with a variety of health effects in humans, including skeletal fluorosis and an increased risk of bone fractures. Skeletal fluorosis, which is caused by the accumulation of too much fluoride in the bones, results in biochemical changes in blood and bone tissues and may result in chronic pain in the bones and joints.[29] The more severe form, crippling skeletal fluorosis, has been observed only in individuals who consumed from 15 to 20 mg of fluoride per day in drinking water for ten to twenty years. Crippling skeletal fluorosis is rare, with only five reported cases in the last thirty years in the United States.[30] The relationship between fluoride and increased risk of bone fracture has been explored in several epidemiologic studies, but only two included information on individual exposures. One found no association, but the other found an increased risk of hip fracture at fluoride concentrations of 4 mg/L.[31] Additional health effects in animals that may be related to

[24] (Bell 1992, 21)

[25] (Hileman 1988, 27)

[26] (Hileman 1988, 29-30)

[27] (NRC 1993, 45—48)

[28] (Hileman 1988, 31)

[29] (Hileman 1988, 34)

[30] (NRC 1993, 59-60)

[31] (NRC 1993, 61)

fluoride exposure include reproductive effects, kidney disease, hypersensitivity reactions, and cancer. Of these, only hypersensitivity is well understood in humans.[32]

Several organizations [33]submitted comments critical of EPA's recent decision not to revise the MCLG for fluoride. Most of the commenters asserted that the public health dangers of fluoride have been downplayed or ignored and that the benefits have been overstated or are unproven. Several objected to the involuntary nature of fluoridation. Many commenters pointed to Europe and Japan, where fluoridation has largely been discontinued. For example, the Netherlands no longer fluoridates drinking water due to legal concerns about the government's right to add a medicine to the water supply, West Germany discontinued fluoridation due to concerns about legality and potential long-term health impacts, and France and Denmark do not allow fluoridation because long-term health effects are not well understood.[34]

Evaluation of the Carcinogenicity of Fluoride

The potential for fluoride to cause cancer and other health effects in humans has been explored in a number of epidemiologic studies. A series of ecological [35]studies begun in 1975 purporting to associate fluoridated drinking water with increased cancer in humans further sparked the controversy.[36] In addition to the general limitations of ecological studies, these studies were criticized because they did not adjust adequately for differences in age, race, and sex of the compared populations.[37] These studies are therefore not currently considered to constitute evidence of an association between fluoride and cancer risk.[38] Other epidemiologic studies conducted at this time did not associate an excess cancer risk with consumption of fluoridated drinking water.[39]

---

[32] See (NRC 1993, 73-90).

[33] Organizations submitting comments included the Pure Water Committee of Cumberland, Inc. (Frostburg, Maryland), Safe Water Coalition of Washington State (Anacortes, Washington), New York State Coalition Opposed to Fluoridation, Inc. (Old Bethpage, New York), Grassroots Fluoride Alert (Tacoma, Washington), Citizens for Better Health (Portland, Oregon) and Safe Water Association, Inc. (Fond du Lac, Wisconsin). Comments are available for public inspection in the Docket for Phase IIA-D, Fluoride at the EPA Water Docket, Washington, D.C.

[34] (Hileman 1988, 28)

[35] Ecological studies explore associations between occupation or environment and disease by focusing on the group—rather than the individual—as the unit of comparison. Disease rates among various groups, generally defined by geographic location, are compared. Ecological studies are "hypothesis-generating," but cannot test hypotheses (e.g., is lung cancer associated with elevated indoor radon levels?). Ecological studies are also subject to the "ecological fallacy," which limits the applicability of group risk estimates to individual risks (Mausner and Kramer 1985, 304-305).

[36] *See* (Yiamouyiannis and Burk 1977).

[37] (NRC 1993, 110) See also Chapter 12, "Workplace Indoor Air Quality" for a discussion of the interpretation of epidemiologic studies.

[38] See (DHHS 1991, 76-78) for additional discussion of the problems associated with the Yiamouyiannis and Burk studies.

[39] (Hileman 1988, 42)

Over time, numerous epidemiologic studies have been performed to examine the relationship between fluoridation and adverse health effects. Two reviews[40] of the available epidemiologic studies were conducted in the early 1980s. In its review, the International Agency for Research on Cancer (IARC) concluded:

> *Variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans.*[41]

The Knox report concluded that there is "no reliable evidence of any hazard to man in respect to cancer."[42] Two recent reviews[43] support the earlier conclusion that the available epidemiologic studies "provide no credible evidence for an association between fluoride in drinking water and risk of cancer."[44] The NRC has suggested that, if any risk exists, it would be more likely to be identified with case-control and cohort studies, [45]which are based on individual outcome and exposure information, rather than with ecological studies, which are limited in explanatory power. The NRC recommended that case-control and cohort studies be conducted in order to better determine if cancer risks exist.[46]

Fluoride has been studied to determine if it is carcinogenic in animals. In 1990, a National Toxicology Program (NTP) bioassay[47] showed "equivocal"[48] evidence of carcinogenicity in male rats—but not in mice or female rats[49]—consuming fluoridated drinking water. The Procter & Gamble Company published results of a fluoride bioassay in 1990 which concluded that sodium fluoride is not carcinogenic in male or female Sprague-Dawley rats—even at doses higher than those used in the NTP study.[50]

---

[40] (International Agency for Research on Cancer (IARC) 1982; Knox 1985)

[41] (NRC 1993, 110)

[42] (NRC 1993, 110)

[43] (NRC 1993; DHHS 1991)

[44] (NRC 1993, 113)

[45] *Case-control studies* are retrospective in nature because they rely on identification of people who are already diseased. In a case-control study, people with a disease (cases) are compared with people who are not diseased (controls) to determine if the portion of people exposed to a particular substance or factor differs between groups. Cohort studies are prospective in nature. A group of people (cohort) who are free of disease and who have differing exposures to a factor or substance is followed over time to determine if differences in exposures result in different rates of disease (Mausner and Kramer 1985, 156-157). Case-control and cohort studies rely on individual outcomes whereas ecological studies focus on disease rates at the population level.

[46] (NRC 1993, 122-123)

[47] (National Toxicology Program (NTP) 1990)

[48] The meaning and interpretation of equivocal is further discussed below.

[49] NTP bioassays typically use both sexes of mice and rats, resulting in a total of four species/sex groups per bioassay.

[50] (EPA 1993, 68827)

Whether to characterize fluoride as a human carcinogen involves evaluating the available animal and human data in an effort to predict whether it is likely to cause cancer in humans. Classification systems, such as those established by EPA, IARC, and NTP, have been developed to guide risk assessors in classifying chemicals as to their potential human carcinogenicity. These classification systems constitute a series of science policy decisions and assumptions in that they are designed to overcome the lack of understanding and knowledge concerning the relevance of carcinogenic effects seen in animals to those likely to be observed in humans. As discussed below, a judgment was required regarding the relevance to humans of equivocal evidence of carcinogenicity in rats that ingested fluoride.

- **Science policy issue.** Does an equivocal carcinogenic response to fluoride exposure in one species/sex group in an animal bioassay indicate potential cancer risk in humans?
- **Science policy decision.** Equivocal evidence of carcinogenicity in animals, in the absence of supporting epidemiologic data, does not indicate a potential cancer risk in humans.

The DHHS[51] and the NRC[52] conducted reviews of the available data concerning the potential carcinogenicity of fluoride. Results from six animal bioassays were evaluated, including the 1990 NTP bioassay, the 1990 Procter & Gamble bioassay, and four earlier bioassays.[53] Both of these reviews sought to answer the same science policy question: In light of the database concerning potential health effects of fluoride, what is the likelihood that fluoride is a human carcinogen?

In the 1990 NTP bioassay, rats were administered drinking water containing up to 175 mg/L[54] sodium fluoride. The incidence of osteosarcomas in rats from the bioassay is summarized in Table 5-1. No evidence of carcinogenicity was found in female rats or mice. Osteosarcomas were observed in four of the male rats—one at 100 mg/L and three at 175 mg/L. The observed responses were judged as equivocal evidence of carcinogenicity for fluoride in male rats only. The observed response in male rats was considered equivocal because the increased incidence of osteosarcomas in the highest-dose group was not statistically significantly different from the zero-dose group, but the

[51] , (DHHS 1991)

[52] (NRC 1993) In addition to carcinogenicity, the NRC reviewed available data on the following health effects: dental fluorosis; risk of bone fracture; reproductive effects; renal, gastrointestinal and immune system effects; genotoxicity; and intake, metabolism and disposition of fluoride.

[53] None of these four earlier animal studies indicated an association between fluoride and cancer, but they were dismissed from the reviews because of deficiencies in design or documentation of results. See (NRC 1993, 113).

[54] The maximum dose of 175 mg/L was set lower than the 300 mg/L used in six-month studies, in which notably lower weight gain was observed at this dose, and higher than the maximum level used in previous two-year studies (100 mg/L) because it was determined that rats could tolerate higher doses (NTP 1990, 36).

trend in response to increased dose was significant.[55] The significant dose-response trend in combination with an insignificant increase in tumor incidence led "to the conclusion that a weak association may exist between the occurrence of [osteosarcomas] and the administration of sodium fluoride."[56] "Equivocal" is applied to uncertain findings and is used by NTP to describe studies that are interpreted as showing a marginal increase of cancer that may be related to the administered substance.[57]

Table 5-1. Incidence of Osteosarcomas in Rats Exposed to Sodium Fluoride in Drinking Water[58]

Rats	Concentration (mg/L)	Number of Animals	Number of Osteosarcomas
Males	0	80	0
	25	51	0
	100	50	1
	175	80	3
Females	0	80	0
	25	50	0
	100	50	0
	175	81	0

When classifying chemicals as to their potential carcinogenicity in humans, NTP relies on criteria originally developed by IARC. These criteria are in effect decision rules based on science policy decisions. For example, using these criteria, animal bioassay data will be judged to constitute "sufficient evidence of carcinogenicity" if they indicate:

> *... that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments... or (c) to an*

[55] (NTP 1990, 42; NRC 1993, 116-117)

[56] (NTP 1990, 6)

[57] (DHHS 1991, 76)

[58] Derived from Table 9 (NTP 1990, 45).

> *unusual degree with regard to incidence, site or type of tumor, or age at onset.*[59]

Compounds for which sufficient evidence of carcinogenicity in animals exists are then assumed to be human carcinogens. Clearly, the NTP bioassay results—which consist of negative evidence in three species/sex groups and equivocal evidence in one species/sex group—do not constitute sufficient evidence of carcinogenicity in animals by the criteria above.

The weight of the evidence concerning the carcinogenicity of fluoride in animals was reviewed, evaluated, and summarized by the NRC subcommittee:[60]

- Four early studies failed to demonstrate an association between fluoride and osteosarcoma in laboratory animals.
- The 1990 NTP bioassay reported equivocal evidence of carcinogenicity in male rats only (No evidence was found in mice or female rats).
- No osteosarcomas were observed in rats or mice in the Procter & Gamble studies at doses two to three times greater than the maximum dose in the NTP bioassay.
- The osteomas observed in mice in the Procter & Gamble mice study were judged to be of no relevance to humans because the study was contaminated by a retrovirus, the lesions were benign, and there is no human counterpart to the mouse osteoma.

The NRC subcommittee concluded that "the available laboratory data are insufficient to demonstrate a carcinogenic effect of fluoride in animals" and "the weight of the evidence from the epidemiological studies completed to date does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans."[61] The DHHS review had previously concluded that "[tjaken together, the data available at this time from these two animal studies fail to establish an association between fluoride and cancer" and that "optimal fluoridation of drinking water does not pose a detectable cancer risk in humans...."[62]

The conclusion that fluoride is not a human carcinogen appears to be reasonable and prudent given that the preponderance of epidemiologic data do not indicate a carcinogenic risk associated with ingestion of fluoride in drinking water and that only one animal species/sex group showed any evidence of carcinogenicity. EPA has not classified fluoride as to its potential carcinogenicity, [63]but were it to do so, the available

---

[59] (NTP 1991, vii)

[60] (NRC 1993, 113-121)

[61] (NRC 1993, 11)

[62] (DHHS 1991, ES-6) The studies referred to are the NTP and Procter & Gamble studies mentioned above.

[63] (Integrated Risk Information System [IRIS] 1994a)

data would most likely support classification of fluoride as a Group D carcinogen (i. e., not classifiable as to human carcinogenicity).[64]

A classification of fluoride as a possible or probable carcinogen on the basis of the available data by EPA would have been precedent setting. Under current EPA guidelines, equivocal evidence of carcinogenicity in one species/sex group is insufficient to classify a chemical as to its potential carcinogenicity in humans.[65] For comparison, of the 415 chemical substances evaluated in published NTP bioassays, approximately twenty-four were shown to have equivocal evidence of carcinogenicity in one species/sex group and negative evidence in the other three.[66] Of these twenty-four, six[67] are included in EPA's Integrated Risk Information System (IRIS).[68] None of these six compounds has been classified by EPA as to its potential human carcinogenicity. Carcinogenicity evaluations for styrene, picloram, and rotenone are pending. EPA notes that a pending evaluation, however, does not imply that the compound in question is necessarily thought to be a carcinogen.[69]

On December 29, 1993, EPA announced a decision not to revise the existing MCLG for fluoride in drinking water.[70] EPA based its decision partly on the findings of the 1991 DHHS report and mostly on those of the 1993 NRC report. EPA stated that it had "no evidence suggesting that the MCLG does not protect against adverse health effects with an adequate margin of safety...." and therefore concluded that the NRC report "support[s] a decision not to revise the current MCLG for fluoride at this time."[71]

The overall conclusion offered by the NRC subcommittee, with which EPA concurred, was stated as follows:

Based on its review of available data on the toxicity of fluoride, the subcommittee concludes that EPA's current MCL of 4 mg/L for fluoride in drinking water is

---

[64] See (EPA 1986, 33999-34000).

[65] (EPA 1986, 33999-34000)

[66] (National Institute of Environmental Health Sciences (NIEHS) 1993) The twenty-three compounds with equivocal findings in one species/sex group and negative findings in three species/sex groups are: acetaminophen, ampicillin trihydrate, p-anisidine, aspirin/phenacetin/caffeine (mixture), azinophosmethyl, gamma-butyrolactone, 2-chloroacetophenone, C.I. pigment red 23, dimethoxane, dimethyl terephthalate, 2,5-dithiobiurea, p,p -ethyl-DDD, fenthion, fluometuron, fluoride, 4-hexylresorcinol, hydrochlorothiazide, alpha-methyldopa sesquihydrate, 3-nitropropionic acid, rt-phenyl-2-naphthylamine, picloram, rotenone, roxarsone, and styrene.

[67] The six compounds are: 2-chloroacetophenone, dimethyl terephthalate, fluometuron, picloram, rotenone, and styrene.

[68] IRIS was developed by EPA staff in order to achieve consistency in risk information used in regulatory decision making. Individual chemical profiles in IRIS represent EPA consensus positions on chronic health effects. IRIS contains information on approximately 500 chemicals. Absence of a chemical from IRIS does not indicate that the chemical may not be hazardous to health and the environment.

[69] (IRIS 1994b)

[70] (EPA 1993, 68826-68827)

[71] (EPA 1993, 68827)

appropriate as an interim standard.... The subcommittee further recommends that EPA's interim standard of 4 mg/L should be reviewed when results of new research become available and, if necessary, revised accordingly.[72]

Consequently, EPA opted not to revise the MCLG for fluoride, allowing it to remain at 4 mg/L.

Evaluation

The issue of drinking water fluoridation is complicated because:

- Fluoridation at optimal levels has both demonstrable and recognized benefits (reduction in dental caries) and risks (dental fluorosis).
- Other potential human health risks at optimal fluoridation levels are not well defined and may be nonexistent.
- Fluoridation is not voluntary, but is imposed by a local government.
- Artificial fluoridation is intentional.
- Fluoridation, although cost-effective, may become obsolete as other exposures to fluoride sources increase.

Thus, the need to maximize protection against dental caries and minimize potential cosmetic and adverse health effects is central to any regulatory approach to fluoride in drinking water. Science alone cannot determine how or at what level drinking water should be fluoridated.

> *The decision to fluoridate a community's water or not boils down to a matter of values. Scientific evidence can make the choice more clearcut, more rational, but the choice can't be made purely on the basis of scientific evidence. So long as there is uncertainty about risk from fluoridation, some people will not want to accept that risk. And others who favor fluoridation will demand proof of harm beyond a reasonable doubt before they reject it.*[73]

EPA recently faced the decision of whether to revise its regulatory standards for fluoride in drinking water. The resolution of the question turned on the science policy decision that the evidence of carcinogenicity in animals was insufficient to warrant regulation of fluoride as a possible human carcinogen. Although based in science, determining the relevance of the animal data to humans was a matter of science policy. The equivocal evidence of carcinogenicity in male rats from the NTP bioassay, which was not supported in a subsequent bioassay, was judged to be insufficient to suggest that fluoride is carcinogenic in humans. Neither did the available epidemiologic data

[72] (NRC 1993, 11)

[73] (Hileman 1988, 42)

suggest an association between fluoride and cancer in humans, lending further support to the conclusion that fluoride is not carcinogenic in humans.

Given the vast and proven benefits of fluoridation and the ease with which cosmetic and potentially adverse effects can be minimized or avoided, it would have been imprudent of the EPA, PHS, NTP, and other agencies to suggest a change in the regulation of fluoride in drinking water on the basis of unsupported and inconclusive evidence of carcinogenicity in male rats. Another motivation behind the decision not to change the MCLG might have been fear of the tumult that would have ensued in the public health community and in the public at large if fluoride were judged to be carcinogenic. Classification of fluoride as a possible human carcinogen could have critically damaged the credibility of the PHS, which has aggressively promoted fluoridation for fifty years.

REFERENCES

BELL, R. 1992. Some just don't like drinking arsenic—Calgary's water fluoridation fight isn't over yet. Alberta Report (February 17): 18-21.

DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS). 1991. Review of Fluoride Benefits and Risks—Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993. Drinking water maximum contaminant level goal; Fluoride. Fed. Reg. 58(248):68826-68827.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985. Drinking Water Criteria Document on Fluoride, TR-832-5. Office of Drinking Water, Washington, D.C.

HILEMAN, B. 1988. Fluoridation of water. Chem. Eng. News (August 1, 1988):26-42.

INTEGRATED RISK INFORMATION SYSTEM (IRIS). 1994a. Chemical Profile: Fluoride (soluble fluoride). Environmental Criteria and Assessment Office, Environmental Protection Agency, Cincinnati, Ohio.

INTEGRATED RISK INFORMATION SYSTEM (IRIS). 1994b. Chemical Profiles: 2-Chloroacetophenone, Dimethyl Terephthalate, Fluometuron, Picloram, Rotenone, and Styrene. Environmental Criteria and Assessment Office, Environmental Protection Agency, Cincinnati, Ohio.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 1982. Inorganic fluorides. In IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-Water and Dental Preparations (Volume 27). Lyon, France, 235-303.

KNOX, E.G., Chair. 1985. Fluoridation of Water and Cancer: A Review of the Epidemiological Evidence. Report of the Working Party, Department of Health and Social Security. London, England: Her Majesty's Stationery Office.

MAUSNER, J.S., and S. KRAMER. 1985. Epidemiology—An Introductory Text. Philadelphia, Penn.: W.B. Saunders Company.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS). 1993. Compendium of abstracts from long-term cancer studies reported by the National Toxicology Program from 1976 to 1992. Environ. Health Persp. 101(Suppl. 1).

NATIONAL RESEARCH COUNCIL (NRC). 1993. Health Effects of Ingested Fluoride. Washington, D.C.: National Academy Press.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1991. Sixth Annual Report on Carcinogens. National Institute of Environmental Health Sciences, Research Triangle Park, N.C. PB92-120666.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1990. Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3F, Mice, Technical Report Series No. 393. National Institute of Environmental Health Sciences, Research Triangle Park, N.C. NIH Publication No. 91-2848.

U.S. PUBLIC HEALTH SERVICE (PHS). 1962. Public Health Service Drinking Water Standards, Revised 1962. PHS Publ. No. 956. U.S. Government Printing Office, Washington, D.C.

YIAMOUYIANNIS, J., and D. BURK. 1977. Fluoridation and cancer: Age dependence of cancer mortality related to artificial fluoridation. Fluoride 10:102-125.

6
ASBESTOS IN CONSUMER PRODUCTS

Introduction

Because of its durability and heat-resistant properties, asbestos has been used in a variety of economically important products since the late nineteenth century. Concern about asbestosis and lung cancer associated with asbestos exposure emerged and has grown throughout the twentieth century. Asbestos is regarded by the Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC) as a known human carcinogen. New uses of asbestos have been banned in the United States since the 1980s. EPA has devoted considerable effort and resources to removing asbestos from public buildings, especially schools.

EPA initiated a rulemaking in 1979 to ban the manufacture, importation, processing, and distribution of existing consumer products containing asbestos in response to growing concerns about adverse health effects associated with asbestos. The ban was not finalized until 1989. The ban was remanded by the U.S. Court of Appeals for the Fifth Circuit in 1991 because EPA did not sufficiently justify the ban and did not fulfill the requirements of the Toxic Substances Control Act (TSCA). The main science policy issues supporting the court's decision were EPA's inadequate consideration of risks to health and safety posed by potential asbestos substitute products and EPA's use of analogous exposure estimates to assess benefits of the ban without providing for public review and comment. EPA has yet to take further action on the remanded rule.

Science Policy Issues Addressed in This Case Study
➢ Use of "analogous" exposure estimates ➢ Consideration of substitution risks

Uses of Asbestos

Asbestos is the general name applied to a group of naturally occurring fibrous silicate minerals.[1] Asbestos is useful in construction and industry because its fibers are heat-

[1] (Meek, Shannon, and Toft 1985, 122). The six minerals collectively called asbestos are chrysotile, crocidolite, amosite, tremolite, anthophyllite, and actinolite.

resistant and durable.[2] The modem asbestos industry dates from 1870, when asbestos was first used in building materials. The twentieth century brought asbestos textiles, asbestos/cement pipe, and asbestos in brake linings.[3] Eventually, asbestos was used in more than 5,000 products, including roofing, thermal and electrical insulation, cement pipe and sheet, flooring, gaskets, friction materials, coatings, plastics, textiles, and paper products.[4] Production and use of asbestos increased until the mid-1970s, when economic recession and concerns about health effects led to decreased demand.[5] Annual U.S. production of asbestos peaked at about 300 million pounds per year, but by 1989 annual production had fallen to 37 million pounds.[6]

Health Concerns Associated With Asbestos

Pliny the Elder noted diseases of the lung in slaves working with asbestos in the first century, but asbestos exposure was not generally associated with disease until 1906. Two studies in 1935 reported lung cancer in asbestos workers who had died of asbestosis, suggesting a link between asbestos and cancer.[7] Scientific consensus linking asbestos to lung cancer and mesothelioma[8] was finally achieved in the United States in 1964 at a conference sponsored by the New York Academy of Sciences.[9] Classification of asbestos as a human carcinogen is based on epidemiologic studies of highly exposed workers.[10] EPA, IARC, and the Department of Health and Human Services (DHHS) have all concluded that asbestos is a known human carcinogen.[11] Asbestos is currently regulated as a carcinogen under several statutes, including the Clean Air Act (CAA), Clean Water Act (CWA), Superfund (CERCLA), Federal Food, Drug and Cosmetic Act (FFDCA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and TSCA.[12]

When inhaled, all types of asbestos have been found to cause lung cancer in occupational studies. After a latency period of ten to thirty years, lung cancer risk

---

[2] Environmental Protection Agency [EPA] 1986a, 2)

[3] (Meek, Shannon, and Toft 1985, 122)

[4] (National Toxicology Program (NTP) 1991, 48-49)

[5] (Meek, Shannon, and Toft 1985, 122)

[6] (Agency for Toxic Substances and Disease Registry [ATSDR] 1993)

[7] (Meek, Shannon, and Toft 1985, 123) Asbestosis is a slow buildup of scar-like tissue in the lungs and surrounding membranes that makes breathing increasingly difficult and may ultimately lead to death.

[8] Mesothelioma is a cancer of the thin membranes surrounding the lungs and other internal organs.

[9] (Enterline 1991, 693)

[10] (ATSDR 1993, 21-23)

[11](ATSDR 1993, 4)

[12] (NTP 1991, 51)

increases proportionately with cumulative asbestos exposure.[13] Risk of mesothelioma has been found to depend primarily on latency period and increases with the third power of time (time3) after a period of ten years.[14] Although the reported risk is quite small, mesothelioma has been observed in people living near asbestos factories and in people living with asbestos workers.[15] Small increased risks of gastrointestinal cancers have also been reported in some studies of asbestos workers, and death rates increase linearly with cumulative inhalation exposure.[16] Ingestion of asbestos has been linked, although not conclusively, with increased incidence of gastrointestinal cancers.[17]

Ban on Asbestos-Containing Consumer Products

EPA promulgated a rule to prohibit the manufacture, importation, processing, and distribution in commerce of a variety of existing consumer products containing asbestos on July 12, 1989.[18] The promulgation followed publication of an advance notice of proposed rulemaking by nearly ten years.[19] The proposed rule was published on January 29, 1986.[20]

EPA promulgated the asbestos ban under the authority of TSCA. Section 6(a) of TSCA authorizes EPA to impose restrictions, including labeling requirements, limitations, and bans, on "activities involving a chemical substance or mixture if EPA finds that there is a reasonable basis to conclude that the manufacture, processing, distribution in commerce, use, or disposal of the chemical substance, or any combination of such activities, presents or will present an unreasonable risk of injury to human health or the environment."[21] Under this authority, EPA concluded that exposure to asbestos poses an "unreasonable risk to human health and the environment"[22] and initiated the rulemaking process.

Following are categories of asbestos-containing consumer products included in the ban: asbestos/cement (A/C) sheet, A/C shingles, A/C pipe, asbestos protective clothing and

---

[13] (ATSDR 1993, 21-22) Cumulative exposures to asbestos are expressed in terms of f yr/MI, which is the product of exposure concentration, measured as the number of fibers in a milliliter of air (f/mL), and the number of years exposed. For example, five years of exposure to asbestos at a level of 0.05 f/mL results in a cumulative exposure of 0.25 f yr/mL.

[14] (ATSDR 1993, 23)

[15] (NTP 1991, 47; Meek, Shannon, and Toft 1985, 123-124) Only thirty-seven cases of mesothelioma in nine countries attributed to household exposure had been reported by 1976, but one study found the relative risk of mesothelioma from having an asbestos worker in the house to be ten.

[16] (ATSDR 1993, 23)

[17] (ATSDR 1993, 29-32)

[18] (EPA 1989)

[19] See 44 FR 60061.

[20] See 51 FR 3738.

[21] (EPA 1989, 29460)

[22] (EPA 1989, 29460)

vinyl/asbestos floor tile, paper products, felt products, gaskets, disc and drum brake pads for original equipment market (OEM) and brake blocks, aftermarket (AM) disc and brake pads, other asbestos friction products, and coatings.[23] The ban featured a three-phase schedule, with different requirements for various product categories.[24] The ban was estimated to eliminate 94 percent of U.S. asbestos consumption, based on 1985 consumption levels.[25]

Benefits of the Ban

EPA justified the ban on the basis of a cost-benefit analysis. EPA estimated that the ban would avert 148 to 202 cancer cases[26] at a total cost of $458.89 to $806.51 million over thirteen years.[27] Most of the averted cancer cases were expected to result from the bans on OEM and AM vehicle brake products, while most of the costs were associated with the bans on A/C pipe and gaskets.[28] The estimated benefits associated with the ban included averted mesothelioma and lung and gastrointestinal cancers, but did not include averted cases of asbestosis and other diseases or the avoided costs of treating asbestos diseases, lost productivity, *etc*[29] EPA overestimated costs and underestimated benefits to "ensure that the analysis provides a strong basis for the regulatory decision made in this rule." [30]

A number of science policy decisions were required in assessing the risk reductions, or benefits, anticipated from the ban. Chief among these are the assumption of low-dose

---

[23] EPA granted petitions requesting the prohibition of asbestos in A/C pipe in 1979 (44 FR 60155) and motor vehicle brakes in 1984 (49 FR 49311) and decided to address these two categories as part of the final rulemaking. The Natural Resources Defense Council (NRDC) filed the petition regarding the use of asbestos in brakes. In granting the NRDC petition, EPA noted that an estimated 2,750 people were exposed during brake manufacture as well as 550,000 during servicing and repair. Asbestos from vehicle brakes was thought to increase ambient concentrations. The agency noted that substitutes for asbestos brake products were potentially more costly, not proven, and given to erratic behavior.

[24] (EPA 1989, 29461-29463). The manufacture, import, and processing ban schedule was published as follows: Stage 1—8/27/90, Stage 2—8/25/93, and Stage 3—8/26/96. The distribution in commerce ban schedule was published as follows: Stage 1—8/28/92, Stage 2—8/25/94, and Stage 3—8/25/97. See (EPA 1989, 29462-29463) for the products included in each stage.

[25] (EPA 1989, 29468)

[26] The lower end of the range of averted cancer cases assumes discounting of benefits at 3 percent. The range associated with the final ban is reduced to 120-164 if analogous exposures are not included (EPA 1989, 29468) (see discussion in text). In contrast, the proposed rule had claimed that 1,000 cancers would be averted. The final rule was lowered because of use of updated exposure data, modifications of the risk estimates for gastrointestinal cancer and mesothelioma, and omission of averted cancers associated with products no longer manufactured in the United States (EPA 1989, 29486).

[27] (EPA 1989, 29468) The high cost estimate assumes that substitute costs will not decline, whereas the low estimate assumes a 1 percent annual decline in the prices of substitutes. EPA believed that the ban would encourage the development of substitutes and result in decreased costs (EPA 1989, 29481).

[28] (EPA 1989, 29484-29485**)**

[29] (EPA 1989, 29468)

[30] (EPA 1989, 29484)

linearity for the carcinogenic effects of asbestos, extrapolation of gastrointestinal cancer risks, and the use of "best" estimates to calculate averted cancer cases. Because the benefits estimated to result from the ban are based on assumptions, the degree of conservatism in the assumptions determines the magnitude of the estimated benefits. In other words, conservative science policy assumptions will result in greater estimates of risk reduction associated with the ban, whereas less conservative assumptions will result in lower estimates. Thus, use of conservative assumptions would tend to magnify the anticipated benefits resulting from a ban on asbestos.

In order to extrapolate risks observed in highly exposed asbestos workers to those workers exposed at lower levels, EPA concluded that "[a]sbestos exposure is compatible with a linear, no-threshold dose-response model for lung cancer."[31] EPA used the relative risk model, which assumes a linear increase with cumulative exposure, to calculate risks of lung cancer associated with inhalation of asbestos.[32] Risk of mesothelioma was estimated using a model that assumes linearity with respect to exposure level and a third-power dependence on latency period and duration of exposure.[33] These two risk estimates were combined, resulting in a lifetime risk of lxlO^{-4} (1 in 10,000) at a concentration of 0.0004 f/mL asbestos.[34]

The assumption of linearity at low doses is supported by approximate linear relationships in the observable response range and is necessitated by the limited sensitivity of the available epidemiologic studies, which cannot detect low-level risks.[35] However, it has been suggested that asbestos may be a threshold carcinogen because it is not genotoxic.[36] Genotoxic compounds, because of their direct action on DNA, are thought to induce cancer at any dose, whereas nongenotoxic compounds might act

---

[31] (EPA 1989, 29467)

[32] The relative risk model used to estimate risk of lung cancer resulting from exposure to asbestos is given by the equation: Relative Risk = 1.00 + KL * (cumulative dose) where KL is the fractional increase in relative risk of lung cancer per f-yr/mL. Estimates of KL range from 0.0006 to 0.067 (f-yr/mL) - 1, with a geometric mean of 0.010 (f yr/mL) - 1 when studies involving mining and milling workers were excluded (ATSDR 1993, Dl).

[33] (ATSDR 1993, D l—D-3). The available exposure-incidence data for mesothelioma were fit to the following equation:

Incidence = KM * f * [(T - 10)3 - (T - 10 - d) [3]]

where:

K_m = empirical constant

f = intensity of exposure (f/mL)

T = latency (years since first exposure) d = duration of exposure (years)

Estimates for KM ranged from 1x10^{-8} to 3x10^{-8}, with lxlO^{-8} chosen as the most reasonable value.

[34] (Integrated Risk Information System (IRIS) 1993)

[35] (Davis and McDonald 1988, 506)

[36] (Gots 1993, 211)

through threshold mechanisms.[37] It cannot be proven that asbestos is not carcinogenic at low doses, but neither is the assumption of linearity at low doses proven.

Due to the uncertainty in extrapolation to low doses, it is considered prudent to calculate an upper-bound estimate of the risk, especially when animal bioassay data are used. However, when epidemiologic data are available, EPA tends to calculate a "best" estimate of risk. The EPA carcinogenic potency estimate for asbestos is the geometric mean of the best estimates obtained from several epidemiologic studies. Had EPA used upper-bound estimates, predicted lung cancer risks would have increased ten-fold, and deaths from mesothelioma would have increased twenty-fold.[38] Upper-bound risk estimates would have tremendously increased the apparent benefits of the ban.

Several epidemiologic studies suggest an association between gastrointestinal cancer and occupational exposure to asbestos. However, the magnitude of this risk is lower than that of lung cancer or mesothelioma, and adequate dose-response data in humans are not available.[39] EPA believes that the following evidence supports a strong causal relationship between asbestos exposure and gastrointestinal cancers: [40]

- A statistically significant increase in gastrointestinal cancers is reported in ten of twenty-three epidemiologic studies.
- The magnitude of the observed gastrointestinal cancer risk is about 10 to 30 percent of the observed lung cancer risk.
- Asbestos could be associated with gastrointestinal cancers because most inhaled fibers are cleared from the respiratory tract and subsequently swallowed.[41]
- Supporting evidence of gastrointestinal cancers in male rats fed diets containing intermediate size chrysotile asbestos has been reported.[42]

Following the approach originally adopted by the Occupational Safety and Health Administration (OSHA), EPA assumed that incidence of gastrointestinal cancers would equal 10 percent of that for lung cancer. EPA believes this assumption underestimates

---

[37] *See* Section VIII in Chapter 4.

[38] (EPA 1989, 29467). These calculations were taken from (EPA 1986a). See also the discussion of quantitative risk assessment in the rule (EPA 1989, 29471-29472).

[39] (EPA 1989, 29469)

[40] (EPA 1989, 29469)

[41] "[A]ny effect of asbestos on the gastrointestinal tract after inhalation exposure is most likely the result of mucociliary transport of fibers from the lung to the stomach" (ATSDR 1993, 29, 36-37).

[42] (NTP 1985) Note, however, that most other studies, including several bioassays performed by NTP have been negative. Also, the tumors observed in male rats in the NTP bioassay were not observed in female rats, nor were any tumors observed in rats fed short-range size chrysotile (ATSDR 1993, 30).

the incidence of gastrointestinal cancers because the data indicate that the gastrointestinal cancer rate could be as high as 30 percent of the lung cancer rate.[43]

Petition Challenging the Ban

A petition for review of the final rule was brought by Corrosion Proof Fittings, Inc., and others before the Fifth Circuit Court of Appeals, challenging that the rulemaking procedure had been flawed and that it was not based on "substantial evidence."[44] On October 18, 1991, the petition was granted, the regulation was vacated, and the matter was remanded to EPA for reconsideration. In its decision, the court concluded that EPA did not consider all necessary evidence or give adequate weight to statutory language requiring it to promulgate the least burdensome, reasonable regulation sufficient to protect the environment adequately.[45]

Several other issues contributed to the court's ultimate judgment to vacate the regulation and remand it to EPA:

- EPA was found not to have accorded petitioners adequate cross-examination during public meetings and hearings and, more important, to have introduced information related to analogous exposure estimates[46] into the final rule without provisions for public comment and questioning.[47]
- EPA was held not to have met the "substantial evidence" standard required under TSCA.48
- EPA did not demonstrate that the ban was the least burdensome method of achieving an acceptable risk level, as is required by TSCA.49
- Without considering health and safety risks associated with use of substitutes, EPA did not demonstrate a reasonable basis for the regulation.[50]

---

[43] (EPA 1989, 29472) citing (EPA 1986b).

[44] Corrosion Proof Fittings v. Environmental Protection Agency, 947 F.2d 1201 (5th Cir. 1991).

[45] (Corrosion Proof Fittings at 1215)

[46] Because some exposures were recognized but unmeasured, EPA developed analogous exposure estimates for occupational exposures associated with the installation, repair, and disposal of certain products on the basis of the limited available data for these products and processes and on the basis of known exposure data for similar products and processes (EPA 1989, 29476).

[47] (Corrosion Proof Fittings at 1211)

[48] (*Corrosion Proof Fittings* at 1213-1214) Note also that "substantial evidence" is a standard for judicial review of the regulation, not of the potential carcinogenicity of exposures to asbestos.

[49] (*Corrosion Proof Fittings* at 1216)

[50] (*Corrosion Proof Fittings* at 1220-1221). "The EPA's explicit failure to consider the toxicity of likely substitutes thus deprives its order of a reasonable basis."

- EPA did not demonstrate that it was taking only those steps necessary to prevent "unreasonable" risks,[51] and EPA did not perform a meaningful economic review of the ban.[52]

Two of these issues—the use of analogous exposure estimates without appropriate public review and comment and EPA's inadequate assessment and consideration of risks to health and safety of substitute products—involve science policy. With respect to exposure, EPA found that data did not exist for some categories of asbestos-containing products. Exposures were not estimated for all product categories, but EPA used an indirect approach to quantify exposures and risks associated with installing and repairing millboard, pipeline wrap, beater-add gaskets, specialty papers, A/C pipe, clutch facings, sheet gaskets, and nonroof coatings.[53]

- **Science policy issue.** Exposure data for certain occupational exposures to asbestos are lacking or inadequate.
- **Science policy decision**. The limited available data can be augmented with or substituted by exposure data pertaining to similar products and processes.

Although exposure data were limited, EPA believed that significant exposures during installation, repair, and disposal of certain asbestos products could occur.[54] EPA used the limited data for these products and processes and exposure data for similar products and processes to estimate analogous exposures. Population estimates were based on production volumes and the person-hours typically required for each activity of concern. The analogous exposure estimates indicate that exposures for some occupational categories may have been underestimated by 21 percent for paper products and 383 percent for gaskets.[55] without analogous exposures, the asbestos ban was estimated to avert from 120 to 168 total cancer cases. When analogous exposures were included, however, the estimated number of avoided cancer cases increased to 148 to 202.[56] Thus, inclusion of the analogous exposures resulted in an approximate 20 percent increase in the net benefits of the ban.

The court did not fault EPA for the methodology and assumptions used in generating the analogous exposure estimates. Rather, the court found that EPA did not provide sufficient notice before the public record was closed and that it relied on analogous exposure estimates to calculate expected benefits. The court stated:

---

[51] (*Corrosion Proof Fittings* at 1222). A determination of what is "unreasonable" requires that EPA consider the environmental, economic, and social impact of proposed actions.

[52] (*Corrosion Proof Fittings* at 1223). To support this point, the court stated that "EPA's willingness to argue that spending $23.7 million to save less than one-third of a life reveals that its economic review of its regulations, as required by TSCA, was meaningless."

[53] (EPA 1989, 29476)

[54] (EPA 1989, 29473). See also (EPA 1985).

[55] (EPA 1989, 29473, 29476, 29485). EPA prepared analogous exposure estimates for the following product categories: A/C pipe, paper products, felt products, gaskets, and coatings.

[56] (EPA 1989, 29468)

> *EPA should not hold critical analysis in reserve and then use it to justify its regulation despite the lack of public comment on the validity of its basis. Failure to seek public comment on such an important part of the EPA's analysis deprived its rule of the substantial evidence required to survive judicial scrutiny....*[57]

The use of analogous exposures in this case is an issue both from a science policy perspective (How can gaps in exposure data be overcome?) and from a rulemaking procedure perspective (Is it appropriate to use a method that has not been subject to public comment and review?).

With respect to substitution risks, a thorough risk analysis in support of a ban should consider the risks of likely substitute products or processes. Banning a certain product or class of products on the basis of health risks is not reasonable if likely substitutes would be associated with even greater health or safety risks. Because limited data made evaluation of substitutes difficult, EPA largely ignored the risks associated with substitute products. An examination of how EPA and the court addressed the issue of substitution risks associated with asbestos brake products is presented below.

- **Science policy issue.** The reduced risks associated with a ban on asbestos-containing products are quantifiable, albeit imperfectly and with limitations, but the health and safety risks of potential substitute products are not well understood and are not readily quantifiable.
- **Science policy decision.** The ban on asbestos-containing products can be justified solely on the basis of the avoided cancer cases that are estimated to result from its implementation.

Asbestos was used in a variety of products at the time the ban was promulgated. Therefore, EPA should consider the risks associated with asbestos-containing products to be a "virtual" background risk. In other words, risks associated with the use of asbestos were necessary and largely unavoidable as long as substitute products did not exist. Net risk reductions associated with the ban should also include an evaluation of the relative costs and risks associated with substitute products.[58] As discussed below,

---

[57] (*Corrosion Proof Fittings* at 1212)

[58] An analogous concept to substitution risk is "lifecycle" risk. For example, in the cleanup of Superfund sites, workers are at risk from construction activities. Additionally, the disposal of any hazardous or radioactive wastes likely also entails some risk. Logically, any regulatory action should be based on a consideration of the risk posed by contamination at the site, as well as the worker and disposal risks associated with cleanup. If the disposal and worker risks are equal to, or greater than the risk posed by the contamination at the site itself, an alternative to removing and disposing of the waste may be desirable. A current example of this issue is the current EPA rulemaking concerning the development of standards for the cleanup of sites contaminated with radionuclides. In the advanced notice of rulemaking for the standards, EPA indicated that the rulemaking would only address the cleanup of radionuclide-contaminated sites and not waste management issues. There was no mention that worker risks would be considered in the cleanup of such sites. *See* (EPA 1993a). Thus, through this rulemaking, site cleanup standards could be developed which, when implemented, will produce no net risk reduction or health benefits.

the court's decision to vacate the ban rested partly on EPA's incomplete assessment of substitution risks.

The court stated that EPA had done the most impressive job in justifying a ban on asbestos in friction products, including vehicle brakes.[59] However, the court could not ignore that:

> *... the EPA failed to study the effect of non-asbestos brakes on automotive safely, despite credible evidence that non-asbestos brakes could increase significantly the number of highway fatalities, and that the EPA failed to evaluate the toxicity of likely brake substitutes. „..[T]he EPA, in its zeal to ban asbestos, cannot overlook, with only cursory study, credible contentions that substitute products actually might increase fatalities.*[60]

The "credible evidence" referred to above is a study by the American Society of Mechanical Engineers (ASME) that was commissioned by the EPA to determine "whether the proposed ban could have adverse effects on vehicle braking safety."[61]

Potential substitutes for asbestos brake products include nonasbestos organic (NAO), resin-bonded metallic (semimetallic), sintered metallic, and carbon-carbon products. Of these, NAO and semimetallic show the most promise for common automotive uses.[62] The ASME study distinguished between OEM and AM brake products. While many new vehicles have been sold with asbestos-free OEM brake systems, little is known about the service performance characteristics of AM brake products.[63] ASME concluded:

> *Despite substantial engineering efforts, non-asbestos replacement friction materials are not available, at a proven quality and performance level that is equivalent to that of the original brake linings, for vehicles which originally were released with asbestos-based brake linings.*[64]

There are no legal standards for AM brake products and aftermarket suppliers generally lack the facilities to conduct safety and performance tests.[65] OEM brakes, however, must meet federal and state safety standards and be completely tested according to the Society of Automotive Engineers' practices.[66] ASME noted that vehicle performance and

---

[59] (*Corrosion Proof Fittings* at 1224)

[60] (*Corrosion Proof Fittings* at 1224)

[61] (EPA 1987, 1). An earlier EPA-commissioned study had concluded that cost-effective substitutes existed for all segments of the brake lining market but failed to address safety and risk issues (EPA 1985).

[62] (EPA 1987, 52)

[63] (EPA 1987, 56)

[64] (EPA 1987, 57)

[65] (EPA 1987, 54, 56)

[66] (EPA 1987, 28)

safety data for nonasbestos AM brake products were not generally available.[67] Limited laboratory data suggested that NAO brake products require greater pedal force to achieve a normal stop than existing asbestos AM brake products.[68] Nonasbestos brake material displayed greater variability in performance than asbestos brakes.[69]

The lack of performance data precluded a quantitative risk comparison between asbestos and nonasbestos AM brake products, but ASME concluded that use of nonasbestos AM brake products "could result in a loss of vehicle controllability during braking" and therefore pose a large potential safety issue."[70] The ASME report concluded that further study would be required if elimination of all asbestos in friction products is to be achieved. The court held that this was insufficient to support EPA's judgment that substitution of nonasbestos brakes would not reduce safety. Thus, the court concluded that not including the ASME study "renders the ban of asbestos friction products unreasonable."[71]

EPA and the court disagreed on the relative risks and benefits of the asbestos ban and substitute products. EPA adopted a "better safe than sorry" stance with respect to eliminating risks due to asbestos exposure. EPA stated that risks associated with all potential substitutes for asbestos could not be estimated. Therefore, EPA concluded that it would be prudent public health policy to regulate asbestos immediately rather than to wait until risks associated with all substitutes could be determined because it appeared that substitutes posed lower health risks.[72] The court, however, did not find this argument persuasive.

The issue of substitute risks in the asbestos ban was not limited to brake products. With respect to the ban as a whole, the court noted two major problems with EPA's approach to substitute risks: [73]

- TSCA requires EPA to consider the relative merits and economic effects of a ban, which it cannot do without considering the effects that substitutes will pose after the ban is implemented.
- EPA's refusal to evaluate potential harm resulting from use of substitutes renders it unable to state with any degree of certainty that the ban will increase workplace safety.

---

[67] (EPA 1987, 56)

[68] (EPA 1987, 67-69)

[69] (EPA 1987, 70-71)

[70] (EPA 1987, 3). In comments to EPA, automobile and truck manufacturers also contended that use of unproven nonasbestos AM brake products could compromise vehicle safety (EPA 1987, 85).

[71] (*Corrosion Proof Fittings* at 1224)

[72] (EPA 1989, 29481)

[73] (Corrosion Proof Fittings at 1221)

The court determined that EPA did not arrive at the correct conclusion regarding substitute risks. EPA was also judged not to have met the requirements of TSCA in demonstrating the existence of an unreasonable risk associated with asbestos products.[74]

Current Status of the Asbestos Ban

EPA believed that the court did not vacate the ban on asbestos-containing products that are not currently produced or imported. EPA filed a motion for clarification with the Fifth Circuit Court to determine the extent of the ruling in *Corrosion Proof Fittings v. EPA.* The court granted EPA's motion and "left intact the portion of the rule that regulates products that were not being manufactured, produced, or imported on July 12, 1989" (the date the ban was promulgated).[75] EPA next solicited information from the regulated community in order to determine which asbestos product categories were no longer being manufactured, processed, or imported as of July 12, 1989. Based on this analysis, EPA concluded that the following asbestos-containing product categories remained subject to the ban: corrugated paper, rollboard, commercial paper, specialty paper, flooring felt, and new uses of asbestos.[76] Other uses of asbestos are not covered by the ban.

Evaluation

The asbestos ban was vacated by the U.S. Court of Appeals primarily on procedural and legal grounds. The court ruled that EPA did not fulfill the TSCA requirement to achieve risk reduction in the least burdensome manner, nor did it fully consider all available information or provide the public with sufficient time to review and comment on information regarding methods used to estimate some exposures. The court was especially concerned that substitute risks were not adequately addressed and determined that the conclusions in an EPA-authorized study of the safety of substitute brakes were inappropriately considered by EPA. In this case, issues of science policy, such as linear extrapolation, conservatism in risk estimates, *etc*., took a backseat to regulatory rulemaking procedural issues. However, these procedural issues involve uncertainty and gaps in knowledge, and are therefore matters of science policy, as well.

The benefits of the ban, as quantified in the final rule, appear to be modest. The aggregate costs may seem large, but when distributed across the entire population they

---

[74] Another instance of incomplete consideration of the potential risks associated with substitutes is the reformulation of gasoline to include oxygenates. Reformulation is being pursued in order to improve fuel combustion and reduce emissions of carbon monoxide. The most frequently used oxygenates are **ethanol** and **methyl tertiary butyl ether (MTBE).** Concern over adverse health effects associated with MTBE has resulted in a ban on its use in Alaska. A resolution of the American Medical Association calls for a moratorium on its use until health studies can be performed (Bureau of National Affairs [BNA] 1994).

[75] (EPA 1993b, 58965)

[76] (EPA 1993b, 58966)

amount to only $3.25 per person. Changes in product safety, increased risks to health, and market disruptions resulting from a ban could conceivably lead to net losses—in terms of lives and dollars—that outweigh the estimated benefits. For example, if asbestos use results in twenty deaths and use of substitution products would result in ten deaths, there is an excess risk associated with asbestos use, and an asbestos ban would save lives. However, if asbestos use causes ten deaths and use of substitutes would result in twenty deaths, an asbestos ban would result in a net loss of life.

Should EPA decide to reconsider the regulation of asbestos-containing products under TSCA, the court has identified several issues that require increased scrutiny and evaluation. Special attention should be paid to substitute risk issues in devising a regulatory approach to asbestos-containing consumer products. Any risk analysis supporting a proposed regulation is not complete unless the full consequences of the regulation are evaluated.

REFERENCES

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). 1993. *Toxicological Profile for Asbestos—Update (Draft for Public Comment).* Department of Health and Human Services, Atlanta, Ga.

BUREAU OF NATIONAL AFFAIRS (BNA). 1994. Daily Environment Report No. 131, A-3 (June 12, 1994).

Corrosion Proof Fittings v. Environmental Protection Agency. 947 F.2d 1201 (5th Cir. 1991).

DAVIS, J.M., and J.M. McDONALD. 1988. Low level exposure to asbestos: Is there a cancer risk? Br. J. Ind. Med. 45:505-508.

ENTERLINE, P.E. 1991. Changing attitudes and opinions regarding asbestos and cancer 1934-1965. Am. J. Ind Med 20:685-700.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993b. Radiation Site Cleanup Regulations. Fed. Reg. 58:54474-01.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993b. Asbestos, manufacture, importation, processing, and distribution prohibitions. Fed. Reg. 58(213):58964-58968.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1989. Asbestos; Manufacture, importation, processing, and distribution in commerce prohibitions (Final rule). Fed. Reg. 54:29460-29513.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1987. Analysis of the Feasibility of Replacing Asbestos in Automobile and Truck Brakes. Final Report. April 15, 1987. Office of Pesticides and Toxic Substances, Washington, D.C. Prepared under contract by the American Society of Mechanical Engineers.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986a. The Asbestos Fact Book. Office of Public Affairs, Washington, D.C. A-107-86-002.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986b. Airborne Asbestos Health Assessment Update. Office of Research and Development, Washington, D.C. EPA/600/8-84/003F.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985. Substitution Analysis for Asbestos Brake Linings for On-Road Vehicles. Office of Pesticides and Toxic Substances, Washington, D.C. Prepared under contract by ICF Incorporated.

GOTS, R.E. 1993. Toxic Risks: Science, Regulation, and Perception. Boca Raton: Lewis

Publishers, CRC Press. Inc.

INTEGRATED RISK INFORMATION SYSTEM (IRIS). 1993. Chemical Profile: Asbestos

(Updated 1/1/93). Environmental Criteria and Assessment Office, Environmental Protection Agency, Cincinnati, Ohio.

MEEK, M.E., H.S. SHANNON, and P. TOFT. 1985. Case study—Asbestos. Chapter 7 in D.B. Clayson, D. Krewski and I. Munro (eds.), Toxicological Risk Assessment—Volume II: General Criteria and Case Studies. Boca Raton: CRC Press, Inc.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1991. Sixth Annual Report on Carcinogens—Volume 1. National Institute of Environmental Health Sciences, Research Triangle Park, N.C. PB92-120666.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1985. Toxicology and Carcinogenesis Studies of Chrysotile Asbestos in F344/N Rats (Feed Studies). Research Triangle Park, N.C. NTP TR No. 295.

7
UNLEADED GASOLINE

Introduction

Automobiles and other motor vehicles are a widely recognized source of significant air pollution. Pollutants of concern associated with motor vehicles include lead, hydrocarbons, carbon monoxide, and nitrogen oxides. Unleaded gasoline, which was originally required for use with catalytic converter-equipped cars, has been on the market for more than twenty years. Continuing attention to reducing air pollution, especially from mobile sources, has resulted in increasingly stringent exhaust emissions requirements on automobiles and the eventual elimination of leaded gasoline as a fuel.

The focus of this case study is on unleaded gasoline, which has figured heavily in the Environmental Protection Agency's (EPA) clean air programs and which has been associated with kidney cancer in male rats. The central science policy issue in this case study is the relevance of a particular type of kidney tumor in male rats to human cancer risk assessment. As a default science policy decision, cancer in animals is assumed to be predictive of carcinogenic effects in humans. EPA scientists evaluated mechanistic data and determined that certain kidney tumors observed only in male rats exposed to unleaded gasoline were of no relevance to potential human cancer risk. If unleaded gasoline had been implicated as a potential human carcinogen, significant upheaval concerning the use of unleaded gasoline may have ensued.

Science Policy Issue Addressed in This Case Study
➢ Relevance of male rat kidney tumors to human cancer risk assessment

Concern over Lead in Gasoline

Lead-containing additives originally were added to gasoline to boost octane ratings, which improves engine performance. Lead additives accounted for 264,240 tons—about one-fifth—of total lead usage in 1971.[1] Increasing concern over emissions of pollutants from car exhausts and the potential health effects of lead created a push to reduce the use of lead in fuels.[2] According to EPA, man-made uses of lead constitute the

[1] (Environmental Protection Agency (EPA) 1973a, II-4)

[2] Approximately 70 percent of lead additives in gasoline were estimated to be emitted to the air as particulate matter from tailpipes (EPA 1973a, 1-4).

main source of lead in the environment. In the 1970s, lead in gasoline was characterized as the "single most significant contributor" to environmental lead levels.[3] In 1973, EPA and the international public health community identified lead additives in gasoline as a source that was amenable to control and reduction.[4] In other words, reduction of lead in gasoline was believed to result in similar reductions in environmental lead levels. The long history of regulatory involvement in reducing lead in and eliminating lead from gasoline had begun.

Regulating Lead in Gasoline

This section summarizes the history of EPA regulatory involvement in reducing the lead content of gasoline over the last twenty years. There is a range of issues, especially with respect to the costs and benefits associated with both the introduction and use of unleaded gasoline and reductions in the lead content of leaded gasoline.[5]

In January 1973, EPA promulgated a rule requiring the production of unleaded gasoline of suitable octane for 1975 model-year light-duty vehicles.[6] The primary purpose of this rule was to ensure the general availability of lead-free gasoline for use in cars equipped with catalytic converters designed to reduce auto emissions of hydrocarbons, carbon monoxide, nitrogen oxides, etc. Catalytic converters were in general use by 1975, so it was important to secure a fuel supply that would not impair their effectiveness.[7] Two benefits ensued from this rule. The primary benefit was the prevention of fouling and subsequent impairment of emissions-reducing catalytic converters, while the secondary benefit was reduction of lead emissions. [8]

EPA considered the risks associated with the prohibition of lead additives from gasoline qualitatively and concluded that elimination of lead would not require the substitution of "any other fuel or fuel additive that will produce emissions which will endanger the public health or welfare to the same or greater degree."[9] Costs associated with the provisions for unleaded gasoline were estimated to be relatively low. The total incremental costs resulting from the use of unleaded gasoline in a car equipped with a

---

[3] (EPA 1973a, II-12, VIII-1)

[4] (EPA 1973a, II-12, VIII-7)

[5] Although the emphasis in this case study is on the potential carcinogenicity of unleaded gasoline, we have included discussions of EPA actions requiring reduced lead in leaded gasoline in order to illustrate the level of EPA investment and involvement in reducing overall lead exposures.

[6] (EPA 1973b) The rule was proposed on February 23, 1972 (37 FR 3882). Unleaded gasoline is defined as "gasoline containing not more than 0.05 gram of lead per gallon and not more than 0.005 gram of phosphorus per gallon."

[7] (EPA 1973b, 1254; EPA 1972, 3882)

[8] The proposed rule discussed the potential health effects of airborne lead and the need to reduce lead exposures at some length. See (EPA 1972, 3882).

[9] (EPA 1973b, 1254). See also (Moran 1973).

catalytic converter was estimated to be $860 over the average 1970 vehicle costs for the lifetime of a car (85,000 miles). The total per-car cost estimate consisted of: [10]

- $362 due to increased gasoline prices and due to reductions in fuel economy;
- $388 for the initial installed emissions control system; and
- $110 net increased maintenance costs.

Compared to the large—although difficult to quantify in monetary terms—health benefits believed to be associated with reduced emissions from motor vehicles, the costs associated with use of unleaded gasoline were considered minor.

In December 1973, EPA promulgated a rule that called for the reduction of the amount of lead in leaded gasoline.[11] The maximum allowable lead concentrations in gasoline, which were averaged over all grades of leaded and unleaded fuel, were gradually decreased from 1.70 grams per gallon in 1975 to 0.50 grams per gallon in 1979. EPA justified the reduction in lead levels on the basis of: [12]

- A 60 to 65 percent reduction in lead usage;
- The attendant reductions in lead emissions from vehicles using leaded fuel;[13] and
- The decreased incidence of childhood lead poisoning.

In 1973, 90 percent of airborne lead was determined to be emitted by vehicles using leaded gasoline, and 200,000 tons of lead additives were used in gasoline each year.[14] The rule was estimated to require an industry investment of $82 million, which would increase the price of gasoline by less than 0.1 cent per gallon, and to result in a 0.4 percent increase in crude oil usage.[15]

In 1982, a maximum limit on lead in leaded gasoline—1.10 grams per leaded gallon (gplg)—was adopted.[16] previously, refiners had been allowed to average lead concentrations over all grades of leaded and unleaded fuel. The purpose of this rule was

---

[10] (EPA 1971, 1-9—1-10)

[11] (EPA 1973c). This rule was first proposed on February 23, 1972 (37 FR 3882) and was reproposed on January 10, 1973 (38 *FR* 1258). The authority for the rule comes from §211(c) (1) of the Clean Air Act (CAA).

[12] (EPA 1973c, 33734)

[13] It was later demonstrated that the use of lead in gasoline declined by 73 percent, and airborne lead levels decreased 71 percent from 1975 to 1984 (Gots 1993, 224). Recent data indicate that average blood lead levels decreased by 78 percent between 1976 and 1991 (Pirkle et al. 1994).

[14] (EPA 1973c, 33734)

[15] (EPA 1973c, 33739)

[16] (EPA 1985a, 1-6) The rule was published on October 29, 1982 (47 FR 49331).

to ensure the reduction of total lead usage as sales of leaded gasoline declined because older cars allowed to use it were retired from use.[17]

In March 1985, EPA announced a two-year, phased-in approach to further reduce the lead content of leaded gasoline from 1.10 to 0.10 gplg.[18] This reduction in lead content, first proposed in August 1984, [19]stemmed from EPA's growing concerns about the health effects of lead in the environment, the slower than anticipated decrease in the overall amount of lead being used in gasoline, and the widespread misuse of leaded gasoline in catalyst-equipped vehicles.[20]

At issue in the 1985 rule were the costs of potentially higher prices for leaded gasoline, the possibility of increased cancer risks associated with the increased benzene content in reformulated leaded gasoline, [21]and the health benefits of reduced lead poisoning. The benefits of reduced lead poisoning were anticipated in the form of reductions in the number of children with nervous system disorders, learning deficits, *etc*., and reductions in hypertension and attendant health problems in adults.[22] Following adoption of this rule, total lead usage from 1986 to 1994 was estimated to reduce by 91 to 94 percent.[23] The concern over potential cancer risks was allayed because the estimated increased benzene risk was very small and the benefits were thought to be quite large. In this trade-off, EPA determined that an estimated four cancer cases per year due to emissions of benzene from service stations were more than compensated for by improvements in emissions and air quality attributable to reduced numbers of disabled catalytic converters.[24]

EPA justified the reduction of lead content in leaded gasoline from 1.10 to 0.10 gplg on the basis of tremendous benefits, including:

---

[17] (EPA 1985a, 1-5)

[18] (EPA 1985b) An interim standard of 0.50 gplg was effective July 1, 1985, and the final standard of 0.10 gplg was effective January 1, 1986. The phased schedule was adopted to allow refineries to adjust with minimum difficulty.

[19] The citation for the notice of proposed rulemaking is 49 FR 31032.

[20] (EPA 1985a, 1-8, 1-9; EPA 1985b, 9386) Leaded gasoline damages catalytic converters and may increase emissions by a factor of up to 8 (EPA 1985a, VI-5). A 1983 survey found overall misfueling rates that ranged from 1.6 to 25.9 percent, depending on the vehicle model-year, with a weighted average of 15.5 percent, indicating that misfueling was a significant problem (EPA 1985a, VI-8).

[21] Reduction in lead content would reduce the octane rating of leaded gasoline, and reformulation, possibly involving additional benzene, would be necessary to restore the octane rating to desirable levels.

[22] *See* Chapters IV and V in (EPA 1985a). Evaluation of hypertension benefits was limited to white males due to data limitations.

[23] (EPA 1985b, 9387)

[24] *See* (EPA 1985a, VI-45-VI-47; Nichols and Zeckhauser 1988, 69-70).

- Reductions in adverse health and cognitive effects resulting from childhood lead exposures were associated with annual benefits ranging from $602 million in 1986 to $361 million in 1992.[25]
- The annual benefits of reduced mortality among middle-aged white men associated with a decreased incidence of hypertension were estimated to range from $5.9 billion in 1986 to $4.7 billion in 1982.[26]
- Annual benefits associated with an estimated 80 percent reduction in the incidence of misfueling were estimated to range from $222 million in 1986 to $248 million in 1992.[27]
- Decreased annual vehicle maintenance costs associated with reduction of lead content of leaded gasoline were estimated to range from $933 million in 1986 to $776 million in 1992.28 Improved fuel economy was estimated to result in benefits exceeding $100 million in most years.[29]

The costs associated with the 1985 rule were estimated to be $96 million for the second half of 1985 and to range from $608 million per year in 1986 to $441 million per year in 1992.[30] increased production costs were expected to result primarily from the reformulation of gasoline and the use of more octane-boosting additives. Since lead is the lowest-cost octane enhancer, alternative additives were expected to increase production costs and market prices.[31]

The estimated benefits associated with reducing the amount of lead allowed in leaded gasoline were not comprehensive due to gaps in data or difficulties in monetizing some of the benefits. Nevertheless, the net benefits far exceeded the estimated costs, even if the benefits associated with reduced hypertension and mortality were not included.[32] These estimated costs and benefits are considered to be compelling and have great weight because the EPA regulatory impact analysis in which they were developed has been described as "one of the best cost-benefit studies ever published."[33]

---

[25] (EPA 1985a, IV-55)

[26] (EPA 1985a, V-45) Data were available for white, middle-aged men only. Benefits for men of other races and women could not be quantified using the available data. Hence, these values underestimate the likely benefits resulting from the reduced incidence in hypertension and mortality among the entire population.

[27] (EPA 1985a, E-8, VI-74)

[28] (EPA 1985a, VII-17)

[29] (EPA 1985a, VI-21)

[30] (EPA 1985a, 11-38)

[31] (EPA 1985a, E-2-E-3)

[32] Excluding the benefits associated with reductions in hypertension and mortality, the cost-benefit ratio was estimated to be approximately 3.05 in 1986 and 3.37 in 1992.

[33] (Graham 1994)

Evaluation of the Carcinogenicity of Unleaded Gasoline

In 1987, EPA's Carcinogen Assessment Group (CAG) classified unleaded gasoline as a probable human carcinogen.[34] This classification was endorsed by the Science Advisory Board (SAB) and the Health Effects Institute. Animal evidence of the carcinogenicity of unleaded gasoline included increased kidney tumor incidence in male rats (6/100) and increased incidence of liver cancer in female mice (20/100) observed in lifetime inhalation bioassays. Taken together, the findings in these two species/sex groups were judged to constitute sufficient evidence of carcinogenicity in animals. Epidemiologic evidence was judged to be inadequate.[35] Thus, classification of unleaded gasoline as a probable human carcinogen rested solely on the assumption that cancer seen in animals is predictive of potential carcinogenic effects in humans.

CAG also noted that a protein, $\propto$-2μ-globulin, may be the cause of the kidney toxicity observed in male rats and that only male rats produce the protein in large quantities. CAG recognized that if the observed kidney tumor response in male rats resulted from this toxicity, then "the case for human carcinogenicity [of unleaded gasoline] would be weakened."[36] However, CAG did not disregard the male rat kidney data at this time because: [37]

- The link between kidney toxicity and tumor response was not proven;
- With few exceptions, human carcinogens also cause cancer in animals; and
- The kidney of experimental animals is a known target organ for more than 100 carcinogens.

With the inclusion of the male rat kidney data, CAG held that sufficient evidence of carcinogenicity existed in two species/sex groups, and that therefore unleaded gasoline was a probable human carcinogen. This conclusion, however, was not to be the final word on the relevance of certain kidney tumors in male rats to human cancer risk assessment.

Following exposure to some compounds, development of certain kidney tumors in male rats is preceded by lesions that are associated with nephropathy.[38] This nephropathy appears to result from the accumulation of α-2μ.-globulin in renal proximal tubules (a portion of the nephron). These lesions and associated tumors are not found in mice, female rats, or other laboratory animals—none of which produce α-2μ.-globulin in appreciable amounts. Consequently, a science policy decision was required to resolve

---

[34] (EPA 1987)

[35] (EPA 1987, M, I-5-1-6)

[36] (EPA 1987, 1-5)

[37] (EPA 1987, 1-5)

[38] *Nephropathy* refers to an abnormality or disease of the kidneys with respect to a pathological process. Nephrons are component cells of the kidney in which filtration occurs.

the issue of whether these renal tumors observed in male rats were indicative of potential carcinogenicity in humans.

- **Science policy issue**. Are certain renal lesions that are observed only in male rats the result of a species/sex-specific mechanism and, if so, what relevance does their occurrence have for human carcinogenic risk assessment?
- **Science policy decision**. Renal tumors observed in male rats following accumulation of ∝-2μ-globulin are the result of a species/sex-specific mechanism and are therefore not relevant to potential carcinogenicity in humans.

In 1991, EPA's Risk Assessment Forum (RAF) evaluated data concerning compounds that induce the accumulation of ∝-2μ-globulin in the kidneys of male rats, and the resultant toxicity and carcinogenicity.[39] A technical group was convened to consider the available data for eight model substances: 1, 4-dichlorobenzene, dimethyl methylphosphonate, hexachloroethane, isophorone, d-limonene, pentachloroethane, tetrachloroethylene (PCE), and unleaded gasoline.

Following exposure to a chemical inducing ∝-2μ-globulin accumulation (CIGA), the sequence leading up to the kidney tumors observed in male rats is believed to be as follows: [40]

- An excessive accumulation of hyaline droplets containing a-2p-globulin in renal proximal tubules;
- Subsequent cytotoxicity and single-cell necrosis of the tubule epithelium;
- Sustained regenerative tubule cell proliferation, providing exposure continues;
- Development of intralumenal granular casts from sloughed cell debris associated with tubule dilation and papillary mineralization;
- Foci of tubule hyperplasia in the convoluted proximal tubules; and
- Renal tubule tumors.

Data indicate that CIGA bind to ∝-2μ-globulin, resulting in complexes that appear to be more resistant to degradation than unbound ∝-2μ- -globulin. Inhibition of this degradation in male rats "provides a plausible basis for the initial stage of protein overload in the nephropathy sequence."[41] Furthermore, the available data also indicate

[39] (EPA 1991)

[40] (EPA 1991, 2). See Chapters III, IV, and X in EPA 1991 for a more complete description of the events leading from exposure to a chemical that induces accumulation of ∝-2μ-globulin to the eventual production of renal tumors.

[41] (EPA 1991, 3)

that CIGA typically do not interact with DNA, are negative in short-term genotoxicity tests, and act via different mechanisms from classical renal carcinogens.[42]

Some researchers, however, believe that an alternative explanation of the mechanism, in which α-2μ.-globulin accumulation is an indicator rather than a cause of renal toxicity, is equally or more plausible than that identified by the RAF. If this alternative hypothesis is proven correct, the conclusion that certain kidney tumors in male rats are irrelevant to potential human risks might be erroneous.[43]

The RAF study is particularly significant. EPA scientists carefully evaluated data concerning a possible mechanism of carcinogenicity in animals and concluded that a "plausible" explanation existed which required the distinction between kidney tumors in male rats associated with CIGA-induced α-2μ-globulin nephropathy and other kidney tumors when extrapolating risks to humans.[44] The RAF concluded as a matter of science policy that CIGA induce cancer by a mechanism that is limited to male rats, and that the resulting kidney tumors do not contribute to a weight-of-evidence determination or quantitative estimation of potential carcinogenicity in humans.[45] The SAB concurred with the RAF.[46]

Unleaded gasoline, which was included as one of the substances in this study, is therefore not considered to be a human carcinogen. The National Research Council (NRC) identified the RAF report as an example of where EPA has departed from a default assumption in risk assessment.[47] Typically, EPA has not departed from a default assumption on the basis of only a plausible explanation.

Current Regulatory Status of Unleaded Gasoline

EPA is currently developing a rule that will prohibit the sale, transport, and introduction into commerce of fuels containing lead or lead additives. EPA faces a statutory deadline for promulgating this rule by December 31, 1995, under the Clean Air Act. A proposed rule is expected by December 1994.[48]

Evaluation

EPA has spent more than twenty years promoting the use of unleaded gasoline to reduce both air pollution and ambient lead concentrations. EPA addressed the risks associated with reducing lead in gasoline on three separate occasions. In the early

---

[42] (EPA 1991, 3; National Research Council (NRC) 1994, 6-8)

[43] *See* (NRC 1994, 6-8) discussing (Melnick 1992, 111-125).

[44] (EPA 1991, 4)

[45] (EPA 1991, 85)

[46] (EPA 1991, xi)

[47] (NRC 1994, 6-7-6-9)

[48] (EPA 1994)

1970s and the mid-1980s, concerns over the potential risks due to increased concentrations of substitute fuel additives were addressed and allayed on the basis of relative risk. In the early 1990s, the increased cancer risk associated with unleaded gasoline in male rats was determined to be of no relevance to humans, despite lack of complete scientific consensus on the existence and relevance of a species-specific mechanism of carcinogenicity. In the first two instances, careful analysis demonstrated that the increased risks were small, especially in relation to the enormous benefits associated with reducing lead in gasoline. In the second case, EPA departed from a default assumption as a matter of science policy. In both cases, the need to preserve credibility may be viewed as an incentive for the actions taken.

REFERENCES

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994. Regulatory agenda; Prohibition of leaded gasoline for highway use. Fed. Reg. 59(79):21110.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991. Alpha-2 p-Globulin: Association

with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. Risk Assessment Forum, Washington, D.C. EPA/625/3-91/019F.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1987. Evaluation of the Carcinogenicity of Unleaded Gasoline. Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, D.C. EPA/600/6-87/001.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985a. Costs and Benefits of Reducing Lead in Gasoline: Final Regulatory Impact Analysis. Office of Policy Analysis, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985b. Regulations of fuels and fuel additives; Gasoline lead content (Final rule). Fed. Reg. 50:9386-9398.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1973a. EPA's Position on the Health Implications of Airborne Lead. Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1973b. Regulation of fuels and fuel additives (Final rule). Fed. Reg. 38(6): 1254-1256.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1973c. Control of lead additives in

gasoline (Final rule). Fed. Reg. 38(234):33734-33741.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1972. Lead and phosphorus additives in motor vehicle gasoline (Final rule). Fed. Reg. 37(36):3882-3884.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1971. Final Report: An Assessment of the Effects of Lead Additives in Gasoline on Emission Control Systems Which Might Be Used to Meet the 1975-76 Motor Vehicle Emission Standards (Aerospace Report). Prepared for the Office of Air Programs by the Aerospace Corporation, El Segundo, Ca. under Contract No. F04701-71-C-0172.

GOTS, R.E. 1993. Toxic Risks: Science, Regulation, and Perception. Boca Raton: Lewis

Publishers, CRC Press, Inc.

GRAHAM, J.D. 1994. Regulation: A risky business. New York Times, May 18.

MELNICK, R.L. 1992. An alternative hypothesis on the role of chemically induced protein droplet (a-2(i-globulin) nephropathy in renal carcinogenesis. Regul. Toxicol. Pharmacol. 16:111-125.

MORAN, J.B. 1973. Lead in Gasoline, Impact of Removal on Current Automotive Emissions. National Environmental Research Center, Environmental Protection Agency, Research Triangle Park, N.C.

NATIONAL RESEARCH COUNCIL (NRC) COMMITTEE ON RISK ASSESSMENT OF HAZARDOUS AIR POLLUTANTS. 1994. Science and Judgment in Risk Assessment (Prepublication Draft). Washington, D.C.: National Academy Press.

NICHOLS, A.L., and R.J. ZECKHAUSER. 1988. The perils of prudence: How conservative risk assessments distort regulation. Regul. Toxicol. Pharmacol. 8:61-75.

PIRKLE, J.L., D.J. BRODY, E.W. GUNTER, R.A. KRAMER, D.C. PASCHAL, K.M. FLEGAL, and T.D. MATTE. 1994. The decline in blood lead levels in the United States: The National Health and Nutrition Examination Surveys (NHANES). JAMA 272(4):284-291.

8
USED OIL

Introduction

Oil is an essential part of modem industry and transportation. More than 1 billion gallons of used oil are generated each year in the United States. Used oil contains a variety of toxic and carcinogenic substances, including benzene, naphthalene, lead, chromium, and chlorinated solvents and can therefore pose a threat to human health and the environment, especially when improperly managed or disposed. The Environmental Protection Agency (EPA), in developing the Hazardous Waste Management System mandated under the Resource Conservation and Recovery Act (RCRA), had to decide whether or not to designate used oil as a "hazardous waste." Hazardous wastes must be managed under strict standards in Subtitle C of RCRA.

As a matter of science policy, EPA faced the decision of whether used oil met the criteria for hazardous waste listing under RCRA. The ultimate decision not to list used oil as a hazardous waste came fourteen years after the first proposal to list in 1978. During the intervening fourteen years, EPA evaluated and re-evaluated the requirements of RCRA and other statutes and changed its position several times. Litigation ensued over the validity of an EPA proposal not to list used oil as a hazardous waste on the inappropriate and nontechnical basis that the resulting stigma would have negative effects on used oil recycling. Eventually, EPA fulfilled the RCRA mandate to protect human health and the environment and to foster used oil recycling by instituting special management standards without listing used oil as a hazardous waste.

Used Oil

Oil is widely used for lubrication purposes, as hydraulic fluid, as insulation, and in every mode of transportation and virtually all industrial processes.[1] In 1988, about 1.35 billion gallons of used oil were generated by households and industrial and nonindustrial generators in the United States. Of these 1.35 billion gallons, 949 million gallons (70 percent) were recycled through the used oil management system and, of these, 784 million gallons were burned for energy recovery.[2] Do it yourselfers (DIY)

[1] Used oil in this case study includes much more than automotive crankcase oil, which is the type that most readers will be familiar with. Used automotive oil accounts for approximately 60 percent of the used oil generated in the United States (Beiring 1993, 160).

[2] Environmental Protection Agency (EPA) 1991a, 48064)

changing their own automotive crankcase oil disposed about 183 million gallons of used oil,[3] which is about one-third of all used oil disposed in the environment.[4]

Science Policy Issue Addressed in This Case Study
➢ Whether or not used oil should be classified as a hazardous waste

Used oil is ubiquitous and potentially harmful to human health and the environment. Improper disposal of used oil creates pollution and wastes resources. Regulating used oil is made more challenging because it is generated by millions of cars and trucks and thousands of industrial facilities. Improper disposal can result in used oil passing untreated through sewers and water treatment plants.

Criteria for Listing as a RCRA Hazardous Waste

The criteria for listing a solid waste as a hazardous waste under RCRA are codified at 40 CFR 261.11. Upon listing, a hazardous waste is brought under the control of the Hazardous Waste Management System established under Subtitle C of RCRA. The hazardous waste management system provides a "cradle-to-grave" regulatory structure for the transportation, treatment, storage, and disposal of hazardous wastes.

Pursuant to Section 3001 of RCRA and regulations developed thereunder, a waste may be found to be "hazardous" using two distinct mechanisms.[5] First, EPA may list a waste if it is found to exhibit one of the characteristics of hazardous waste (toxicity, ignitability, reactivity, or corrosivity).[6] Second, a waste may be listed if it contains any one of a number of toxic constituents.[7] However, a waste containing any of the toxic constituents need not be listed if:

> *... after considering any of the following factors, the Administrator concludes that the waste is not capable of posing a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported or disposed of, or otherwise managed:*
>
> *(i) The nature of the toxicity presented by the constituent.*
>
> *(ii) The concentration of the constituent in the waste.*

[3] (EPA 1991a, 48003)

[4] (Beiring 1993, 157)

[5] A third mechanism, codified at 40 CFR 261.11(a)(2), applies to acutely toxic wastes found to be lethal to humans or animals in low doses.

[6] Codified at 40 CFR 261.11(a) (1).

[7] Codified at 40 CFR 261.11(a)(3). The specific constituents are listed in Appendix VIII to 40 CFR 261.

(iii) The potential of the constituent or any toxic degradation product of the constituent to migrate from the waste into the environment under the types of improper management considered in (vii) below.

(iv) The persistence of the constituent or any toxic degradation product of the constituent.

(v) The potential for the constituent or any toxic degradation product of the constituent to degrade into non-harmful constituents and the rate of degradation.

(vi) The degree to which the constituent or any degradation product of the constituent bioaccumulates in ecosystems.

(vii) The plausible types of improper management to which the waste could be subjected.

(viii) The quantities of the waste generated at individual generation sites or on a regional or national basis.

(ix) The nature and severity of the human health and environmental damage that has occurred as a result of the improper management of wastes containing the constituent.

(x) Actions taken by other governmental agencies or regulatory programs based on the health or environmental hazards posed by the waste or waste constituent.

(xi) Such other factors as may be appropriate.[8]

Consideration of the factors above constitutes a balancing test. Wastes containing toxic constituents may or may not be designated as hazardous, depending on the overall evaluation of the factors above.

Under RCRA, EPA is free to list a waste as hazardous under either Section 261.11(a) (1) or (a) (3). As has been recently clarified in court, [9]EPA must find that a waste satisfies one of these criteria as a prerequisite to listing, but the regulations do not compel EPA to list a waste that it finds to satisfy one of these criteria. In other words, EPA may find that a waste is hazardous, but is not obligated to list and regulate it as such. Considerable discretion is afforded to EPA in making listing decisions. Due to uncertainty and the multiplicity of considerations faced by EPA, the decision to list a waste as hazardous is essentially a matter of science policy.

- **Science policy issue.** Should used oil be listed as a hazardous waste under RCRA?
- **Science policy decision**. Used oil should/should not be listed as a hazardous waste under RCRA.

EPA has judged used oil both to be and not to be a hazardous waste at different times. The rationale for each decision to list or not to list is discussed below. That the resolution of the central science policy issue in this case study changed over time illustrates the discretion afforded EPA in making hazardous waste listing decisions under RCRA.

---

[8] (40 CFR 261.11 (a)(3))

[9] Natural Resources Defense Council, Inc. v. U.S. Environmental Protection Agency. 62 USLW 2764 (D.C. Cir. 1994).

Regulatory Interest in Used Oil

Regulatory interest in used oil and its designation as a hazardous waste goes back to 1978. The primary issues that EPA dealt with between the first proposal to list used oil as a hazardous waste and the final decision not to list in 1992 were:

- The toxicity of constituents and contaminants in used oil;
- The potential threat to groundwater and the environment posed by used oil when improperly disposed; and
- A desire not to discourage recycling of used oil, which could lead to increased uncontrolled disposal.

The timeline of regulatory developments regarding used oil is summarized in Table 81. Each of the individual events—and the science policy issues that were involved—is discussed in the text below.

On December 18, 1978, EPA first proposed to list used oils as hazardous wastes as part of general guidelines and standards for hazardous waste management issued under Section 3001 of the RCRA.[10] The foundation for this proposal was a regulatory program to manage and control hazardous waste, which Congress had directed EPA to create in 1976.[11]

On May 19, 1980, EPA deferred the listing decision until later in 1980 when specific management and recycling regulations could be promulgated [12] because it wanted to address the entire waste oil issue at one time. Although waste used oil was not listed as a hazardous waste in the final rule, [13]EPA established that, in the meantime, used oil found to exhibit one of the characteristics of hazardous waste would be regulated as a hazardous waste when disposed, accumulated, stored, or treated before disposal.[14] This compromise was part of EPA's efforts to balance the Subtitle C requirements that hazardous wastes be properly managed and RCRA's general objective of promoting the use, re-use, recycling, and reclamation of wastes.[15] The final regulation also explained that EPA could list types of wastes found to be typically or frequently hazardous.[16]

[10] (EPA 1978)

[11] (EPA 1978, 58946)

[12] (EPA 1980, 33094)

[13] (EPA 1980, 33123)

[14] (EPA 1980, 33090-33092)

[15] (EPA 1980, 33091)

[16] (EPA 1980, 33107)

Table 8-1. The History of Used Oil Regulation	
Date	**Regulatory or Legislative Action**
December 18, 1978	First EPA proposal to list used oil as a hazardous waste.
May 19, 1980	Listing decision deferred by EPA until management standards and recycling regulations could be developed.
October 15, 1980	Used Oil Recycling Act, encouraging used oil recycling, passed.
January, 1981	EPA Report to Congress indicates intention to list certain categories of used oil.
November, 1984	HSWA passed; EPA directed to regulate used oil so that recycling would not be discouraged.
November 29, 1985	EPA proposal to list used oils based on toxic constituent content.
March 10, 1986	EPA requested comments on impact of listing on recycling.
May 19, 1986	House subcommittee found listing to be "counterproductive."
November 19, 1986	EPA decision not to list based on "stigma" and potential negative impacts on recycling.
October 7, 1988	Petition for review granted by U.S. Court of Appeals on basis that consideration of "stigma" is not allowed in listing decisions.
September 23, 1991	Final EPA proposal features three options for listing, including option not to list but to rely on management standards.
May 20, 1992	Final EPA decision not to list used oil destined for disposal.
September 10, 1992	Management standards for recycled used oil promulgated by EPA.

Congress recognized the potential hazards of mismanagement and passed the Used Oil Recycling Act (UORA) on October 15, 1980, in order to encourage used oil recycling. In UORA, used oil is defined as "any oil which has been refined from crude oil, used, and as a result of such use, contaminated by physical or chemical impurities."[17] UORA required EPA to determine if used oil is a hazardous waste and report the findings to Congress.

[17] (Used Oil Recycling Act, §3)

EPA was also authorized to establish standards for the management of used oil intended for recycling that would protect public health and the environment without discouraging recovery and recycling of used oil. Essentially, UORA created special conditions for the regulation of used oil: EPA was required to consider the effects of regulation and listing on recycling, and EPA retained authority to regulate recycled oil under Subtitle C without first listing it as hazardous.[18]

In January 1981, EPA indicated in its *Report to Congress* that it intended to list several categories of used oil as a hazardous waste.[19] EPA based this decision on the toxic substances found in crude and refined oil, including polynuclear aromatic hydrocarbons, chlorinated benzenes, naphthalenes, and nitrosamines, and on the presence of contaminants as a result of use, such as lead, chromium, barium, and cadmium.[20] The potential for improper management of oil and used oil to render groundwater nonpotable through contamination was cited in the report.[21] Additional justifications for listing used industrial and automotive oils as hazardous waste included:[22]

- The volume of used oil generated each year;
- Environmental hazards posed by applying oil to land or disposing in insecure landfills;
- Potential hazards associated with uncontrolled burning;
- The persistence and bioaccumulation potential of many contaminants in used oil; and
- The documented damage caused by improper management.

Despite the UORA requirement to promulgate final used oil regulations by October 15, 1981, [23]no action was taken by EPA.

In November 1984, the Hazardous and Solid Waste Amendments (HSWA) to RCRA were signed into law. HSWA authorized the EPA administrator to:

> *... promulgate regulations ... as may be necessary to protect human health and the environment from hazards associated with recycled oil.... The Administrator shall ensure that such regulations do not discourage*

[18] (EPA 1986a, 41900)

[19] (EPA 1981, 1)

[20] (EPA 1981, 16-34, 63-70, 77) The International Agency for Research on Cancer has concluded that there is sufficient evidence that used motor oil is carcinogenic (Beiring 1993, 163).

[21] (EPA 1981, 76)

[22] (EPA 1981, 76-77)

[23] (EPA 1981, 1)

> *the recovery or recycling of used oil consistent with the protection of human health and the environment.*[24]

Thus, Congress recognized the need to balance environmental protection and health safety with the need to promote used oil recycling. HSWA established deadlines for EPA regulation of used oil. A proposed listing decision for used automobile and truck crankcase oil was required by November 8, 1985, and a final determination to identify and list any or all used oils was required by November 8, 1986.[25]

On November 29, 1985, EPA proposed listing all used oils as hazardous waste based on the presence of toxic constituents at levels of concern.[26] The proposed listing applied to "used oil when disposed of, recycled or when accumulated, stored, or treated prior to being disposed or recycled."[27] EPA evaluated used oils against the criteria for listing and determined that they posed a "substantial present or potential hazard to human health or the environment when improperly managed."[28] EPA justification for the listing decision was stated as follows: [29]

- Used oil typically and frequently contains toxic contaminants, such as lead and other metals, chlorinated solvents, toluene, and naphthalene, in significant quantities.
- These contaminants are mobile and persistent in the environment.
- Used oil is generated in large quantities.
- Therefore, used oil may pose a substantial threat to human health and the environment if improperly managed.

EPA also proposed special management standards for recycled used oil (as opposed to oil destined for disposal).[30]

On March 10, 1986, EPA requested additional comments on several aspects of listing used oil as a hazardous waste.[31] Commenters to the 1985 proposal had suggested that only used oil destined for disposal be designated as hazardous and that the special management standards for recycled used oil be promulgated. In public hearings, commenters stated that designating used oil as hazardous would discourage recycling and lead to increased disposal and dumping, especially among DIY oil changers.[32] EPA

---

[24] (RCRA §3014(a))

[25] (EPA 1992a, 21525)

[26] (EPA 1985a)

[27] (EPA 1985a, 49621)

[28] (EPA 1985a, 49260)

[29] (EPA 1985a, 49265-19267)

[30] (EPA 1985b)

[31] (EPA 1986b)

[32] (EPA 1986b, 8206)

specifically requested documentation and comments addressing the impact of hazardous waste listing on used oil recycling. Areas of concern included insurance costs, Superfund and non-Superfund liabilities, fuels used by waste oil burners, effects on service stations and oil change stations, consistency with existing state-level programs, and the implications of issuing special management standards under RCRA Section 3014(a).[33]

Congress continued to monitor the used oil issue. The House Subcommittee on Energy, Environment, and Safety Issues Affecting Small Business held a hearing on May 19, 1986 that addressed the issue of used oil recycling. The subcommittee found that listing used oil as a hazardous waste would be counterproductive because of the "adverse impacts" that would be associated with the listing.[34] Later in 1986, Congress passed the Superfund Amendments and Reauthorization Act (SARA), which extended RCRA state authorization and criminal enforcement provisions to used oil regardless of whether EPA listed or identified it as a hazardous waste.[35]

On November 19, 1986, EPA issued a decision not to list recycled used oil as a hazardous waste.[36] EPA believed that designating recycled used oil as hazardous would stigmatize it and discourage recycling.[37] An overwhelming number of comments[38] received by EPA concerning the proposal to list contended that designation of recycled used oil as hazardous would "disrupt collection and recycling networks and ultimately lead to improper used oil disposal."[39] EPA found "inherently reasonable the argument that listing will discourage voluntary participation in the used oil recycling system"[40] and therefore concluded:

> *The stigma associated with designation [of recycled used oil] as a hazardous waste, although difficult to quantify, is nevertheless sufficiently apparent on this record for legitimate Agency action.*[41]

In support of its decision not to list recycled used oil on the basis of stigmatic effects, EPA noted "objective costs" that would be associated with listing recycled used oil as a hazardous waste:[42]

---

[33] (EPA 1986b, 8206-8207)

[34] (EPA 1986a, 49100)

[35] (EPA 1986a, 41901)

[36] (EPA 1986a)

[37] (EPA 1986a, 41901)

[38] EPA received more than 800 public comments on the 11/29/85 proposal.

[39] (EPA 1986a, 41902)

[40] (EPA 1986a, 41903)

[41] (EPA 1986a, 41903)

[42] (EPA 1986a, 41903)

- Absent delisting, residues from use of oil would automatically be hazardous waste.
- Recycled oil that is not already hazardous under Superfund would automatically become a hazardous waste.

The listing decision for disposed used oil was deferred, apparently because of the potential impacts of such a listing on recycled used oil. [43] EPA outlined a plan to address issues such as making a listing determination for disposed used oil and promulgating special management standards for recycled oil. The listing decision for used oil destined for disposal was scheduled for mid-1988.[44]

The Hazardous Waste Treatment Council (HWTC), the Association of Petroleum Re-Refiners (APR), and the Natural Resources Defense Council (NRDC) challenged EPA's decision not to list recycled used oil as hazardous on the basis that RCRA does not allow consideration of stigma in listing determinations.[45] The U.S. Court of Appeals for the D.C. Circuit found that the decision not to list was "based on a factor not allowed by [RCRA]" and granted the petition for review on October 7, 1988.[46] The court directed EPA to determine whether recycled used oils warranted listing as hazardous waste based on the technical criteria alone.[47]

On September 23, 1991, EPA published yet another proposed rule that concerned: [48]

- The availability and evaluation of new data on the composition of used oil;
- The possible designation of four wastes associated with reprocessing and re-refining used oil as hazardous; and
- Proposed used oil management standards for recycled oil under Section 3014 of RCRA.

This proposal featured a presentation, discussion, and evaluation of composition data for a variety of used oils.[49] This data-gathering exercise was made in response to

---

[43] (EPA 1986a, 41903) EPA was also considering whether TSCA authority could be used to regulate disposed oil.

[44] (EPA 1986a, 41904)

[45] Hazardous Waste Treatment Council, et al. v. Environmental Protection Agency. 861 F.2d 270 (D.C. Cir. 1988).

[46] 861 F.2d 270 (D.C. Cir. 1988), at 274.

[47] 861 F.2d 270 (D.C. Cir. 1988), at 277.

[48] (EPA 1991a, 48000)

[49] Categories of used oil for which data were collected and evaluated included: automotive crankcase oils (as generated and from storage tanks), diesel engine crankcase oil from trucks and buses, diesel engine oil from maintenance facility storage tanks, diesel heavy equipment crankcase oil, heavy equipment maintenance facility storage tanks, diesel railroad engine crankcase oil, marine used oil from storage tanks, marine oil from foreign cargo ships, miscellaneous marine oils, hydraulic oil/fluids, metalworking oil/fluids, electrical insulating fluids, natural gas-fired engine oil, and aircraft engine oil, aircraft engine oil/fluids from storage tanks.

commenters on the 1985 proposal, who had suggested that some used oils were not typically and frequently hazardous, and in an effort to determine whether a basis existed for listing separate types of used oils. [50] Used oil samples were prepared according to the Toxicity Characteristic Leaching Procedure (TCLP), [51]and the resulting filtrates were analyzed for selected constituents of concern.[52] The data indicated that automotive crankcase oil generally contains high quantities of polynuclear aromatic hydrocarbons (PAHs) and exhibited the toxicity characteristic for lead 75 percent of the time. EPA concluded that automotive crankcase oil, piston-engine aircraft oil, and gasoline-powered marine craft oil would frequently exhibit the toxicity characteristic for at least one constituent.[53]

Three proposed options for listing or identifying used oil as hazardous were included in the 1991 proposal: [54]

- **Option One**. As originally proposed in 1985, list all used oils as hazardous based on the potential for adulteration and environmental damage resulting from mismanagement.
- **Option Two.** List only those used oils typically and frequently found to be hazardous based on the presence of lead, PAHs, and other toxic constituents.
- **Option Three.** Do not list used oils, but develop special management standards under RCRA Section 3014 for all used oils, and require that used oil destined for disposal that is found to be characteristically hazardous be subject to all RCRA Subtitle C hazardous waste regulations.

EPA felt that Option Three would be feasible and concluded that:

> *... since the management standards address the types of mismanagement that historically have occurred with used oil, ... the need to list used oil to attain environmental control may be greatly reduced.*[55]

Mismanagement of used oil has been associated with significant damage to the environment. An EPA report identified 177 individual sites, including 25 Superfund sites, at which used oil was implicated in causing environmental damage.[56] Over half of these sites involved contamination of surface waters, and approximately one-third involved soil contamination. Exposure to used oil may result from burning oil in uncontrolled devices, dumping on land, improper disposal in landfills, spills, and leaks,

---

[50] (EPA 1991a, 48006)

[51] The TCLP replaced the earlier Extraction Procedure (EP) for determining if hazardous wastes are characteristically toxic.

[52] (EPA 1991a, 48007)

[53] (EPA 1991a, 48018—48019)

[54] (EPA 1991a, 48019-48021)

[55] (EPA 1991a, 48021)

[56] (EPA 1991b)

and oiling roads for dust suppression. Contaminants of concern include heavy metals (lead), chlorinated solvents (trichloroethylene, tetrachloroethylene, and 1, 1, 1-trichloroethane), and other organic chemicals (naphthalene, benzene, and toluene).

EPA estimated the compliance costs associated with the proposed special management standards—including costs associated with storage requirements, spill response and cleanup standards, preparedness and prevention standards, used oil tracking, recordkeeping and reporting requirements, testing costs, and permitting requirements—to be $24.5 million annually. Industrial and transportation-related generators were estimated to bear more than 90 percent of the total costs.[57] The costscreening analysis also estimated the costs[58] of the following actions contained in the various proposed options: [59]

- Ban on road oiling—$7.4 million ($3.7 to $11.1 million) per year;
- Ban on land disposal—$16.3 million ($8.3 to $24.4 million) per year;
- Listing processing and re-refining residuals—$5.1 million ($0.64 to $9.6 million) per year;
- Regulation of used oil distillation bottoms as hazardous waste or as recycled used oil—if listed as hazardous waste: $7 million ($1 to $13 million) per year, or if regulated as recycled oil: <$40,000 per year; and
- Combustion residuals derived from burning listed used oil fuels—$1 million ($0 to $3.7 million) per year.

The most likely estimate of total costs ranged from $29.8 to $36.8 million, depending on the regulatory approach chosen for distillation bottoms.[60]

Based on the estimates above, EPA concluded that the total annual cost "would not much exceed $60 million and could be less than $10 million per year."[61] As such, EPA concluded that none of the listing options would constitute a major rulemaking according to Executive Order 12291 (i. e., a rule having an annual economic impact of more than $100 million). The Office of Management and Budget (OMB) reviewed EPA's cost screening analysis, found fault with many of the assumptions in it, and concluded that a thorough regulatory impact analysis should be conducted. OMB believed that the cost of compliance with the special management standards could "very probably exceed

[57] (EPA 1991c, IIT-II-3, 11-24)

[58] A11 costs are incremental above current practices and assume use of the best demonstrated available technology for treating wastes banned from land disposal (EPA 1991c, HIT).

[59] Values in parentheses indicate ranges reported by EPA. See Section III of (EPA 1991c).

[60] (EPA 1991c, III-14)

[61] (EPA 1991a, 49068)

$600 million per year" [62] and that the other costs were understated by a factor of three.[63]

Finally, on May 20, 1992, EPA promulgated a final rule based on Option Three, which had enjoyed the overwhelming support of commenters on the 1991 proposal.[64] Used oil destined for disposal was not listed as a hazardous waste, although disposal of used oil found to be characteristically hazardous would be subject to RCRA Subtitle C requirements. EPA deferred a listing determination and/or management standards for recycled oil until an unspecified future date.[65]

The basis for EPA's decision not to list used oil destined for disposal is summarized by the following quotes from the final rule:

> *EPA evaluated the technical criteria for listing in light of the current regulatory structure controlling the management of used oils and concluded that any plausible mismanagement of used oil that is destined for disposal is addressed by current requirements.*[66]
>
> *EPA finds that the current regulatory structure*[67] *controlling the management of used oil destined for disposal provides adequate controls so that used oil will not pose a substantial threat to human health or the environment.*[68]

Essentially, EPA argued that listing disposed used oil as hazardous was not necessary because existing federal programs and controls would protect human health and the environment. EPA based this argument on consideration of technical criteria (vii) and (x) in 40 CFR 261.11(a) (3). EPA's rationale is evident in its responses to several comments[69] that opposed the proposed listing of used oil as a hazardous waste:

> *After consideration of all public comments and an evaluation of the technical criteria in 40 CFR §261.11, EPA has determined that used oil destined for disposal should not be listed as a hazardous waste. EPA evaluated existing environmental regulations governing disposal of used*

---

[62] (MacRae 1992, 2)

[63] (MacRae 1992, 4)

[64] (EPA 1992a, 21527)

[65] (EPA 1992a, 21524)

[66] (EPA 1992a, 21258)

[67] The regulatory structure governing the management of used oils includes: EPA and U.S. Coast Guard regulations for oil discharges into navigable waters; Department of Transportation requirements; EPA regulations for polychlorinated biphenyls under the Toxic Substances Control Act; hazardous waste characteristics under RCRA; underground storage tank requirements under RCRA; underground injection permits under the Safe Drinking Water Act; regulations der the Clean Water Act; and the reduction of lead in gasoline under the Clean Air Act.

[68] (EPA 1992a, 21528)

[69] See Section L.l of (EPA 1992b) and Section III.D.1-01 of (EPA 1992c).

> *oil and determined that they provide adequate protection of human health and the environment as required by 40 CFR §261.11 (a)(3) (x). Thus, listing used oil destined for disposal as a hazardous waste is not necessary at the present time....*[70]

The discretion afforded EPA in making listing decisions enabled it to decide not to list disposed used oil. While used oil is clearly toxic, the balancing factors contained in 40 CFR 261.11(a) (3) allowed EPA to consider the impact of current federal regulations governing used oil in its deliberations and decision making.

A court challenge against the final decision not to list was brought in the U.S. Court of Appeals, District of Columbia Circuit, by NRDC, HWTC, and APR.[71] The petitioners alleged that EPA did not comply with the statutory requirements of RCRA nor with the agency's own hazardous waste listing regulations because EPA had found used oil to frequently exhibit the toxicity characteristic but did not list used oil. The court denied the petition, and EPA's decision not to list disposed used oil as a hazardous waste stands. Based on a careful analysis of the language in 40 CFR 261.11(a), the court held that the listing regulations require EPA to find that a waste is hazardous before listing, but do not obligate EPA to list a waste found to be characteristically hazardous.[72] The court concluded that the wording of the regulations grants EPA considerable discretion in "determining when to employ any of its three criteria to list a particular waste as hazardous."[73] The court also found that EPA appropriately considered and evaluated the balancing factors in 40 CFR 261.11(a) (3) in determining that the existing network of regulations could control used oil mismanagement so that listing was not required.[74] Finally, the Court stated that, whether used oil is regulated as a "listed" or "characteristic" hazardous waste, any used oil that is indeed hazardous must be appropriately disposed of according to RCRA Subtitle C requirements.[75]

On September 10, 1992, EPA promulgated special management standards for recycled used oil in conjunction with a decision not to list recycled used oil as hazardous.[76] "EPA determined that recycled used oil does not have to be listed as a hazardous waste, because the used oil management standards issued in this rulemaking are adequately protective of human health and the environment."[77] With the promulgation of this rule, EPA had finally come to the end of a fourteen year rulemaking journey.

---

[70] (EPA 1992b, 5)

[71] Natural Resources Defense Council, Inc. et al. v. U.S. Environmental Protection Agency. 62 USLW 2764 (D.C. Cir. 1994).

[72] 62 USLW 2764, at 3-1

[73] 62 USLW 2764, at 6.

[74] 62 USLW 2764, at 8.

[75] 62 USLW 2764, at 8.

[76] (EPA 1992d)

[77] (EPA 1992d, 41566)

Evaluation

In this case study, EPA is seen to have balanced competing needs and mandates in a way that perhaps could be applied more frequently in environmental regulation. On one hand, used oil is clearly a hazardous substance, particularly when mismanaged. On the other hand, listing used oil as a hazardous substance could actually reduce the reclamation and recycling of used oil. Consequently, EPA carefully evaluated the listing criteria in the regulations and determined that the existing framework for the management of used oil was sufficient to protect human health and the environment even though EPA's own studies had shown used oil to be toxic and potentially hazardous. EPA, through its several years of deliberation and evaluation, has ultimately ensured that used oil will be disposed in a manner that protects human health and the environment and that recycling of used oil will be fostered and conducted safely.

REFERENCES

BEIRING, E. 1993. Used oil in the United States: Environmental impact, regulation, and management. Buffalo Law Review 41:157-204.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992a. Hazardous waste management system; General; Identification and listing of hazardous waste; Used oil (Final rule). Fed. Reg. 57(98):21524-21534.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992b. Public Comment and Response on Used Oil Proposed Rule: Listing Used Oil on Disposal and Used Oil Filter Exemption (November 29, 1985). Office of Solid Waste, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992c. Public Comment and Response on Used Oil Proposed Rule: Listing Used Oil on Disposal and Used Oil Filter Exemption (September 23, 1991). Office of Solid Waste, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992d. Hazardous waste management system; Identification and listing of hazardous waste; Recycled used oil management standards (Final rule). Fed. Reg. 57:41566-41626.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991a. Hazardous waste management system; General; Identification and listing of hazardous waste; Used oil (Supplemental notice of proposed rulemaking). Fed. Reg. 56(184):48000-48074.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991b. Environmental Damage from Used Oil Mismanagement—Final Draft Report. Prepared by Science Applications International Corporation for Office of Solid Waste, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991c. Cost and Economic Impact

Screening Analysis for the 1991 Used Oil Proposal. Prepared by Temple, Barker & Sloane/Clayton Environmental Consultants for Office of Solid Waste, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986a. Identification and listing of

hazardous waste; Used oil (Decision not to adopt proposed rule). Fed. Reg. 51(233):41900-41905.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986b. Hazardous waste management system; Identification and listing of hazardous waste (Notice of data availability and request for comments). Fed. Reg. 51(46):8206-8208.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985a. Hazardous waste management system; General; Identification and listing of hazardous waste; Used oil (Proposed rule). Fed. Reg. 50(230):49258—49270.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985b. Hazardous waste management system; Recycled used oil standards (Proposed rule). Fed. Reg. 50:(230):49212-49258.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1981. Report to Congress: Listing of Waste Oil as a Hazardous Waste. Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1980. Hazardous waste management system; Identification and listing of hazardous waste (Final rule, interim final rule, and request for comments). Fed. Reg. 45(98):33084-33133.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1978. Hazardous waste guidelines and regulations (Proposed rules). Fed. Reg. 43(243):58946-59028.

Hazardous Waste Treatment Council et al. v. Environmental Protection Agency. 861 F.2d 270 (D.C. Cir. 1988).

MacRAE, Jr., J.B. 1992. Letter to William K. Reilly, EPA Administrator, regarding the Cost and Economic Impact Screening Analysis for the 1991 Used Oil Proposal, dated January 7, 1992. Office of Management and Budget, Executive Office of the President, Washington, D.C.

Natural Resources Defense Council, Inc. et al. v. U.S. Environmental Protection Agency. 62 USLW 2764 (D.C. Cir. 1994).

9
TRICHLOROETHYLENE

Introduction

Trichloroethylene (TCE) has long been used in a variety of industries. As a consequence, TCE is now found in the groundwater at numerous contaminated sites. Superfund law and policy require that contaminants in certain groundwater aquifers be cleaned up to drinking water standards. Remediation of contaminated groundwater often drives the cost and duration of Superfund site cleanups.

TCE is classified as a probable human carcinogen by the Environmental Protection Agency (EPA). However, evidence is gathering that TCE is either not a human carcinogen or not as potent a human carcinogen as once thought, particularly at environmental exposure levels. Incorporation of alternatives to default science policy decisions could result in less stringent drinking water standards for TCE. Therefore, the standards applied to groundwater cleanup would also be less stringent, which would reduce remediation costs but would not reduce public health protection.

Science Policy Issues Addressed in This Case Study
➢ Relevance of mouse liver tumors to human cancer risk assessment ➢ Consideration of interspecies differences in mechanisms ➢ The use of advanced modeling techniques in extrapolating exposures and risks from animals to humans

Uses of Trichloroethylene

TCE is a colorless, volatile, dense, sweet-smelling, non-aqueous, man-made chemical which, in liquid form, is widely used because of its excellent solvent properties. TCE is predominately used for degreasing prefabricated metal parts, with the rest used in adhesives, paint strippers, industrial painting systems, and textile dyeing and finishing. TCE has also been used in a variety of consumer products, including household drain cleaners, degreasing products, typewriter correction fluid, spot removers, rug cleaning fluids, and metals cleaners.[1]

[1] (Jaeger and Weiss 1993, 229)

Because of its widespread use as a cleaning agent and solvent, TCE has been detected at over one-third of all hazardous waste sites and in 10 percent of groundwater sources.[2] As of 1993, TCE had been identified at 829 of the 1,260 sites on the National Priorities List (NPL) of Superfund sites.[3] The remediation of TCE in groundwater is therefore of central importance at many Superfund sites.

Evaluation of the Carcinogenicity of Trichloroethylene

The *Health Assessment Document for Trichloroethylene*[4] was published in 1985. This document is a comprehensive evaluation of the data concerning the carcinogenicity, mutagenicity, developmental, and reproductive effects of exposure to TCE. Available epidemiologic data do not indicate an increased cancer risk in humans. However, TCE was classified as a probable human carcinogen (Group B2) based on an increased incidence of liver tumors in mice.[5] EPA withdrew the carcinogenicity assessment for TCE in 1989, but TCE is still regulated as if it were a Group B2 carcinogen. An EPA Work Group is currently reviewing the carcinogenicity classification for TCE, [6] but has yet to reach a final conclusion.

Science policy issues central to the evaluation of the carcinogenicity of TCE in humans include:

- The relevance of mouse liver tumors to cancer risk assessment in humans;
- Possible differences in mechanisms between species that may indicate that TCE may not be carcinogenic in humans; and
- Additional research that implies that TCE may not be as carcinogenic in humans as it is in animals.

Each of the science policy issues and associated impacts on the regulatory approach for TCE is discussed below. The science policy issues and decisions discussed here represent *de facto* science policy decisions inferred from the regulatory status of TCE before the carcinogenicity classification was withdrawn.

The available epidemiologic studies on TCE fail "to demonstrate an increased incidence of liver tumors in humans exposed to trichloroethylene,"[7] and are therefore "insufficient to confirm that TCE is a human carcinogen."[8] However, when administered by gavage or

---

[2] (Campos-Outcalt 1992)

[3] (Agency for Toxic Substances and Disease Registry (ATSDR) 1994)

[4] (Environmental Protection Agency (EPA) 1985)

[5] (EPA 1985, 1-4-1-5) A Group B2 human carcinogen is one with "inadequate" evidence of carcinogenicity in humans and "sufficient" evidence in animals. Group C (possible) human carcinogens are those with only "limited" evidence of carcinogenicity in animals (EPA 1986a).

[6] Integrated Risk Information System (IRIS) 1993)

[7] (Steinberg and DeSesso 1993, 143)

[8] (Jaeger and Weiss 1993, 238)

via inhalation, high doses of TCE have been demonstrated to induce liver cancer in male and female mice.[9] Exposure to high doses of TCE is also associated with lung cancer in mice and kidney and testicular cancer in rats, but the relevance of these findings is disputed.[10] Considerable controversy and uncertainty surround the validity of the mouse liver tumor as an indicator of potential human carcinogenicity. The relevance of mouse liver tumors is especially questionable and controversial when there is a high spontaneous background rate of liver tumors[11] and when liver tumors are the only response observed.

- **Science policy issue.** What is the relevance to human cancer risk assessment of mouse liver tumors when they are the only significant response observed in an animal bioassay?
- **Science policy decision.** When mouse liver tumors are the only response observed and when all other conditions for sufficient evidence of carcinogenicity are met, an increased incidence of mouse liver tumors is regarded as sufficient evidence of carcinogenicity in mice and may therefore be indicative of potential carcinogenicity in humans.

As a matter of science policy, EPA decided in the 1986 *Guidelines for Carcinogen Risk Assessment* that mouse liver tumors constitute sufficient evidence of carcinogenicity, even when they are the only observed tumors, as long as all other conditions for sufficient evidence of carcinogenicity are met.[12] According to the guidelines, "sufficient" evidence of carcinogenicity in animals consists of:

> *...an increased incidence of malignant tumors or combined malignant and benign tumors: (a) in multiple species or strains; or (b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or (c) to an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset.13*

On the other hand, characterization of the animal evidence as "limited" implies that data suggesting a carcinogenic effect are limited because:

> *... (a) the studies involve a single species, strain, or experiment and do not meet criteria for sufficient evidence; (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure*

---

9 (EPA 1985, 8-2-8-3, 8-69-8-70)

10 (Campos-Outcalt 1992, 497; IRIS 1993)

11 A high spontaneous background rate is said to occur when the unexposed control group also develops liver tumors. Some mouse strains are known to exhibit high spontaneous background rates of liver tumors. In such instances, the relevance of an increased incidence of these tumors in exposed animals to potential human cancer risks is questionable.

12 (EPA 1986a, 33995)

13 (EPA 1986a, 33999)

> *to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only.*[14]

According to EPA guidelines, an increased incidence of liver tumors in mice, which would otherwise be considered sufficient evidence of carcinogenicity, may be changed to limited evidence of carcinogenicity on a case-by-case basis, if warranted, by the following factors: (1) an increased incidence of liver tumors only in the highest dose group and/or only at the end of the study; (2) no dose-related increase in the portion of total liver tumors that are malignant; (3) the predominant occurrence of benign liver tumors; (4) no dose-related decrease in time to the appearance of liver tumors; (5) nonpositive or inconclusive results from short-term tests of mutagenicity; or (6) the occurrence of excess liver tumors in only one sex.[15]

The regulatory fate of TCE rests on whether the increased incidence of mouse liver tumors is judged to be limited or sufficient evidence of carcinogenicity in animals. According to EPA guidelines, sufficient evidence of carcinogenicity in animals suggests that TCE is a probable human carcinogen (Group B2), whereas limited evidence in animals suggests that TCE is a possible human carcinogen (Group C).[16] EPA generally regulates Group C carcinogens less strictly than Group B2 carcinogens.[17]

An Addendum[18] to the 1985 Health Assessment Document was published in 1987. The Addendum identified positive evidence of carcinogenicity in rats and additional positive evidence in mice via inhalation exposures. The new and previous data were judged to constitute sufficient evidence of carcinogenicity, and affirmed EPA's earlier determination that TCE is carcinogenic in animals.[19] However, the Science Advisory Board (SAB) reviewed the analysis in the Addendum and concluded that:

> *... interpretation of the weight of evidence falls on the continuum between sufficient and limited evidence and could be reasonably judged either way.*[20]

---

[14] (EPA 1986a, 33999)

[15] (EPA 1986a, 33995)

[16] (EPA 1986a, 33400)

[17] For example, a review of Integrated Risk Information System (IRIS) Chemical Profiles indicates that quantitative risk assessments are not performed for many Group C carcinogens. In the Clean Closure Program under the Resource Conservation and Recovery Act, cleanup standards for Group A and B carcinogens are estimated at a 10^{-6} risk, whereas standards for Group C carcinogens are at estimated at a 10^{-5} risk (EPA 1990).

[18] (EPA 1987)

[19] (EPA 1987, 6-4)

[20] (SAB 1988)

Furthermore, neither the National Toxicology Program (NTP) nor the International Agency for Research on Cancer (IARC) considers TCE to be a probable human carcinogen.[21]

EPA withdrew its carcinogenicity assessment of TCE for review in 1989. The current review focuses on whether the available data are limited or sufficient evidence of carcinogenicity in animals.[22] Considerable EPA attention is currently devoted to revising the 1986 Guidelines for Carcinogen Risk Assessment and, within them, the carcinogen classification scheme as well.[23] The revised classification scheme will address issues such as the relevance of mouse liver tumors. Until the guidelines are revised, however, EPA is unlikely to complete the review of the carcinogenicity assessment for TCE. Regulation of TCE as a B2 carcinogen is likely to continue until another major regulatory decision point occurs.

Recent data suggest that the toxicity and carcinogenicity of TCE may be mediated through its metabolites and that the ability of these metabolites to induce peroxisome proliferation[24] may influence the degree of carcinogenicity observed in animal species and humans. A science policy decision was needed to determine whether evidence of species differences in metabolism and peroxisome proliferation might indicate a reduced likelihood that TCE is a human carcinogen.

- **Science policy issue**. Does evidence that the toxicity and carcinogenicity of TCE may be mediated through its metabolites and that the ability of the metabolites to induce peroxisome proliferation indicate a species-specific response that cancer observed in animals is of no relevance to humans?
- **Science policy decision.** Evidence suggesting the possibility of a causal role for peroxisome proliferation in inducing mouse liver tumors is plausible, but unproven, and does not indicate that TCE is not carcinogenic in humans.

Once ingested or inhaled into the body, TCE is metabolized to trichloroacetic acid (TCA) in rats, mice, and humans. TCA—rather than TCE—may be responsible for the liver tumors observed in mice. Mice metabolize very high doses of TCE to TCA more rapidly and completely than other species. TCA is thought to produce liver cancer in mice via a mechanism that is not believed to occur in humans.[25] If induction of liver cancer by TCE is indeed "dependent upon rapid and complete metabolism [to TCA] and subsequent induction of peroxisomal beta oxidation, it would be expected that mice would be

---

[21] (Campos-Outcalt 1992, 497) IARC is scheduled to conduct a re-evaluation of the weight-of- evidence carcinogen classification for TCE in February, 1995.

[22] Note that the interpretation of the existing mice data as being "sufficient" or "limited" has always been of central importance to the debate concerning regulatory approaches to TCE.

[23] (EPA 1992)

[24] *Peroxisome proliferation* refers to an increase in the number of peroxisomes, which are cell organelles that catalyze the production and breakdown of hydrogen peroxide.

[25] (Jaeger and Weiss 1993, 239)

predisposed to that toxicity to a much greater extent than larger species."[26] In other words, mice would be more susceptible to the carcinogenic effects of TCE than humans.

In 1987, the SAB considered the possibility that peroxisome proliferation plays a causal role in inducing mouse liver tumors and concluded that the mechanism was "plausible but unproven."[27] The SAB encouraged further research into this mechanism. If this mechanism were proven, mouse liver tumors could be considered differently in risk assessment because human liver cells may be less sensitive than mouse liver cells to this mechanism.[28]

The carcinogenicity of TCE appears to be mediated through metabolites such as TCA and dichloroacetic acid (DCA). Therefore, it has been suggested that acceptable levels for TCA and DCA in drinking water (175 and 420 µg/L, respectively) indicate that the current drinking water standard for TCE (5 pg/L) is too stringent. Increasing the drinking water standard for TCE by a factor of ten to a level of 50 µg/L would approximately double current TCE exposures.[29]

The current cancer potency estimate for TCE is derived from animal data using a linearized nonthreshold model. However, recent research involving physiologically based pharmacokinetic (PBPK) models indicates that linearized extrapolation of administered doses may be inappropriate in the case of TCE.

- **Science policy issue.** Should PBPK models be used for carcinogenic risk assessment of TCE in humans?
- **Science policy decision.** Results from PBPK models are not suitable for use in estimating carcinogenic risks of TCE exposure in humans.[30]

PBPK models are useful in risk assessment because they describe the distribution and biotransformation of chemicals and estimate target tissue doses of chemicals and their metabolites. [31] In other words:

> *... pharmacokinetic models permit the calculation of internal doses through integration of information on the administered dose, the physiological structure of the mammalian species, and the biochemical properties of the specific chemicals. Predicted internal doses can be*

---

[26] (Steinberg and DeSesso 1993, 141)

[27] (National Research Council (NRC) 1994, 6 15)

[28] (NRC 1994, 6-15-6 16)

[29] (Steinberg and DeSesso 1993, 145-146) Total estimated exposure to TCE assumes inhalation of 20 m^3/day of air containing 5.4 µg/m^3 TCE and ingestion of 2 L/day of drinking water containing: 5 µg/L: Exposure = (20 m^3/day)(5.4 µg/m^3) + (2 L/day)(5 µg/L) = 118 µg TCE/day

50 µg/L: Exposure = (20 m^3/day) (5.4 µg/m3) + (2 L/day) (50 µg/L) = 208 µg TCE/day

[30] This statement is inferred from past actions and does not reflect possible changes in the future.

[31] (Bois, Zeise, and Tozer 1990, 300)

> *correlated with toxicity and/or tumor incidence to yield hypotheses of the mechanisms of action of particular chemicals.*[32]

PBPK modeling shows tremendous promise and some experts consider it "likely to move quantitative risk assessment (and low-dose extrapolation models) to the next level of refinement."[33] Valid data from studies of the absorption, distribution, metabolism, and elimination (ADME) of a chemical are essential for successful PBPK modeling. Bioassays are designed to observe increased incidence of cancer and do not generally include detailed study of ADME. Despite increased research interest in PBPK modeling over the last few years, as of 1988, ADME data were not used in setting 90 percent of regulatory exposure standards because sufficient data had not been developed.[34]

A PBPK model describing how ingested and inhaled TCE is metabolized and distributed in humans has been developed.[35] The model was based on previous work by other researchers[36] and was parameterized with data on urinary levels of TCE and its metabolites obtained from workers.[37] Fifty upper-bound cancer potency estimates ranging from 0.00034 to 0.098 $(mg/kg/day)^{-1}$ were estimated using the linearized multistage model and the PBPK-modeled effective dose of TCE metabolites.[38] For comparison, the EPA potency estimate for ingested TCE is 0.011 $(mg/kg/day)^{-1}$,[39] which is within the range estimated using the PBPK model. This research illustrates that detailed knowledge of the ADME of chemical agents and of the mechanism through which their carcinogenic effects are exerted can both improve and increase the complexity of risk assessment.

Drinking Water Regulations for Trichloroethylene

The Maximum Contaminant Level Goal (MCLG) for TCE in drinking water was set at zero in 1985.[40] EPA policy is to set MCLGs, which are "goals" rather than legally enforceable standards, for known and probable human carcinogens (Groups A and B, respectively) at zero. EPA currently regards TCE as a Group B2 probable human carcinogen. A change in classification of TCE as a Group C possible human carcinogen

---

[32] (Andersen et al. 1987, 186)

[33] (Paustenbach 1989, 39)

[34] (Watanabe, Schumann, and Reitz 1988, 412)

[35] (Bogen 1988)

[36] (Ramsey and Andersen 1984; Fernandez et al. 1977)

[37] (Ikeda et al. 1972)

[38] (Bogen 1988, 463-164)

[39] (EPA 1985)

[40] 50 FR 46880.

could trigger a change in the MCLG because Group C carcinogens are not regulated as carcinogens under the Safe Drinking Water Act (SDWA).

The Maximum Contaminant Level (MCL) for TCE, which is the maximum allowable concentration in drinking water, was finalized at 5 µg/L in 1987.[41] The MCL is not a risk-based number, but was established on the basis of detection limits.[42] EPA followed the statutory mandate of the SDWA and established the MCL as close as "feasible" to the MCLG. "Feasible" is defined in the Act to be the best that can be achieved using the "best technology, treatment techniques and other means which ... are available (taking cost into consideration)." If the MCLG were revised upward, the MCL likely would follow.

Remediation of Trichloroethylene in Groundwater

The Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) requires that cleanups at hazardous waste sites reduce contaminant concentrations to below applicable or relevant and appropriate requirements (ARARs).[43] EPA's ARARs policy for contaminants in groundwater states:

> *Non-zero MCLGs and, if none, MCLs promulgated under SDWA, generally will be the relevant and appropriate standards for ground water that is or may be used for drinking, considering its use, value and vulnerability as described in EPA's Ground-Water Protection Strategy, e.g, for Class I and II aquifers.*[44]

MCLs may not be applied as ARARs if it is technically impracticable to achieve them.[45] Cleanup standards for TCE in groundwater at Superfund sites range from 1 to 5 µg/L.[46] In 80 percent of the cases, the TCE cleanup standard is based on the MCL. More stringent standards are based on site-specific risk assessments, "background" concentrations, and different state standards. The relative consistency of cleanup standards for TCE in groundwater at Superfund sites is due to the availability of federal

---

[41] The final MCL was published on July 8, 1987 (52 FR 25690).

[42] (IRIS 1993)

[43] (EPA 1989) Applicable requirements are "cleanup standards, standards of control, and other substantive environmental protection requirements, criteria, or limitations promulgated under Federal or State law that specifically address a hazardous substance, pollutant, contaminant, remedial action, location, or other circumstance at a CERCLA site." Relevant and appropriate requirements are "substantive environmental protection requirements ... promulgated under Federal or State law that, while not 'applicable,' ... address problems or situations sufficiently similar to those encountered at the CERCLA site that their use is well suited to the particular site."

[44] (EPA 1991) As determined by an evaluation consistent with the EPA Ground-Water Protection Strategy, Class I aquifers are either ecologically vital or an irreplaceable source of drinking water, while Class II aquifers are either current or potential sources of drinking water (EPA 1986b, 46-51).

[45] (EPA 1989, 5) Other waiver mechanisms are available, including: interim measure waiver, equivalent standard of performance waiver, greater risk to health and the environment waiver, inconsistent application of state standard waiver, and fund-balancing waiver.

[46] (Booth and Jacobson 1992, 764)

criteria such as MCLs. EPA's emphasis on standardized human health risk assessments—especially at sites where the groundwater is not potable and at which cleanup standards have been set below the MCL—has been criticized because it "has resulted in many sites being cleaned up even though there is no present human exposure, future public health risks are unlikely, and there is no ecological risk."[47] Applying ARARs as cleanup standards has been identified as one of the main drivers of excessively expensive cleanup costs.[48] Average cleanup costs at Superfund sites currently range from $30 to $50 million. Cleaning up the 1,256 sites on the National Priorities List (NPL) will cost at least $38 to $62 billion, and some cost estimates range from $0.5 to $1 trillion for all hazardous waste sites.[49] A recent Congressional Budget Office study suggested that cleanup of nonfederal Superfund sites will cost approximately $74 billion through the year 2070.[50]

The requirement to reduce TCE concentrations to the MCL drives the costs of cleanups at sites where this contaminant is detected. Remediation costs for TCE-contaminated groundwater can be quite expensive, ranging from $1 million to contain a contaminated groundwater plume[51] up to $17.3 million and even up to $40 million for long-term pump-and-treatment systems.[52] Requiring cleanup of groundwater that is not a source of drinking water to health-based levels increases the cost and time horizon for groundwater remediation. Revising the basis of the MCL to noncarcinogenic effects or implementing another standard for applicability to nonpotable or nonproductive groundwater aquifers could reduce remediation costs at all sites where groundwater is contaminated with TCE.

Evaluation

The classification of TCE as a probable human carcinogen (Group B2) currently drives all regulatory actions concerning TCE by the EPA. This situation persists:

- While EPA considers a revision of weight of evidence of the carcinogenicity of TCE;
- Despite the conclusions of the NTP and IARC that TCE is probably not a human carcinogen; and
- While evidence—and support—is building for the case that TCE is not as carcinogenic as once thought or that it is not carcinogenic in humans at all.

---

47 (Booth and Jacobson 1992, 765)

48 (Hazardous Waste Cleanup Project (HWCP) 1993, 5)

49 (Insurance Information Institute 1993)

50 (Congressional Budget Office (CBO) 1994, 13)

51 (Bureau of National Affairs (BNA) 1989a)

52 (BNA 1990; BNA 1989b)

Although the likelihood for change is uncertain, this case study illustrates that the carcinogenicity evaluation of TCE could be changed if alternatives to the default science policy assumptions are used.

Were the EPA re-evaluation of the carcinogenicity of TCE to conclude that it is not a probable human carcinogen, widespread changes could result in the regulatory landscape. The MCLG could be changed to a nonzero value, and then the MCL might also be revised upwards. Records of decision for Superfund sites would reflect this change by applying the new MCL as a cleanup standard. Standards for TCE under other regulatory programs could also be subject to change. However, pressures to change groundwater cleanup requirements may have an even greater impact on simplifying and reducing the expenses of remedial actions at Superfund sites.

REFERENCES

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). 1994. 1993 CERCLA Priority List of Hazardous Substances That Will Be the Subject of Toxicological Profiles & Support Document. Atlanta, Ga.

ANDERSEN, M.E., H.J. CLEWELL III, M.L. GARGAS, F.A. SMITH, and R.H. REITZ. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87:15—205.

BOGEN, K.T. 1988. Pharmacokinetics for regulatory risk analysis: The case of trichloroethylene. Regul. Toxicol. Pharmacol. 8:447—466.

BOIS, F.Y., L. ZEISE, and T.H. TOZER. 1990. Precision and sensitivity of pharmacokinetic models for cancer risk assessment: Tetrachloroethylene in mice, rats, and humans. Toxicol. Appl. Pharmacol. 102:300-315.

BOOTH, P.N., and M.A. JACOBSON. 1992. Development of cleanup standards at superfund sites: An evaluation of consistency. J. Air Waste Manage. Assoc. 42(6):762-766.

BUREAU OF NATIONAL AFFAIRS (BNA). 1990. Environment Reporter 21:1258 (November 2, 1990).

BUREAU OF NATIONAL AFFAIRS (BNA). 1989a. Environment Reporter 19:2267 (February 17, 1989).

BUREAU OF NATIONAL AFFAIRS (BNA). 1989b. Environment Reporter 20:1434 (December 22, 1989).

CAMPOS-OUTCALT, D. 1992. Trichloroethylene: Environmental and occupational exposure.

American Family Physician 46(2):495-500.

CONGRESSIONAL BUDGET OFFICE (CBO). 1994. The Total Costs of Cleaning Up Non- Federal Superfund Sites. Natural Resources and Commerce Division, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992. Working Paper for Considering Draft Revisions to the U.S. EPA Guidelines for Cancer Risk (Review Draft). Office of Research and Development, Washington, D.C. EPA/600/AP-92/003.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991. ARARs Q's & A's: General Policy, RCRA, CWA, SDWA, Post-ROD Information, and Contingent Waivers. Office of Solid Waste and Emergency Response, Washington, D.C. OSWER Pub. No. 9234.2-01/FS-A.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1990. Corrective action for solid waste management units at hazardous waste management facilities (Proposed rule). Fed. Reg. 55(145):30798-30884.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1989. Overview of ARARs: Focus on ARAR Waivers. Office of Solid Waste and Emergency Response, Washington, D.C. OSWER Pub. No. 9234.2-03/FS.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1987. Addendum to the Health Assessment Document for Trichloroethylene: Updated Carcinogenicity Assessment for Trichloroethylene. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/006FA.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986a. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1986b. Guidelines for Ground-Water Classification under the EPA Ground-Water Protection Strategy (Final Draft). Office of Ground Water Protection, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1985. Health Assessment Document for Trichloroethylene. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/006F.

FERNANDEZ, J.G., P.O. DROZ, P.E. HUMBERT, and J.R. CAPEROS. 1977. Trichloroethylene exposure simulation of uptake, excretion, and metabolism using a mathematical model. Br. J. Ind. Med. 34:43-55.

HAZARDOUS WASTE CLEANUP PROJECT (HWCP). 1993. Sticker Shock: Recognizing the Full Cost of Superfund Cleanups. Hazardous Waste Cleanup Project, Washington, D.C.

IKEDA, M., H. OHTSUJI, T. IMAMURA, and Y. KOMOIKE. 1972. Urinary excretion of total trichloro-compounds, trichloroethanol, and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. Br. J. Ind. Med. 29:328—333.

INSURANCE INFORMATION INSTITUTE. 1993. What You Need to Know About Superfund. New York, N.Y.

INTEGRATED RISK INFORMATION SYSTEM (IRIS). 1993. Chemical Profile: Trichloroethylene (Updated 11/01/93). Environmental Criteria and Assessment Office, Environmental Protection Agency, Cincinnati, Ohio.

JAEGER, R.J., and A.L. WEISS. 1993. Trichloroethylene: Toxicology and epidemiology: A

critical review of the literature. Chapter 10 in K.R. Foster, D.E. Bernstein, and P.W. Huber (eds.), Phantom Risk—Scientific Inference and the Law. Cambridge, Mass.: MIT Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on Risk Assessment of Hazardous Air Pollutants. 1994. Science and Judgment in Risk Assessment. Washington, D.C.: National Academy Press.

PAUSTENBACH, D.J. 1989. A survey of risk assessment. Chapter 1 in D.J. Paustenbach (ed.), The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

RAMSEY, J.C., and M.E. ANDERSEN. 1984. Species differences in response to trichloroethylene: Pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol. 73:159-175.

SCIENCE ADVISORY BOARD (SAB). 1988. Evaluation of draft addendum to the health assessment document for trichloroethylene: Letter to Lee M. Thomas, EPA Administrator, from the

Halogenated Organics Subcommittee of the Environmental Health Committee, dated March 9, 1988. Environmental Protection Agency, Washington, D.C. SAB-EHC-88-012.

STEINBERG, A.D., and J.M. DeSESSO. 1993. Have animal data been used inappropriately to estimate risks to humans from environmental trichloroethylene? Regul. Toxicol. Pharmacol. 18:137-153.

WATANABE, P.G., A.M. SCHUMANN, and R.H. REITZ. 1988. Toxicokinetics in the evaluation of toxicity data. Regul. Toxicol. Pharmacol. 8:408-113.

10
WORKPLACE INDOOR AIR QUALITY

Introduction

The Occupational Safety and Health Administration (OSHA) recently proposed to regulate indoor air quality (IAQ) in the workplace. Improved IAQ is intuitively desirable, but scientific data concerning IAQ are sparse. This lack of data limits OSHA's ability to assess the health risks posed to workers by poor IAQ. In addition to measures designed to address other IAQ contaminants, the proposed regulation includes a ban on workplace smoking, except in specially designated and separately ventilated areas. A substantial amount of scientific data is available concerning the potential health consequences of exposure to environmental tobacco smoke (ETS). This case study examines the science policy associated with OSHA's risk assessment for ETS and the estimated costs and benefits of the proposed smoking ban. The implications of the ETS risk assessment for the remainder of the proposed rule are also considered. In addition to focusing on OSHA's current use of science policy, this case study describes science policy issues and decisions associated with the use of epidemiology.

Science Policy Issues Addressed in This Case Study
➢ Interpretation of epidemiologic studies ➢ Statistical significance in epidemiologic studies ➢ Use of surrogates for actual exposure data ➢ Estimating risk from epidemiologic studies ➢ Estimating population risk

Background

In May 1987, three public interest groups petitioned OSHA to issue an Emergency Temporary Standard prohibiting smoking in most indoor workplaces.[1] OSHA denied the petitions in September 1989 on the basis that insufficient exposure data were available

[1] The public interest groups are the American Public Health Association, Public Citizen, and Action on Smoking and Health. The petition was filed pursuant to §6(c) of the Occupational Safety and Health Act (OSHAct), 29 U.S.C. 655(c).

to support the finding of "grave danger" required by law.[2] The October 1989 appeal of OSHA's denial by the public interest groups was denied in May 1991. The U.S. Court of Appeals for the District of Columbia Circuit ruled that OSHA could not sufficiently quantify the workplace risk associated with ETS to justify the issuance of an Emergency Temporary Standard.

In September 1991, OSHA issued a Request for Information (RFI) concerning workplace indoor air quality (IAQ) problems, including health effects attributable to poor indoor air quality, ventilation systems performance, exposure assessment, abatement methods, and information concerning specific contaminants such as ETS.[3]

In response to the RFI, OSHA received more than 1,200 comments from interested persons, groups, unions, and industries. OSHA summarized the comments as follows: [4]

- 75 percent favored regulation of IAQ.
- 21 percent favored regulation of ETS only.
- 41 percent favored regulation all indoor air contaminants as a single substance.
- 13 percent favored regulation of ETS separately from, but in addition to, all other indoor air contaminants.

According to OSHA, the submitted data supported the conclusion that indoor air contaminants and other indoor air quality factors can significantly increase the risk of numerous adverse health effects, including: sensory irritation, respiratory allergies, asthma, nosocomial infections, humidifier fever, hypersensitivity pneumonitis, Legionnaire's disease, and the signs and symptoms characteristic of exposure to chemical or biologic substances such as carbon monoxide, formaldehyde, pesticides, endotoxins, or mycotoxins.[5] Additional support for the regulation of ETS was provided by the December 1992 EPA risk assessment for ETS. In that report, EPA concluded that ETS is a human lung carcinogen which is responsible for approximately 3,000 lung cancer deaths in adults each year.[6]

In April 1994, OSHA proposed to regulate IAQ. The proposed regulation would require employers to: [7]

- Eliminate worker exposure to, or achieve a permissible exposure limit (PEL) of zero for ETS by restricting indoor smoking to specially designated, separately ventilated enclosed rooms;[8]

---

[2] (OSHAct, §6(c))

[3] (Occupational Safety and Health Administration (OSHA) 1991)

[4] (OHSA 1994, 15968-15969)

[5] (OSHA 1991, 15969)

[6] (EPA 1992)

[7] (OSHA 1994)

- Implement controls for specific contaminants and their sources, including outdoor contaminants, maintenance and cleaning chemicals, pesticides, and other hazardous chemicals within indoor work environments;
- Limit the degradation of IAQ during renovation and remodeling; and
- Develop a written IAQ compliance plan and implement that plan through actions such as inspection and maintenance of building systems that influence IAQ.

In order for OSHA to finalize this proposed rule, several prerequisites must be met. As for other permanent OSHA standards for health and safety, OSHA must determine that: (1) a significant risk of harm is present in the workplace; and (2) a standard is necessary to reduce or eliminate that risk.[9] Under Section 6(f) of the Occupational Safety and Health Act, OSHA regulations must be supported by substantial evidence in the record considered as a whole. According to OSHA's interpretation of the Benzene decision, a risk from occupational exposure on the order of 1 in 1,000 ($1x10^{-3}$) over a forty-five- year working lifetime may be considered a significant risk.[10] With respect to OSHA's use of science policy:

> *The lesson of Benzene is clearly that OSHA may use assumptions, but only to the extent that those assumptions have some basis in reputable scientific evidence. If the agency is concerned that the standard should be more stringent than even a conservative interpretation of the existing evidence supports, monitoring and medical testing may be done to accumulate the additional evidence needed to support that more protective limit. Benzene does not provide support for setting standards below the level substantiated by the evidence. Nor may OSHA base a finding of significant risk at lower levels of exposure on unsupported assumptions using evidence of health impairments at significantly higher levels of exposure.*[11]

---

[8] This proposal stands in contrast to OSHA's general policy of establishing nonzero PELs for occupational hazards, even for substances widely accepted as human carcinogens, including radiation and benzene.

[9] Industrial Union Department, AFL-CIO v. American Petroleum Institute, 444 U.S. 607, 639-642 (1980) (Benzene decision).

[10] This interpretation is based on the following dicta in the Benzene decision: "It is the Agency's responsibility to determine in the first instance what it considers to be a 'significant' risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk could clearly not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it." (OSHA 1994, 16000), citing (Benzene decision, 655).

[11] *AFL-CIO v. OSHA*, 965 F.2d 962, 979 (11th Cir. 1992). *(Air Contaminants* decision)

OSHA's failure to comply with these requirements has resulted in courts striking down OSHA rules.[12]

In the proposed IAQ rule, OSHA estimated the following risks:

- **Lung cancer attributed to ETS.** OSHA estimated between 144 and 722 cases of lung cancer occur annually among nonsmokers due to ETS exposure in the workplace. The corresponding risk level was calculated to be a lxl O^{-3} increase in risk of lung cancer over a forty-five-year working lifetime of exposure to ETS in the workplace.
- **Heart disease attributed to ETS.** OSHA estimated that between 2,094 and 13,000 deaths from heart disease occur annually among nonsmoking workers due to ETS exposure in the workplace. The corresponding risk level was estimated to be between $7x10^{-3}$ and 16x1 O^{-3} over a forty-five-year working lifetime of exposure to ETS in the workplace.
- **Headache from poor IAQ**. The excess risk of severe, nonmigraine headaches which may require medical attention was estimated to be $5.7x10^{-3}$ over a forty- five-year working lifetime of exposure to poor workplace IAQ.
- **Upper respiratory symptoms.** The excess risk of developing upper respiratory symptoms of sufficient seriousness to require medical attention is estimated to be $8.5x10^{-3}$ over a forty-five-year working lifetime of exposure to poor workplace IAQ.

Under OSHA's interpretation of the *Benzene* decision, these risks are "significant" because they are on the order of $lx10^{-3}$. Because these risk levels are estimates, it is worthwhile to examine the science policy issues and decisions that are essential in calculating them. OSHA's preliminary risk estimate for lung cancer from ETS is discussed in this case study because:

- Significantly more data were available to OSHA concerning lung cancer from ETS exposure. This implies that, for the proposed rule's other risk estimates, the gaps and uncertainties in scientific knowledge and data are greater and the science policy decisions are supported by less scientific knowledge and information.[13]
- The basic methodology used by OSHA to estimate worker lung cancer risk from ETS exposure was also used to estimate heart disease deaths attributed to ETS exposure, and upper respiratory illnesses and headaches attributed to poor workplace IAQ.[14]

---

[12] See e.g., Benzene and Air Contaminants decisions.

[13] There were thirty-one epidemiologic studies available to OSHA concerning lung cancer and ETS exposure, eleven epidemiologic studies available concerning heart disease and lung cancer, and one study available concerning upper respiratory illnesses and headaches.

[14] (OSHA 1994, 15996)

In short, the ETS-lung cancer risk assessment serves as a "yardstick" for the other risk assessments.

OSHA's Preliminary Risk Assessment for ETS and Lung Cancer

OSHA's first step in its preliminary risk estimate was to critically review and interpret the thirty-one relevant epidemiologic studies then available (*see* Table 10^{-1}).[15] The interpretation of epidemiologic studies is not entirely objective, requires judgment, and is therefore a matter of science policy. Although the fundamental strength of an epidemiologic study is that it is based on actual human experience, the fundamental weakness of such a study is that there is a great deal of variability among humans which may not be controllable through epidemiologic study design and methods. As the National Research Council (NRC) characterized such variability:

> *People move around, eat different foods, engage in different social and recreational activities, have different genetic backgrounds, and live lives with the full diversity of the human experience*[16]

As a consequence of this variability, epidemiologic data are not accepted at face value. The NRC has identified a number of basic criteria to be used in the interpretation of epidemiologic data, including: [17]

[15] (OSHA 1994, 15992). Studies cited are all fully identified in the References at the end of this chapter; "Brownson" refers to (Brownson 1992).

[16] (NRC 1991, 29)

[17] (NRC 1991, 32, 35—42)

Table 10·1. Epidemiologic Studies of Spousal Exposure to ETS

Study	OSHA Characterization	Reported Increase in Risk (%)	*P* Value[a]	95% Confidence Interval	Reported as Statistically Significant?
Brownson 1992	Positive	0	N/R[d]	(0.80,1.20)	No
Correa	Positive	107	N/R[d]	N/R[d]	No
Fontham	Positive	29	N/R[d]	(0.99,1.69)	No
Garfinkel	Positive	31	N/R[d]	(0.94,1.83)	No
Geng	Positive	116	<0.05	(1.03,4.53)	Yes
Hirayama	Positive	45	0.00178	(1.04,2.02)[e]	No
Humble	Positive	110	N/R[d]	(0.70,6.90)[e]	No
Inoue	Positive	125	N/R[d]	(0.91,7.10)	No
Kalandidi	Positive	111	N/R[d]	(1.09,4.08)	Yes
Lam	Positive	65	<0.01	(1.16,2.35)	Yes
Pershagen	Positive	20	N/R[d]	(0.70,2.10)	No
Sandler[b]	Positive	N/A	N/A	N/A	N/A
Stockwell	Positive	60	N/R[d]	(0.80,3.00)	No
Trichopoulos	Positive	140	<0.02	(1.22,4.71)	Yes
Akiba	Equivocal+	50	0.07	(1.00,2.50)[e]	No
Butler	Equivocal+	101	N/R[d]	(0.39,8.79)	No

Gao	Equivocal+	-10	N/RA[d]	(0.60,1.40)	No
Gillis	Equivocal+	N/A[b]	N/R[d]	N/R[d]	N/R[d]
Kabat[a]	Equivocal+	-11	N/R[d]	(0.69,1.13)	No
Brownson 1987	Equivocal	68	N/R[d]	(0.39,2.97)	No
Buffler	Equivocal	-22	N/R[d]	(0.34,1.81)	No
Chan	Equivocal	-26	N/R[d]	(0.59,1.18)	No
Hole	Equivocal	141	0.30	(0.45,12.83)	No
Janerich	Equivocal	-22	N/R[d]	(0.41,1.50)	No
Katada	Equivocal	N/A[b]	N/R[d]	N/A[b]	No
Koo	Equivocal	55	N/R[d]	(0.94,3.08)	No
Lee	Equivocal	0	N/R[d]	(0.37,2.71)	No
Shimizu	Equivocal	10	N/R[d]	N/R[d]	No
Sobue	Equivocal	23	N/R[d]	(0.91,1.67)	No
Svensson[a]	Equivocal	20	N/R[d]	(0.49,2.90)	No
Wu	Equivocal	20	N/R[d]	(0.50,3.30)	No

[a]ETS exposure includes spousal and occupational.
[b]Lung cancer not reported independently from other cancers.
[c]*See* n.14.
[d]Data not reported.
[e]90 percent confidence interval reported.

- Statistical significance. The results of an epidemiologic study are generally reported in terms of an estimate of relative risk and an accompanying confidence interval.18 By convention, the results of epidemiologic research are usually considered statistically significant if there is less than a 5 percent chance that the observed results occurred by chance.19 For example, of the thirty-one ETS studies, twenty-seven were not reported as statistically significant at the conventional level.[20]

- Strength of the association. Generally, the greater the magnitude of a relative risk statistic, the greater the likelihood that the observed increase is a "true" increase in risk. The relative risk of lung cancer for cigarette smokers may reach as high as 10.0 or greater, but there is less certainty in ETS studies, where relative risk estimates have been reported to range from 0.9 to 2.0. Relative risk estimates in this range, and even those as high as 3.0, are considered to be "weak associations."21 With respect to weak associations:[22]

  ...the closer the risk of some association comes to unity, the more likely it is that choice of the comparison standard, bias, confounding, or inappropriate analysis may explain it and the greater the need for thorough understanding of the underlying biological mechanisms.

- **Specificity of the association**. The exposure of concern should have caused the observed increased incidence in disease. There should be no other factor(s), known as confounding factors, to which the observed incidence of disease could be attributable. In studies concerning ETS exposure and lung cancer, confounding risk factors, such as smoking status, radon exposure, occupational exposure to other lung carcinogens, previous or familial history

---

[18] *Relative risk* is a measure which compares the observed risk of disease in exposed persons with that of unexposed persons (NRC 1991, 35). Other measures of risk include the standard mortality ratio and odds ratio, hereinafter referred to as relative risk. A relative risk of 1.5 indicates that the risk of disease is 50 percent greater among those who are exposed than those who are unexposed. A relative risk of 1.0 or below indicates no observed increase in risk. A relative risk is generally considered to be statistically significant if it has a P-value of 0.05 or less. This means that there is a five percent chance that the observed relative risk is due to chance. Confidence intervals express the range of likely values of the relative risk. For example a relative risk of 1.5 and 95 percent confidence interval of 1.0 to 2.0 means that there is a 95 percent chance that the "true" relative risk is between 1.0 and 2.0

[19] The selection of a level of statistical significance is somewhat arbitrary; i.e., study results may be reported at a 99 percent, 90 percent or even lower confidence level, depending on the level of uncertainty acceptable from a particular analysis. A confidence interval which has a lower bound of 1.0 or less is generally not considered to be statistically significant. Confidence intervals can also be used to make results which are not statistically significant at one level significant at another level. For example, a confidence interval reported at the 95 percent level to be (0.90, 1.6) may be reported at a 90 percent level to be (1.05, 1.8). *See, e.g*. (Congressional Research Service [CRS] 1994, 5).

[20] See Table 10-1.

[21] (Wynder 1987)

[22] (Wynder 1987)

of lung disease, age, and diet, should preferably be controlled for in the study design or, at a minimum, accounted for in the statistical analysis.

- **Consistency of the association.** The observed increase in risk should occur regularly in independently conducted studies. Although the relative risk of lung cancer from ETS exposure may be low, observed increases in relative risk (from 10 percent to 141 percent) have been reported in numerous, independently conducted studies from several countries. However, it also should be noted that a number of studies have not reported an increase in lung cancer risk from ETS exposure.[23]
- **Temporality.** Exposure should occur at a reasonable interval before the onset of symptoms of the disease of interest. For tobacco-induced lung cancer, this period is often twenty-five years or more.
- **Increase in risk with increased exposure.** Generally, increased exposure to a hazardous substance results in increased risk of disease. Epidemiologic data should reflect a positive dose-response relationship.
- **Effects of the removal of a suspected cause**. Removal of the suspected cause should reduce or eliminate the suspected effect, unless it is irreversible. For example, on the basis of population data, reductions in cigarette smoking have been reported to be associated with reduced rates of lung cancer.
- **Biological plausibility.** The observed association between exposure to an agent and increase in risk of disease should make sense from a biological standpoint. Results from animal bioassays can indicate mechanisms of disease or directly corroborate the association observed in the epidemiologic study.

OSHA stated that standard epidemiologic and statistical criteria concerning causation were used to support its characterizations of the ETS epidemiologic studies.[24] Thus, given the necessity for subjective characterization of each ETS epidemiologic study by OSFIA, the relevant science policy issue is as follows:

- **Science policy issue.** For each individual epidemiologic study, does the study suggest an association between exposure to ETS and increased incidence of lung cancer?
- **Science policy decision.** OSHA determined that of the thirty-one available studies concerning ETS exposure and lung cancer, fourteen were characterized as "positive" for the association between ETS exposure and lung cancer, five were "equivocal" but showed a "positive trend of association," and twelve were "equivocal."

[23] *See* Table 10-1.

[24] (OSHA 1994, 15993)

See Table 101 for OSHA characterization of the individual ETS epidemiologic studies. Although detailed discussion of each study's characterization by OSHA is beyond the scope of this report, some observations should be noted:

- **Evaluation of statistical significance.** Of the fourteen studies that were characterized as positive by OSHA, only four studies actually reported increases in risk of lung cancer from ETS which were statistically significant at the conventional 95 percent level. The lack of statistical significance means that there is a 5 percent or greater probability that the study results may be attributable to chance.
- **Evaluation under the other NRC criteria.** Of the four studies reporting a statistically significant increase in risk, EPA evaluated them as follows in its 1992 ETS risk assessment:[25]
  - The study by Geng was determined to be one of the least useful epidemiologic studies on ETS because: (1) former smokers, who have a higher rate of lung cancer than never-smokers, were included in the study population in an uncontrolled manner; and (2) the study was conducted in a region of China where indoor air is heavily polluted with smoke from the burning of coal, another potentially significant confounding factor.26
  - The study by Trichopoulos was determined to be less useful than other epidemiologic studies on ETS because: (1) the study includes former smokers; (2) other confounding factors, such as diet, cooking, and heating practices, were not addressed in the study; (3) lung cancer cases were not histologically confirmed; and (4) data collection may have been biased.[27]
  - The study by Lam was determined to be suggestive of an association between lung cancer and ETS exposure, but the study authors disregarded potential confounding factors.[28]
  - The study by Kalandidi was determined to be a well-conducted study concerning ETS exposure and lung cancer.

Thus, only one of the fourteen studies characterized by OSHA as positive is both statistically significant and well conducted according to EPA. This raises the following science policy issue:

- **Science policy issue**. Is conventional statistical significance a prerequisite for characterizing an epidemiologic study as positive evidence of a causal

[25] The EPA evaluation of these studies is relevant given that OSHA has cited the EPA ETS risk assessment as support for its own risk assessment for ETS and lung cancer.

[26] (EPA 1992, A-56-59)

[27] (EPA 1992, A-124-128)

[28] (EPA 1992, A-96-A-98)

association between exposure to a potential hazard and observed incidence of disease?

- **Science policy decision.** Conventional statistical significance is not required to characterize an epidemiologic study as positive evidence of a causal association. The implication of this science policy decision is that positive epidemiologic associations which occur by chance or as the result of poor study design are considered as evidence of a causal association.

Importantly, none of the thirty-one studies was based on standardized or validated information on actual exposures to ETS, which raises the following science policy issue:[29]

- **Science policy issue**. Where information on actual human exposures to a potential hazard is not available and surrogates for such data are used in an epidemiologic study, should the validity of such surrogates be demonstrated?
- **Science policy decision**. The validity of surrogate exposure information in epidemiologic studies does not need to be verified.

Subjects in the thirty-one studies were generally nonsmoking women who were married to smoking spouses. For purposes of these studies, the amount of exposure to ETS was assumed to be a function of the length of time married to a smoker and the number of cigarettes the smoker smoked, regardless of whether smoking occurred in the presence of the nonsmoking spouse. Data concerning the length of time married to a smoker and amount of tobacco used by the smoker were collected by interview either with the nonsmoking spouse or next of kin. This data collection method may have introduced a potential for recall bias and information bias.

The Congressional Research Service (CRS) recently pointed out that the ETS epidemiologic studies are somewhat limited in their ability to associate lung cancer with ETS exposure:

- *Given the small risks that are often found for passive smoking, the statistical problems inherent in epidemiological studies are of far greater concern for passive smoking than for active-smoking studies.*[30]
- *These studies do not have (and indeed cannot have) very precise estimates of exposure from environmental tobacco smoke. The data are based on interviews of subjects or their relatives. If errors in measurement occur in a systematic way that are correlated with development of the disease, the effect would be to bias the results. An example would be if those individuals who developed lung*

[29] (EPA 1992, 3-49, 3-53). *See also* (Brownson, Alavanja, and Hock 1992).

[30] (CRS 1994, 3)

cancer (or relatives of those individuals) remembered or perceived their exposure differently from those who did not develop the disease.[31]

- *Another concern is the possibility that some subjects classified as nonsmokers are actually current or former smokers and that such current or former smokers are more likely to be married to husbands that smoke... it is not possible to correct precisely for this problem. That is, it remains possible that a relationship observed might reflect the effects of active rather than passive smoking.*[32]
- *If wives of smokers share in associated poor health habits or other factors that could contribute to illness and that are not or cannot be controlled for, statistical associations found between disease and passive smoking could be incidental or misleading. Such an error could also render a relationship between risk and degree of exposure spurious.*[33]

It should be noted that these limitations are not unique to the ETS epidemiology. Consequently, they are more illustrative of the limitations of the epidemiologic method, not a lack of risk. The limitations of the epidemiologic method are such that small actual risks may not be detected but spurious weak associations may be identified.

Nonetheless, although fourteen of the ETS epidemiologic studies were characterized as positive by OSHA, nine of them could alternatively and justifiably be characterized as equivocal based on statistical significance criteria. All studies have some degree of additional uncertainty associated with them due to lack of information concerning the validity of the exposure assumptions and confounding factors. Considering EPA's prior evaluation of the thirty-one studies, only one study with conventional statistical significance merits characterization as positive. So why would OSHA characterize so many studies as positive? Perhaps because such characterization is viewed by OSHA as necessary to support a quantitative risk assessment which will survive judicial scrutiny under the *Benzene* decision.

Having interpreted the available body of data as associating lung cancer risk with ETS exposure, OSHA's next step was to determine the magnitude of the increase in risk.

- Science policy issue. What is the magnitude of the increase in lung cancer risk from ETS exposure?
- Science policy decision. Based on the thirty-one studies, OSHA concluded that the relative risk of lung cancer due to chronic exposure to ETS ranges between 1.20 and 1.50 (i.e., between a 20 and 50 percent increase in risk of lung cancer from chronic ETS exposure).

---

[31] (CRS 1994, 7)

[32] (CRS 1994, 7)

[33] (CRS 1994, 7-8)

This science policy decision involved a substantial amount of judgment, given that:

- Among the fourteen studies characterized by OSHA as positive, relative risk estimates ranged from 1.00 to 2.40, which corresponds to a zero to 140 percent increase in lung cancer risk. Among the four studies which reported statistically significant increases in lung cancer risk, the range is 65 to 140 percent.
- Among the five studies which were characterized by OSHA as equivocal with a positive trend, relative risk estimates ranged from -11 to 101 percent. None of these studies reported statistically significant increases in risk.
- Among the twelve studies which were characterized by OSHA as equivocal, relative risk estimates ranged from -25 to 141 percent. None of these studies reported statistically significant increases in risk.

OSHA did not provide an explicit rationale for the science policy decision that chronic exposure to ETS increases lung cancer risk by 20 to 50 percent. This science policy decision lays a foundation for the next science policy decision.

Having identified a range for the increase in lung cancer risk from ETS exposure, OSHA's next step was to select a point estimate of relative risk on which to base the estimates of lung cancer deaths attributable to ETS exposure in the workplace.

- **Science policy issue.** Given the estimated range of relative risk of lung cancer from ETS exposure, what single relative risk value should be used to calculate lung cancer deaths attributable to occupational ETS exposure?
- **Science policy decision.** OSHA selected the point estimate of 1.34 reported in the study by Fontham for occupational exposure to ETS.

Of the thirty-one studies, six studies (presented in Table 10-2) reported relative risks for occupational exposures to ETS:

Table 10-2. Occupational Exposure to ETS

Study	OSHA Characterization	Reported Risk Increase (%)	P Valuea	Confidence Interval	Reported As Statistically Significant?
Brownson 1992[b]	Positive	0	N/R[c]	N/R[c]	N/R[c]
Fontham	Positive	34	<0.05	(1.03, 1.73)	Yes
Garfinkel	Positive	-12	N/R[c]	(0.66, 1.18)	No
kabat	Equivocal+	-17	<0.045	(0.56, 1.21)	No
Shimizu	Equivocal	20	>0.05	N/R[c]	No
Wu	Equivocal	30	N/R[c]	(0.50, 3.30)	No

[a] *See n.18.*

[b] *Authors reported a 20 percent increase in risk with a 95 percent confidence interval of (0.90,1.70) at the highest quartile of workplace exposure. This increase is not statistically significant.*

[c] *Data not reported.*

The selected point estimate falls in the middle of the previously determined range of lung cancer risk from ETS exposure. OSHA's stated basis for using the Fontham study is that it: (1) was conducted in the United States; (2) contained a large population- based study whose results can be generalized to the public; (3) controlled for misclassification of smokers; (4) used multiple sources to ascertain nonsmoking status and validate subject response; (5) questioned study subjects twice; (6) confirmed self- reported smoking status by urinary cotinine measurements; (7) cross-referenced medical records with the physician's assessment; (8) collected occupational exposure data; and (9) ascertained an estimate of lung cancer risk attributable to the workplace.

However, the Fontham study's occupational risk estimates may be overstated because they may be confounded by uncontrolled and unaccounted for nonoccupational exposures to ETS, including exposures in the household and social settings. The Fontham study reported increases in lung cancer risk of 23 percent from household exposures to ETS, 50 percent from social exposures to ETS, and 39 percent from occupational exposure to ETS.[34] The authors acknowledge that these exposures may be concurrent *(i.e.*, study subjects may have lived with smokers, worked with smokers, and

[34] These estimates are from the final version of the Fontham study published in June 1994 (Fontham 1994). In its April 1994 notice of proposed rulemaking, OSHA relied on figures from an earlier and not yet completed version of the Fontham study published in 1991 (Fontham 1991).

socialized with smokers during the same period). No statistical adjustment for concurrent exposures was made in the analysis. Without adjustment, the occupational risk estimate may also reflect and be confounded by potential risks from household or social exposures to ETS.

Use of the point estimate from the Fontham study is not the only way occupational lung cancer risk attributable to ETS could be estimated. Alternatives include:

- **Brownson study point estimate**. The Brownson study's point estimate for relative risk of lung cancer from occupational exposure to ETS could have been used in the preliminary quantitative risk assessment. Similar to the Fontham study, the Brownson study: (1) was characterized by OSHA as "positive;"[35] (2) was conducted in the United States; (3) contained a large population-based study whose results can be generalized to the public; and (4) collected occupational data and ascertained an estimate of lung cancer risk attributable to the workplace.

  Although the Brownson study did not adjust for smoker misclassification or confirm smoking status, these differences may be irrelevant because they tend to bias risk estimates upward. Because the Brownson study reported no increase in risk from occupational exposure to ETS, upward bias is not a concern. Thus, based on its attributes, use of the relative risk estimate from the Brownson study is a viable alternative to use of the relative risk estimate from the Fontham study. However, use of the Brownson study would have resulted in a risk estimate of zero deaths from occupational exposure to lung cancer because the Brownson study reported no increase in risk.

- **Meta-analysis of studies with occupational exposure data.** Instead of selecting a point estimate from one study, OSHA could have combined the results of the studies with occupational exposure data (*See* Table 10-2) to arrive at a point estimate of relative risk which is based on more data. This technique is known as meta-analysis and was used by EPA in its 1992 risk assessment of ETS and lung cancer. Because the Fontham relative risk estimate would have been blended with other lower relative risk estimates, the approach would have resulted in a lower estimate of lung cancer deaths from occupational exposure to ETS.

To complete the calculation of the annual risk attributed to ETS exposure in the workplace, OSHA needed values for the following variables: (1) incidence rate of lung cancer for nonsmoking women in the workplace; (2) number of nonsmoking U.S. workers; and (3) number of nonsmoking workers exposed to ETS in the workplace.

---

[35] The Garfinkel study was also characterized by OSHA as being positive. However, Garfinkel may not be as well conducted as the studies by Brownson and Fontham. In its evaluation of the epidemiologic studies of ETS and lung cancer, EPA categorized the Garfinkel study as lower in quality than those by Kabat, Wu, Butler, and Janerich, studies which were characterized by OSHA as equivocal. See (EPA 1992, A13).

- **Science policy issues.** What values should be used for the following: incidence rate of lung cancer for nonsmoking women in the workplace, number of nonsmoking U.S. workers, and number of nonsmoking workers exposed to ETS in the workplace?
- **Science policy decisions**. These values were determined as follows:
  - **Incidence rate of lung cancer for nonsmoking women.** The annual background rate for lung cancer among nonsmoking women is estimated to be 0.121 per 1,000. OSHA believes this figure underestimates the true incidence rates among all U.S. workers because the rate for male nonsmoking workers is believed to be greater than 0.121 per 1,000.
  - **Number of nonsmoking U.S. workers.** Based on 1993 data, the Bureau of Labor Statistics estimated the size of the U.S. workforce to be 101,631,300. Data from the National Health Interview Survey indicate that 73.01 percent of those currently employed are nonsmokers. OSHA therefore estimated that there are 74,201,000 nonsmoking workers in the United States.
  - **Number of nonsmoking workers exposed to ETS in the workplace.** Based on responses from the National Health Interview Survey, 18.81 percent of nonsmokers reported exposure to ETS in the workplace. However, OSHA believes that the 18.81 percent figure may underestimate workplace exposures because it is self-reported. Another analysis reported that 48.67 percent of nonsmoking workers are exposed to ETS in the workplace. Apparently because of the disparity in these estimates, OSHA assumed that the true percentage of nonsmoking workers exposed to ETS in the workplace is in the range between 18.81 and 48.67 percent.

One concern with these numbers lies with the estimate of the number of nonsmoking workers. The population of nonsmoking workers includes workers who have smoked in the past (former smokers) and workers who have never smoked (never-smokers). The risk of lung cancer for never-smokers is the background rate of 0.121 per 1,000. Former smokers have higher rates of lung cancer than never-smokers. Thus, identification as a nonsmoker does not necessarily indicate that the worker's risk of contracting lung cancer is equivalent to the background risk. Therefore, use of the number of nonsmoking workers without adjusting for former smokers will tend to overestimate lung cancer incidence attributable to ETS exposure.

Based on the science policy decisions described above, OSHA estimated that the annual number of lung cancer deaths attributable to ETS exposure in the workplace is between 144 and 722.

Estimated Regulatory Impacts

OSHA proposed to prohibit smoking except in designated areas that are separate, enclosed, and exhausted directly to the outside. OSHA preliminarily estimated that the proposed smoking restrictions would avoid from 0.4 to 1.0 lung cancer deaths per 1,000 workers exposed to ETS over a forty-five-year working lifetime. Based on the estimated 74 million nonsmoking workers, this is equivalent to 144 and 722 lung cancer deaths avoided annually. Over a period of forty-five years the number of lung cancer deaths avoided is estimated to range between 5,583 and 32,502.[36] OSHA further believes that the estimated actual benefits of the proposed rule are underestimated. OSHA claims there are significant economic benefits that cannot be quantified at this time,[37] including improvements in productivity and efficiency,[38] cost reductions in operations and maintenance,[39] and reduced incidence of property damage.[40] OSHA estimated the costs for eliminating exposure to ETS to range from zero to $68 million annually, depending on whether establishments ban smoking or permit it only in designated areas.

When compared to other OSHA standards, the proposed rule's estimated costs ($94,182 to $472,222 per lung cancer death avoided) appear to be reasonable in proportion to the estimated benefits, and the proposed smoking ban appears to be a relatively cost-effective approach to reducing excess occupational health risk from ETS exposure (See Table 10-3).

Table 10-3. Cost Per Premature Death Avoided Through Workplace Regulatory Action[41]

Regulatory Action	Cost Per Premature Death Avoided ($)
Underground construction standards	100,000
Standards for servicing auto wheel rims	400,000
Concrete & masonry construction standards	600,000

[36] (OSHA 1994, 16011)

[37] (OSHA 1994, 16011)

[38] OSHA attempted to monetize the improvements in productivity from implementation of the proposed standard by multiplying the average annual employee salary by 3.0 percent for a total of $15 billion.

[39] OSHA cites a report by Bell Communications Research that the seven regional telephone companies have spent between $10,000 to $380,000 per event to replace, clean, and repair switches and other electronic equipment malfunctioning as a result of indoor air contaminants. In particular, OSHA cited ETS as contributing to increased maintenance and cleaning expenses; a survey indicates cost savings may be as high as $500 per employee.

[40] OSHA stated that the smoking ban would eliminate virtually all smoking related fires, fire fatalities and injuries, and direct property damage. OSHA cited statistics for the period 1989—1990 where there was an average of $115 million in property damage due to nonresidential smoking related fires, 36 fatalities, and 3,212 injuries.

[41] Adapted from (Office of Management and Budget (OMB) 1992, 12).

Crane suspended personnel platform standard	700,000
Trenching and excavation standards	1,500,000
Hazard communication standard	1,600,000
Grain dust explosion prevention standard	2,800,000
Asbestos occupational exposure limit (1972)	8,300,000
Benzene occupational exposure limit	8,900,000
Ethylene oxide occupational exposure limit	20,500,000
Acrylonitrile occupational exposure limit	51,500,000
Coke ovens occupational exposure limit	63,500,000
Lockout/tagout	70,900,000
Asbestos occupational exposure limit (1986)	74,000,000
Arsenic occupational exposure limit	106,900,000
Formaldehyde occupational exposure limit	86,201,800,000

Notwithstanding the apparent cost-effectiveness of the proposed smoking ban the estimated benefits depend entirely on multiple and compounded science policy decisions concerning:

- The characterization of the available epidemiology for ETS exposure;
- The estimated increase in risk attributable to ETS exposure and point estimate for occupational risk of lung cancer attributable to ETS exposure; and
- The estimated background rate of lung cancer, number of nonsmoking U.S. workers, and number of nonsmoking U.S. workers exposed to ETS.

Depending on the science policy decisions made, the estimated risk of lung cancer from occupational exposure to ETS ranges from zero to OSHA's estimates. Based on the science policy decisions made by OSHA, OSHA's risk estimates are not more plausible than an estimate of zero risk.

Additionally, the preliminary quantitative risk assessment may substantially overstate the potential lung cancer risk from occupational ETS exposure and estimated benefits from the proposed smoking ban. To calculate the risks and benefits, OSHA relied on the Fontham study's point estimate for relative risk of lung cancer from occupational exposure to ETS. This estimate of relative risk may inappropriately include and reflect potential risks from nonoccupational exposures to ETS.

Thus, despite the vast amount of data concerning lung cancer risk and ETS exposure, science policy decisions are required to identify a risk which serves as sufficient basis for the proposed workplace smoking ban. Even so, the proposed ban may not be justifiable because the science policy decisions may be without sufficient basis in fact.

Significance of ETS-Lung Cancer Risk Assessment to Remainder of the IAQ Proposal

More important than the issue of the smoking ban, however, is the remainder of the IAQ rule. The amount and quality of scientific information concerning workers' ETS exposure and lung cancer far exceeds what is available for the other health endpoints addressed in the proposed IAQ rule (heart disease, upper respiratory illness, and severe headaches). For example, the preliminary quantitative risk assessment for upper respiratory illness and severe headaches from poor IAQ is based on a single unpublished analysis by the National Institute for Occupational Safety and Health (NIOSH),[42] so very little is known about a potential association between these health effects and poor IAQ. Yet the costs of the proposed rule are tremendous. OSHA estimated the total costs of the proposed IAQ rule at $8.1 billion annually. Building systems operations and maintenance are the most expensive components at an estimated cost of $8.0 billion.[43] Thus, for the non-ETS portion of the proposed IAQ rule, significant costs may be incurred on the basis of inadequately supported science policy decisions.

Evaluation

Despite a relatively large database of information on human lung cancer risk from exposure to ETS, it was necessary for OSHA to make a number of science policy decisions to conduct the quantitative risk assessment necessary to justify its proposed regulatory action. Some of these science policy decisions may be without the scientific basis required by the Benzene decision, yet are necessary to estimate risks which would survive judicial scrutiny thereunder. Although the estimated costs of the proposed smoking ban are relatively low and the estimated benefits are relatively high, the costs may be incomplete and the benefits may be substantially overstated. The information database for the remainder of the proposed rule for IAQ is not nearly as extensive as that for ETS, and the associated science policy decisions are likely to be more tenuous than those for ETS. Because the estimated costs of the portion of the proposed IAQ rule not addressing smoking are very high, the proposed science policy decisions are even more questionable.

---

[42] This analysis consists of two hand-completed tables with no descriptive prose. OSHA specifically asked for comment concerning the use of only this study for estimating occupational risk in air-conditioned buildings due to poor air quality.

[43] Recurring costs have been estimated at $6.7 billion, and annualized costs have been estimated at $1.37 billion (OSHA 1994, 16014).

REFERENCES

AKIBA S., H. KATO, and W.J. BLOT. 1986. Passive smoking and lung cancer among Japanese women. Cancer Res. 46:4804-4807.

BROWNSON, R.C., M.C.R. ALAVANJA, E.T. HOCK, andT.S. LOY. 1992. Passive smoking and lung cancer in nonsmoking women. Am. J. Public Health 82:1525-1530.

BROWNSON, R.C., J.S. REIF, T.J. KEEFE, S.W. FERGUSON, and J.A. PRITZL. 1987. Risk factors for adenocarcinoma of the lung. Am. J. Epidemiol. 125:25-34.

BUFFLER, P.A., L.W. PICKLE, T.J. MASON, and C. CONTANT. 1984. The causes of lung cancer in Texas. In M. Mizell, et al. (eds.), Lung Cancer; Causes and Prevention. New York: Verlag Chemie International, 83-99.

BUTLER, T.L. 1988. The relationship of passive smoking to various health outcomes among Seventh-Day Adventists in California. Los Angeles: University of California at Los Angeles.

CHAN, W.C., and S.C. FUNG. 1982. Lung cancer in nonsmokers in Hong Kong. In E. Grundmann (ed.), Cancer Campaign, vol. 6, Cancer Epidemiology. Stuttgart, West Germany: Gustav Fischer Verlag, 199-202.

CONGRESSIONAL RESEARCH SERVICE (CRS). 1994. Cigarette taxes to fund health care reform: An economic analysis. (94-214 E). Washington, D.C.

CORREA, P., L.W. PICKLE, E. FONTHAM, Y. LIN, and W. HAENSZEL. 1983. Passive smoking and lung cancer. Lancet 2:595-597.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. EPA/600/6-90/006F.

FONTHAM, E., P. CORREA, P. REYNOLDS, A. WU-WILLIAMS, P.A. BUFFLER, R.S. GREENBERG, V.W. CHEN, T. ALTERMAN, P. BOYD, D.F. AUSTIN, J. LIFF. 1994. Environmental tobacco smoke and lung cancer in nonsmoking women: A multicenter study. JAMA 271(22): 1752-1759.

FONTHAM, E., P. CORREA, A. WU-WILLIAMS, P. REYNOLDS, R.S. GREENBERG, P.A. BUFFLER, V.W. CHEN, P. BOYD, T. ALTERMAN, D.F. AUSTIN, J. LIFF, and S.D. GREENBERG. 1991. Lung cancer in nonsmoking women: A multicenter case control study. Cancer Epidemiol. Biomarkers Prev. 1(1):35—334.

GAO Y., W.J. BLOT, W. ZHENG, A.G. ERSHOW, C.W. HSU, L.I. LEVIN, R. ZHANG, and J.F. FRAUMENI. 1987. Lung cancer among Chinese women. Int. J. Cancer 40:604-609.

GARFINKEL, L., O. AUERBACH, and L. JOUBERT. 1985. Involuntary smoking and lung cancer: A case-control study. J. Natl. Cancer Inst. 75:463-469.

GENG, G., Z.H. LIANG, A.Y. ZHANG, and G.L. WU. 1988. On the relationship between smoking and female lung cancer. In Smoking and Health. Elsevier Science Publishers, 483-486.

GILLIS, C.R. 1984. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur. J. Respir. Dis. 133(Suppl.):121—126.

HIRAYAMA, T. 1984. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort in Japan. Preventive Medicine 13:680-690.

HOLE, D.J., C.R. GILLIS, C. CHOPRA, and V.M. HAWTHORNE. 1989. Passive smoking and cardiorespiratory health in the west of Scotland. Br. Med. J. 299:423-427.

HUMBLE C.G., J.M. SAMET, and D.R. PATHAK. 1987. Marriage to a smoker and lung cancer risk. Am. J. Pub. Health 77:598-602.

INOUE, R., and T. HIRAYAMA. 1988. Passive smoking and lung cancer in women. In Smoking and Health. Elsevier Science Publishers, 283-285.

JANERICH, D.T., W.D. THOMPSON, L.R. VARELA, P. GREENWALD, S. CHOROST, C. TUCCI, M.B. ZAMAN, M.R. MELAMED, M. KEILY, and M.F. McKNEALLY. 1990. Lung cancer and exposure to tobacco smoke in the household. N. Engl. J. Med. 323:632—636.

RABAT, G.C., and E. L. WYNDER. 1984. Lung cancer in nonsmokers. Cancer 53:1214-1221.

KALANDIDI, A., K. KATSOUYANNI, N. VOROPOULOU, G. BASTAS, R. SARACCI, and D. TRICHOPOULOS. 1990. Passive smoking and diet in the etiology of lung cancer among nonsmokers. Cancer Causes Control 1:15—21.

KATADA, H., R. MIKAMI, M. KONISHI, Y. KOYAMA, and N. NARITA. 1988. Effect of passive smoking in lung cancer development in women in the Nara region. Gan To Rinsho 34(l):21-27.

KOO, L.C., J.H-C. HO, D. SAW, and C. HO. 1987. Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int. J. Cancer 39:162-169.

LAM, T.H., l.T. RUNG, C.M. WONG, W.R. LAM, J.W. RLEEVENS, D. SAW, C. HAU, S. SENEVIRATNE, S.Y. LAM, R.R. LO, and W.C. CHAN. 1987. Smoking, passive smoking and histological types in lung cancer in Hong Rong Chinese women. Br. J. Cancer 6:673-678.

LEE, P.N., J. CHAMBERLAIN, and M.R. ALDERSON. 1986. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br. J. Cancer 54:97-105.

NATIONAL RESEARCH COUNCIL (NRC). 1991. Environmental Epidemiology: Public Health and Hazardous Wastes. Washington, D.C.: National Academy Press.

OCCUPATIONAL SAFETY AND HEALTH ACT (OSHAct), 29 U.S.C. 655(c).

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION (OSHA). 1994. Indoor air quality (Proposed rule). Fed. Reg. 59:15968.

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION (OSHA). 1991. Occupational exposure to indoor air pollutants; Request for information. Fed. Reg. 56:47892.

OFFICE OF MANAGEMENT AND BUDGET (OMB). 1992. Regulatory Program of the United States Government (April 1, 1991-March 31, 1992). Executive Office of the President, Washington, D.C.

PERSHAGEN, G., Z. HRUBEC, and C. SVENSSON. 1987. Passive smoking and lung cancer in Swedish women. Am. J. Epidemiol. 125(1): 17—24.

SANDLER, D.P., G.W. COMSTOCR, R.J. HELSING, and D.L. SHORE. 1989. Deaths from all causes in nonsmokers who lived with smokers. Am. J. Pub. Health 79(2): 163-167.

SHIMIZU, H., M. MORISHITA, R. MIZUNO, T. MASUDA, X. OGURA, M. SANTO, M. NISHIMURA, R. RUNISHIMA, R. RARASAWA, R. NISHIWARA, M. YAMAMOTO, S. HISAMICHI, and S. TOMINAGA. 1988. A case-control study of lung cancer in nonsmoking women. Tohoku J. Exp. Med. 154:389—397.

SOBUE, T., R. SUZURI, N. NARAYAMA, C. INUBUSE, M. MATSUDA, O. DOI, T. MORI, K. FURUSE, M. FURUORA, T. YASUMITSU, O. RUWABARA, M. ICHIGAYA, M. RURATA, M. RUWABARA, R. NARAHARA, S. ENDO, and S. HATTORI. 1990. Passive smoking among

nonsmoking women and the relationship between indoor air pollution and lung cancer incidence—results of a multicenter case controlled study. Gan To Rinsho 36(3):329-333.

STOCKWELL, H., A.L. GOLDMAN, G.H. LYMAN, C.I. NOSS, A.W. ARMSTRONG, P.A. PINKHAM, E.C. CANDELORA, and M.R. BRUSA. 1992. Environmental tobacco smoke and lung cancer risk in nonsmoking women. J. Natl. Cancer Inst. 84:1417-1422.

SVENSSON, C., G. PERSHAGEN, and J. KLOMINEK. 1989. Smoking and passive smoking in relation to lung cancer in women. Acta. Oncol. 28:623-629.

TRICHOPOULOS, D., A. KALAND1DI, L. SPARROS, and B. MacMAHON. 1981. Lung cancer and passive smoking. Int. J. Cancer 27:1-4.

WU, A.H., B.E. HENDERSON, M.C. PIKE, and M.C. YU. 1985. Smoking and other risk factors for lung cancer in women. J. Natl. Cancer Inst. 74(4):747-751.

WYNDER, E.L. 1987. Workshop on guidelines to the epidemiology of weak associations. Prev. Med. 16:139-141.

11
TOXICS RELEASE INVENTORY

Introduction

The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) requires industrial facilities to report their releases and transfers of toxic chemicals listed on the Toxics Release Inventory (TRI). The purpose of such reporting is to provide communities with information concerning routine local releases and transfers of toxic chemicals. The Environmental Protection Agency (EPA) administers the TRI program. Although Congress established the initial list of chemicals subject to TRI reporting, EPA is authorized to add chemicals to and delete chemicals from the TRI based on an evaluation of the chemicals' toxicity. The criteria for listing or deleting chemicals from the TRI are expressly stated in EPCRA, but the broad wording requires EPA to exercise judgment in determining whether a chemical is toxic. Decisions to label chemicals as toxic depend on science policy decisions. This case study focuses on EPA's recent proposal to add another 313 chemicals to the TRI and provides insight into how EPA currently makes science policy decisions in the context of TRI reporting.

Science Policy Issues Addressed in This Case Study
➢ Weight-of-evidence classification ➢ Extrapolation based on physical and chemical similarities ➢ Route-to-route extrapolation ➢ High-to-low dose extrapolation ➢ Indirect toxicity

Background

On December 5, 1984, an accidental release of methyl isocyanate from a pesticide plant killed 2,000 people in Bhopal, India. In response to this accident, EPCRA was enacted into law.[1] The purpose of EPCRA is to:

> *... establish programs to provide the public with important information on the hazardous chemicals in their communities, and to establish*

[1] Title III of (Pub. Law 99-499) codified at 42 U.S.C. §11001.

> *emergency planning and notification requirements which would protect the public in the event of a release of hazardous chemicals.*[2]

Section 313 of EPCRA requires owners and operators of certain industrial facilities[3] to report annually releases and transfers of certain toxic chemicals manufactured, processed, or otherwise used in amounts that exceed established levels.[4] EPA is required to maintain a database of these reports, known as the TR1, and to make the information available to the public. The chemicals initially subject to TRI reporting requirements were selected by Congress, [5]but EPA was delegated the authority to add or delete chemicals from the TRI.[6] A chemical may be deleted or "delisted" from the TRI if there is not sufficient evidence to satisfy at least one of the listing criteria.[7] EPCRA expressly states that the determination of whether a chemical satisfies any of the criteria is a judgment call to be made by EPA.

The TRI program is an information collection and dissemination program. Listing decisions should be made in the context of providing the public with useful information. Because listing decisions depend on science policy decisions, science policy decisions should also be made in this context. As a former EPA assistant administrator in charge of the TRI program stated:

> *While there may be hundreds of potential candidates for addition to the TRI list, I believe such additions must be looked at in the light of several factors. First, we should be careful to list those chemicals that clearly meet the statutory criteria and are important from a risk perspective. Individual candidates on any given list of chemicals should be screened so that we can assure ourselves and the public that the reports on these chemicals have meaning in the context of section 313 reporting. Otherwise, we gather data that have little value for promoting pollution prevention and risk reduction and invite numerous petitions to delist those chemicals.*[8]

An argument against this position is that TRI listing decisions are far less burdensome than the regulation of releases and emissions of toxic chemicals, so a lesser standard should be required for listing. Although TRI reporting may be less burdensome than regulation of releases and emissions, the costs of TRI reporting are greater than just the

---

[2] (House of Representatives 1986, 281)

[3] Those with ten or more full time employees and that are in Standard Industrial Classification Codes 20-39, as in effect on July 1, 1985 (EPCRA §313(b)(l)).

[4] (EPCRA §313(a))

[5] (EPCRA §313(c)). The initial list of toxic chemicals subject to TRI reporting was a combination of the Maryland Chemical Inventory Report List of Toxic or Hazardous Substances and the New Jersey Environmental Hazardous Substance List.

[6] (EPCRA §313(d) (1))

[7] (EPCRA §313(d) (3))

[8] (Fisher 1991)

direct reporting costs. Additionally, unnecessary TRI reporting may dilute program benefits, including:

- **Information collection and dissemination.** Data reported under EPCRA Section 313 can increase the public's knowledge of chemical use and releases[9] and facilitate access to such information.[10] Benefits associated with TRI information collected have not been quantified, measured, or otherwise directly or empirically evaluated. EPA stated:

  The benefits of the proposed rule itself are limited to improvements in understanding, awareness and decision-making related to the provision and distribution of information.[11]

  However, some TRI information may be of less value or duplicative of other information collected under other statutory and regulatory authorities.[12] *For example, industry commenters suggested that acid rain, the adverse environmental effect associated with nitrogen dioxide and sulfur dioxide,*[13] *is a regional rather than a local phenomenon.*[14] *Accordingly, release information may not be useful on a community level and, therefore, not within the scope of TRI reporting. There is also the potential for inappropriate use of reported data.*[15]

---

[9] For example, TRI reporting of the criteria air pollutants would supplement the Clean Air Act reporting requirements which cover only major sources of emissions in non-attainment areas (i.e. data from entire states are missing). Additionally, discrepancies between information in various data bases, e.gthose of the TRI, Clean Air Act, and state programs, may be reduced by listing the criteria air pollutants (American Lung Association et al. 1994, 2).

[10] "People should not have to go to three separate databases to find information on emissions of various toxic air pollutants" from the same facility (Natural Resources Defense Council (NRDC) 1994, 7).

[11] (EPA 1993, 45-46)

[12] EPA stated that it collected data on many of the chemicals proposed for TRI listing in a variety of EPA databases including: the Aerometric Information Retrieval System (AIRS) for releases of criteria air pollutants; the Biennial Report System (BRS) for generation and management of RCRA hazardous wastes; the Permit Compliance System (PCS) for releases to navigable or surface waters under the Clean Water Act National Pollutant Discharge Elimination System (NPDES); the Section 7 Tracking System (SSTS) for production and sale of pesticides; and the Chemical Update System (CUS) of certain TSCA chemicals (EPA 1993a, 43).

[13] Nitrogen dioxide and sulfur dioxide have been proposed for addition to the TRI. See discussion in text below.

[14] (American Mining Congress 1994; Arizona Mining Association 1994)

[15] In the November 1993 report entitled "Poisons in Our Neighborhood: Toxic Pollution in the United States" released by the public interest group Citizen Action, the Beaumont, Texas Goodyear Tire & Rubber Co. plant received the lowest ranking for pollution prevention efforts for the TRI- listed substance acetonitrile. This was based on the plant's generation of 2.4 billion pounds of waste annually. However, according to Goodyear, the Beaumont plant recycles acetonitrile many times over a closed-loop system, and each recycling is counted as generation of new waste under TRI reporting procedures. An EPA staff member was reported to have stated that EPA is not the "data police" and individuals or groups can basically do what they like with TRI information (Bureau of National Affairs (BNA) 1993).

- **Follow-on activities.** EPA stated that TRI reporting can create a chain reaction of follow-on activities (*e.g.,* voluntary initiatives by industry to review processes, set goals for reductions in emissions, and institute "good neighbor" policies). These follow-on activities, in turn, create additional costs and benefits, such as decreased costs of treatment and disposal, lower probability of accidental releases and resulting lower cleanup costs, reduced contamination of natural resources from decreased land disposal, improved air and water quality, and lower incidence of cancer deaths and related medical care costs. According to EPA, these benefits are offset by the costs to implement the changes, such as installing scrubbers or substituting less toxic materials.[16]

These important benefits are more likely to be attained by the listing on the TRI of a more limited set of substances which are truly important to communities from a risk perspective. Limiting the TRI to such chemicals can be accomplished through less conservative science policy decisions made in the context of TRI.

Criteria for TRI Listing

Chemicals considered to be toxic are subject to listing on the TRI. A chemical is "toxic" if EPA, in its judgment, determines that the chemical is associated with acute human toxicity, chronic human toxicity, or environmental toxicity. The criteria for making listing determinations are as follows:

- **Acute human toxicity**. According to EPCRA Section 313(d) (2) (A), a chemical may be listed due to acute human toxicity if:

  The chemical is known to cause or can reasonably be anticipated to cause significant adverse acute human health effects at concentration levels that are reasonably likely to exist beyond facility site boundaries as a result of continuous or frequently recurring releases.

  This listing criterion has both toxicity and exposure components; innate toxicity alone is insufficient for listing. EPA believes that a chemical should be listed if its likely concentration beyond facility boundaries would be within that range of levels expected to cause acute human health effects. This margin depends on the type of hazard data (animal or human) and the confidence in the database for acute health effects. EPA uses release estimates and modeling to estimate concentrations beyond facility site boundaries.[17]

[16] (BNA 1993)

[17] (EPA 1994, 1791-1792)

- **Chronic human toxicity.** A chemical may be listed on the TRI on the basis of chronic human toxicity if:

  The chemical is known to cause or can be reasonably anticipated to cause in humans -

  (i) Cancer or teratogenic effects, or

  (ii) Serious or irreversible -

  (I) reproductive dysfunctions,

  (II) Neurological disorders,

  (III) Heritable genetic mutations, or

  (IV) Other chronic health effects[18]

EPA has recently proposed to interpret this statutory provision to require a consideration of toxicity, but not of exposure.[19] Previously, however, EPA delisted substances from the TRI because likely exposure levels were not associated with chronic health effects.[20] Whether this listing criterion includes an exposure component is important. Without considering exposure, substances can be listed even though there is no scenario under which releases may be harmful. Even though a substance may be toxic, no harm will occur without sufficient exposure. Without the possibility of harm, little value will be produced by reporting requirements.

- **Environmental toxicity.** A chemical may be listed on the TRI on the basis of environmental toxicity if:

The chemical is known to cause or can reasonably be anticipated to cause, because of -

(i) Its toxicity,

(ii) Its toxicity and persistence in the environment, or

(iii) Its toxicity and tendency to bioaccumulate in the environment,

a significant adverse effect on the environment of sufficient seriousness, in the judgment of the Administrator, to warrant reporting under this section.[21]

[18] (EPCRA §313(d)(2)(B))

[19] (EPA 1994, 1792)

[20] *See e g*., delisting notices for: **melamine blue**, 54 FR 12912 (March 29, 1989); **sodium sulfate,** 54 FR 7217 (February 17, 1989); and **titanium dioxide**, 53 FR 5004 (February 19, 1988).

[21] (EPCRA §313(d) (2)(C))

The legislative history of EPCRA Section 313(d) provides more specific criteria for determining what constitutes a significant adverse environmental effect. These criteria include: [22]

- Gradual or sudden changes in the composition of animal or plant life, including fungal or microbial organisms in an area;
- Abnormal number of deaths of organisms (e.g., fish kills);
- Reduction of the reproductive success or vigor of a species;
- Reduction in agricultural productivity, whether crops or livestock;
- Alterations in the behavior or distribution of a species; and
- Long lasting or irreversible contamination of components of the physical environment, especially in the cases of groundwater, surface water, and silt resources that have limited self-cleansing capability.

EPA has proposed that the extent to which exposure is considered should depend on inherent toxicity and other chemical-specific characteristics: [23]

- "Highly toxic" chemicals warrant listing on toxicity alone.
- Consideration of potential exposures to "moderately toxic" chemicals is warranted because minimal releases may not have significant adverse effects.
- Consideration of exposure is not required for chemicals that are persistent or bioaccumulate in the environment because even low releases may lead to increased environmental concentrations.
- Exposure assessment is unnecessary for chemicals that induce well-established environmental effects such as stratospheric ozone depletion caused by chlorofluorocarbons (CFCs). EPA believes these effects are of sufficient seriousness across an entire ecosystem that additional exposure considerations are not warranted.

These criteria provide EPA with broad discretion in making listing decisions. EPA judgment extends beyond science policy decisions concerning toxicity to whether potential exposures should also be considered.

Science Policy in the Proposal to Expand the TRI by 313 Chemicals

Science policy issues relevant to the TRI will be discussed in the context of a recent EPA proposal to add 313 chemicals and chemical categories to the list of toxic chemicals

[22] (House of Representatives 1986, 294)

[23] (EPA 1994, 1792-1793)

subject to TRI reporting.[24] Selected chemicals proposed for listing, [25] the rationale for the proposed listings, and related science policy issues and regulatory impacts raised in industry comments are presented below.

Glass wool.[26] EPA proposed establishing a category on the TRI for man-made mineral fibers, which would include glass wool, an insulation material. EPA has proposed listing glass wool based on its carcinogenic potential as indicated by similarities with asbestos and positive animal bioassays: [27]

- Proposed listing basis #1. Man-made mineral fibers, including glass wool, have morphological and toxicological similarities with asbestos, a known human carcinogen.[28]
- **Industry comments.** Man-made mineral fibers, including glass wool, differ from asbestos physically and chemically depending on the type of fiber: [29]
  - Man-made mineral fibers are amorphous silicates, while asbestos fibers are crystalline in structure.
  - Man-made mineral fibers are soluble, while asbestos fibers are not.
  - Man-made mineral fibers tend to split transversely while asbestos fibers split longitudinally.

  Fiber characteristics affect the pathogenesis of disease, the degree of reactivity in biological systems, and the nature and success of lung defense mechanisms.[30]
- **Science policy.** Because it is not known whether similarities between asbestos and glass wool implicate glass wool as a carcinogen and because it may be impossible to ascertain such information, the science policy issue and decision are as follows:
  - **Science policy issue.** Do the chemical, physical, and toxicological similarities between asbestos and glass wool suggest that glass wool is carcinogenic to humans?
  - **Science policy decision**. The chemical, physical, and toxicological similarities between asbestos and glass wool support listing glass wool on the TRI.

---

[24] (EPA 1994)

[25] The chemicals discussed in this case study are examples from the EPA proposal and are not intended to be representative of all chemicals proposed for listing.

[26] *Glass wool* is used to produce fiberglass and is a primary component of building insulation.

[27] (EPA 1994, 1821)

[28] *See* Chapter 3 for a discussion ofEPA's carcinogen classification system.

[29] (Coors Brewing Company 1994; North American Insulation Manufacturers Association (NAIMA) 1994)

[30] *See* also (Edison Electric Institute (EEI) 1994, 11).

- **Proposed listing basis #2.** Studies in which glass wool and glass microfibers were injected into the respiratory airways and the pleural or abdominal cavities of laboratory animals have shown consistent evidence of carcinogenicity.
- Industry comments. Although injection/implantation studies suggest a carcinogenic effect in animals, inhalation studies of worker populations and animals do not. Several epidemiologic studies covering tens of thousands of workers exposed to glass wool have failed to identify a dose-response relationship between respirable glass fibers and cancer.31 In addition, eight high-dose inhalation animal bioassays in several species have not found statistically significant increases in fibrosis or other lung cancers.[32]

  EPA has previously taken the position that:

  Positive results from studies using intrapleural or intraperitoneal injection/implantation method[s] in the absence of positive findings from inhalation experiments do not indicate that these fibers will produce tumors in man upon inhalation.[33]

  The Consumer Product Safety Commission (CPSC) has reached similar conclusions.[34] EPA did not articulate in the proposed TRI rule a rationale for the change in its interpretation of the injection/implantation studies. Recently, the National Toxicology Program determined that, based on the animal injection studies, there was sufficient evidence to conclude that glass wool "may reasonably be anticipated to be" a carcinogen.[35] However, the NTP also acknowledged that:[36]

  Debate continues in the scientific community regarding the use of implantation studies as indicators of carcinogenic potential of fibers.

- **Science policy.** Because it is not known that glass wool causes gastrointestinal cancer in humans and because any potential human carcinogenicity of glass wool may not be knowable, the relevant science policy issue and decision are as follows:
  - **Science policy issue.** Are the available animal injection/implantation studies for glass wool indicative of potential carcinogenicity in humans,

---

31 The International Agency for Research on Cancer (IARC) previously concluded that there is inadequate evidence of the carcinogenicity of glass wool in humans. (IARC 1994)

32 (NAIMA 1994, Appendix B; Edison Electric Institute (EEI) 1994) citing (Agency for Toxic Substances and Disease Registry (ATSDR) 1990).

33 (NAIMA 1994) citing (EPA 1988)

34 (NAIMA 1994) citing (CPSC 1988).

35 (NTP 1994, 219-222)

36 (NTP 1994, 219-222)

given that several high-dose animal inhalation bioassays are nonpositive?[37]

- ❖ **Science policy decision.** Animal injection/implantation studies suggest that glass wool causes or may reasonably be anticipated to cause cancer in humans.

This science policy decision reverses EPA's earlier position concerning glass wool.

- ➢ **Regulatory impacts of the proposed listing.**
  - ❖ Reporting costs. At least twenty-six facilities will be required to report annual glass wool releases.38 Based on EPA figures, at a minimum, the direct costs of reporting glass wool releases are estimated to be $178,906 for the first year and $92,274 for subsequent years.[39]
  - ❖ Costs of complying with other federal and state regulatory requirements triggered by TR1 listing. TRI listing triggers federal stormwater treatment permits.40 State and local requirements based on TRJ chemicals include: pollution prevention plans, 41progress reports on toxics use reduction, payment of fees and taxes geared to use of TRI chemicals, 42and toxics use notification.[43]
  - ❖ Product stigmatization. In addition to the direct costs of reporting requirements, users and customers of glass wool products may be discouraged from purchasing products they believe to be toxic. If this occurs, the ramifications could be significant. For example, according to the North American Insulation Manufacturers Association (NAIMA), 1990 data indicate that the use of glass wool in the residential sector alone may

---

[37] See discussion concerning the default assumption of route-to-route extrapolation in Chapter 3.

[38] (EPA 1993, A-28). A maximum number of facilities required to report is not estimable from the EPA regulatory impact analysis document.

[39] Based on EPA estimates of reporting costs: $6,881 per report per facility for the first year and $3,549 per report per facility for subsequent year reports (EPA 1993, 36).

[40] EPA estimates of annual costs associated with storm water permits for TRI chemicals range from $2,400 to $16,250 (Chemical Specialties Manufacturers Association (CSMA) 1994, 8-9) citing 57 FR 41,253 (September 9, 1992).

[41] Pollution prevention programs are required in ten states (Florida, Indiana, Iowa, Maine, Massachusetts, Minnesota, Mississippi, New Jersey, Oregon, and Vermont) and recommended in three others (Arizona, Illinois and Wisconsin). First-year costs for a facility are estimated to average over $35,000; subsequent-year costs would average $25,500 (CSMA 1994, 9-11).

[42] Thirteen states (Florida, Kansas, Maine, Massachusetts, Minnesota, Mississippi, Nevada, New Jersey, Ohio, Pennsylvania, South Dakota, Texas, and Vermont) impose taxes or fees on the use of TRI chemicals ranging from $25 per reporting form submitted (Texas) to $50,000 depending on the amount of wastes released (Mississippi) (CSMA 1994, 12).

[43] TRI listing may result in listing under the State of California's Proposition 65, which requires public notification of the use of toxic chemicals (Dow 1994, 15).

have saved the equivalent of 33.4 million barrels of oil and avoided the need to produce approximately 6,800 megawatts of power, or 34 new 200 megawatt power plants.[44]

- **Summary**. Glass wool has been proposed for listing on the TRI substantially based on assumptions concerning its physical similarities to asbestos and the relevance of implantation/injection bioassays to predicting human cancer risk. On a weight-of-evidence basis, these assumptions have been judged to outweigh the available nonpositive epidemiologic studies of highly exposed workers and animal inhalation studies. Although the direct costs of TRI reporting are not trivial, they may be overshadowed by the potential indirect costs caused by product stigmatization. No compelling case has been made that: (1) facilities pose a threat to local communities from routine or accidental releases of glass wool; or (2) there is any other benefit to communities from TRI reporting of glass wool which outweighs the costs.

Butylated hydroxyanisole. Butylated hydroxyanisole (BHA) has been approved by the Food and Drug Administration (FDA) for use in the food, cosmetic, pharmaceutical, and food packaging industries. BHA is widely used as a food additive because it inhibits oxidation of fats and oils and prevents the onset of rancidity and spoilage. BHA is added to lard, fat, poultry, fresh sausage, cereals, baked goods, candy, vegetable oils, potato chips, snack foods, nut products, chewing gum, and active dry yeast.[45]

- **Proposed listing basis.** The International Agency for Research on Cancer (IARC) considers BHA to be a possible carcinogen because it has been associated with gastrointestinal tumors in rats and hamsters.[46] Citing IARC's classification, EPA has proposed to list BHA on the basis of potential human carcinogenicity.
- Industry comments. The high dietary dose studies 47 of BHA cited by IARC reported increased incidence of hyperplasia, papilloma, and squamous cell carcinoma formation in the forestomach of rats and hamsters. Humans do not have an organ that is functionally similar to the rodent forestomach. Further, no evidence of cancer in humans has been reported despite long and widespread use of BHA in food. FDA has established a generally recognized as safe (GRAS)48 level for BHA.[49]

---

[44] (NAIMA 1994)

[45] (UOP 1994)

[46] (EPA 1994, 1801)

[47] Bioassay doses were 1,000 times higher than human intake levels. The lowest dose at which hyperplasia was observed was 110 mg/kg/day. The lowest dose at which carcinomas were observed was 1,322 mg/kg/day. Actual human exposures are on the order of 0.1 mg/kg/day (UOP 1994).

[48] GRAS status indicates that there is reasonable certainty in the minds of competent scientists that a particular food ingredient is not harmful under the intended conditions of use. GRAS status is determined by FDA based on the views of experts qualified by scientific training and experience to evaluate the safety

- **Science policy**. Because it is not known if BHA is carcinogenic in humans and because any potential carcinogenicity of BHA may not be knowable, the relevant science policy issues and decisions are as follows:
  - **Science policy issue**. What is the relevance of tumors in the rodent forestomach for predicting carcinogenicity in humans?
  - **Science policy decision.** Carcinogenic activity in the rodent forestomach is predictive of human carcinogenic potential.[50]
  - **Science policy issue.** Is it appropriate to use the animal bioassay data to predict human carcinogenic potential, given that the bioassays were conducted at doses 1,000 times greater than human exposures?
  - Science policy decision. High-to-low dose extrapolation is appropriate to estimate the potential carcinogenicity of BHA in humans.[51]
- ► **Regulatory impacts of the proposed listing.**
  - **Reporting costs.** The total costs of reporting BHA could not be determined because the number of facilities required to report was not estimated. Nonetheless, EPA has estimated the reporting costs to be $6,881 per report per facility for first-year reporting and $3,549 per report per facility for subsequent-year reporting. Given the wide use of BHA as a food additive, the number of facilities required to file TRI reports is likely to be significant.
  - **Regulatory conflict**. In this case, EPA's science policy decision will result in a regulatory conflict between EPA and FDA. The Federal Food, Drug and Cosmetic Act's Delaney Clause prohibits the use of any substance as a food additive "if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal...."[52] TRI listing of BHA on the basis of carcinogenicity is a *de facto* labeling of BHA as a human carcinogen. Such labeling conflicts with FDA approval of BHA as a food additive.
  - **Product stigmatization**. Labeling of BHA as a human carcinogen could stigmatize consumer products containing BHA and result in reduced sales of such products.

---

of substances indirectly or directly added to food. 40 C.F.R § 170.3(i) & §170.30. Under the Federal Food, Drug and Cosmetic Act, substances which are carcinogenic are prohibited from being used as food additives. See 21 U.S.C. 348(c) (3) (A).

[49] BHA content may not exceed 0.02 percent by weight of the total fat or oil content of the food (UOP 1994) citing 21 CFR 182.3169.

[50] See Chapter 3, Section VI.

[51] See Chapter 3, Section IX.

[52] 21 U.S.C. 348(c)(3)(A).

- **Summary**. There may be a factual basis on which EPA could make the science policy decision that BHA is a human carcinogen and therefore should be listed on the TRI. However, should EPA make this science policy decision, given the context of TRI reporting, and the resultant regulatory conflict and product stigmatization? No compelling case has been made that: (1) facilities that manufacture or use BHA pose a threat to local communities from routine or accidental releases of BHA; or (2) there is any other benefit to communities from TRI reporting of BHA which outweighs the costs. Other food additives, including sodium nitrite and tetrasodium ethylene-diamine-tetra-acetate (EDTA), have also been proposed for listing on the TRI.[53] Similar to the listing of BHA, the listing of sodium nitrite and EDTA depends on questionable science policy decisions which may lead to significant indirect regulatory impacts with little benefit to the public.

Phenytoin. Phenytoin is a medicine used in the treatment of seizure disorders such as epilepsy. Normal side effects of treatment with phenytoin include constipation, dysphagia, nausea, vomiting, anorexia, and weight loss.[54]

- **Proposed listing basis.** Because of anecdotal information concerning human exposures in excess of recommended doses and some animal studies, phenytoin has been proposed for listing on the TRI on the basis of chronic neurological and developmental toxicity and potential carcinogenicity.
- **Science policy.** Many, if not most, pharmaceutical products have the potential to be toxic to humans at sufficiently high doses. The key issue here is whether pharmaceutical products should be considered toxic for purposes of the TRI.
  - **Science policy issue.** Is exposure to phenytoin associated with carcinogenicity, developmental toxicity, and neurotoxicity?
  - **Science policy decision.** On a weight-of-evidence basis, phenytoin causes or can reasonably be anticipated to cause developmental or neurotoxicity, and cancer in humans.

  Notably, although EPA has judged this pharmaceutical product to be a potential carcinogen, the National Institutes of Health and the Food and Drug Administration have not found "the data adequate to support a conclusion of carcinogenicity of phenytoin in humans."[55]
- **Regulatory impacts**. The direct reporting costs are likely to be small because only approximately five facilities will be required to report releases of

[53] (EPA 1994, 1836, 1840).

[54] (EPA 1994, 1829).

[55] (NTP 1994, 320)

phenytoin.[56] However, the more significant implication of this listing is that it establishes a precedent for the listing of virtually any pharmaceutical product on the TRI.

This proposed listing appears to provide little benefit at the expense of labeling a valuable pharmaceutical product as toxic. According to the NTP: [57]

> *EPA has no indication of [the presence of phenytoin or its monosodium salt] in effluents, emissions or wastes from pharmaceutical manufacturers.*

What are the benefits to communities of the TRI reporting of phenytoin and other pharmaceuticals? Under what exposure scenario can a pharmaceutical such as phenytoin pose a threat to a community? These questions should be considered before making science policy decisions to list pharmaceutical products on the TRI.

Substances proposed for TRI listing on the basis of indirect environmental toxicity.

Several chemicals have been proposed for listing on the basis of toxicity to the environment, including: (1) certain Clean Air Act criteria air pollutants (*i.e.*, nitrogen dioxide and sulfur dioxide); and (2) nitrate ion and certain phosphorus-containing compounds.[58] These substances are of interest because the TRI listing criteria clearly encompass substances that cause direct environmental toxicity, but are silent concerning substances that do not themselves cause environmental toxicity. The science policy issue for these substances is whether they should be considered to be toxic to the environment for TRI purposes.

- Criteria air pollutants and acid rain. Nitrogen dioxide and sulfur dioxide are subject to national ambient air quality standards promulgated by EPA under the Clean Air Act.
  - Proposed listing basis. Nitrogen dioxide and sulfur dioxide were proposed for TRI listing because nitrogen dioxide and sulfur dioxide air emissions can be converted in the atmosphere into nitric acid and sulfuric acid,

[56] (EPA 1993, A-36)

[57] (NTP 1994, 321)

[58] These compounds are: phosphorus *oxychloride, phosphorus pentachloride, phosphorus pentasulfide*, and *phosphorus pentoxide.* 59 FR 1788, 1829-30. These compounds have been proposed for listing because each reacts with water to form **phosphoric acid,** a chemical already listed on the TRI. In June 1990, Ecolab, Inc. filed a petition under EPCRA §313 to delist phosphoric acid from the TRI. Although the petition was withdrawn, EPA stated that phosphoric acid did not meet the listing criteria for either acute or chronic human health effects but did meet the criteria for listing under environmental toxicity. In November 1990, The Fertilizer Institute submitted a petition to delist phosphoric acid because "eutrophication is not properly characterized as a significant adverse environmental effect caused by the 'toxicity' of phosphoric acid." (The Fertilizer Institute 1994, 17)

respectively. Nitric and sulfuric acids may then be deposited in the form of acid rain, potentially causing numerous adverse environmental effects.[59]

- ❖ Industry comments. While nitrogen dioxide and sulfur dioxide are recognized precursors to acid rain, no data were presented in the proposed rule concerning the direct effects of nitrogen dioxide and sulfur dioxide on the environment. Instead, the proposal focuses on the environmental effects of nitric acid and sulfuric acid, both of which are already subject to TRI reporting.[60] The formation of acid rain depends on a number of factors including the presence of other pollutants, atmospheric residence time, and humidity. [61]

As the National Acid Precipitation Assessment Program (NAPAP) stated in its 1992 Report to Congress.[62]

> *... it is important to note that sulfur and nitrogen oxide emissions are controlled as surrogates for controlling the acidity of precipitation. That is, most acids are not emitted directly during the burning of fossil fuels, they are formed in the atmosphere from the sulfur and nitrogen gases that are released directly to the atmosphere in the combustion process. Therefore, we control the emissions of sulfur and nitrogen in order to control the formation of acids and the deposition of acids to earth. But there is not a simple relationship between emissions of sulfur and nitrogen oxides and the level of acidity in the atmosphere. Basic substances, released into the atmosphere from natural and manmade sources, e.g., ammonia and calcium, can neutralize acids after they have been formed, and many sulfur and nitrogen compounds in the atmosphere are not acidic.*

Thus, although releases of nitrogen dioxide and sulfur dioxide can contribute under certain circumstances to acid rain formation which may lead to environmental toxicity, information has not been presented by EPA that nitrogen dioxide and sulfur dioxide are themselves toxic to the environment.

- ➢ **Nitrate ion, phosphorus compounds, and eutrophication.** Nitrogen and phosphorus are essential elements to all living organisms, including aquatic plantlife. In nitrogen- or phosphorus-limited waters, the addition of nitrogen or phosphorus, respectively, can cause increased growth of algae. This nutrient enrichment in bodies of water is referred to as "eutrophication." Excess algal growth may lead to oxygen depletion in the aquatic environment, which in advanced stages can lead to fish deaths.

---

[59] (EPA 1994, 1826, 1837)

[60] (GeneraI Electric 1994, 19; Exxon 1994)

[61] (American Mining Congress 1994; Arizona Mining Association 1994)

[62] (National Acid Precipitation Assessment Program (NAPAP) 1992, 23)

- **Proposed listing basis.** These substances were proposed at least on the basis of their potential for contributing to eutrophication.[63]
- **Industry comment.** The addition of nitrogen or phosphorus to water is not in itself toxic to the environment and does not necessarily lead to eutrophication. In general, eutrophication is a natural phenomena which requires a particular set of circumstances to occur, including proper amounts of nutrients, including but not limited to nitrogen and phosphorus, slow-moving water, and sunlight.

- **Science policy**. Although sufficient levels of phosphorus and nitrogen clearly are necessary conditions for eutrophication to occur, no information was presented that either, acting on its own, is toxic to the environment.
  - **Science policy issue.** Are chemicals toxic to the environment if they are a necessary component of or ingredient in the occurrence of environmental toxicity?
  - **Science policy decision**. Chemicals are toxic to the environment if they are part of a set of conditions necessary for the occurrence of environmental toxicity.
- **Regulatory impacts**. Some of the potential regulatory impacts from the listing of these chemicals are as follows:
  - **Direct costs of reporting**. Using EPA cost estimates of $6,881 per report per facility for first-year reporting and $3,549 per report per facility for subsequent-year reporting, and available EPA estimates for the number of reporting facilities, the direct costs of reporting are as follows (first-year costs; subsequent-year costs): sulfur dioxide ($17 million; $8.9 million); nitrogen dioxide ($1.36 million; $706,000); and nitrate ion ($14.8 million; $7.6 million).
  - Reduced motivation for voluntary pollution prevention efforts. Industry may be less inclined to undertake voluntary pollution prevention efforts if it receives insufficient credit for such efforts. Increased reporting requirements will tend to reduce the apparent progress of pollution prevention efforts. For example, Merck & Co., Inc., indicated that by the end of 1995 it will have achieved a 90 percent reduction in total releases and transfers of TRI chemicals from 1987 levels at a cost of more than $100 million. If the criteria air pollutants are added to Merck's totals, the total reduction will be reduced to a level of 30 to 40 percent.64 From 1987 to 1992, Exxon Chemical Americas achieved a 46 percent reduction in

[63] With the exception of phosphorus pentoxide, these substances were also proposed for listing on the basis of human health effects. This proposed listing basis is not addressed in this case study.

[64] (Merck 1994, 5)

releases and transfers of TRI pollutants. Including criteria pollutants would decrease reductions to approximately 16 percent.[65]

- **Summary.** EPA has proposed to list these substances because under certain circumstances they contribute to environmental toxicity. None of these substances have been proposed for TRI listing because they cause environmental toxicity directly. The costs of these listing decisions are significant, and the information collection benefits may be duplicative given that existing regulatory programs under the Clean Air Act, Clean Water Act, and other statutes already require similar information collection.

Evaluation

The purpose of TRI reporting is to enhance community knowledge of routine local releases and transfers of toxic chemicals. Toward this end, TRI reporting provides for the collection and dissemination of information to communities. It is not intended to reduce or restrict routine or permitted releases and exposures of chemicals and does not directly reduce risks. Given the significant direct and indirect costs of TRI listing and the benefit of community information dissemination, which is a less compelling benefit than risk reduction and which may be diluted by extraneous information collection, science policy decisions made in the context of TRI reporting can be less conservative and still accomplish the statutory goals of EPCRA. An information collection requirement that is limited to chemicals for which there are more well-established bases for health and environmental concern will assist local communities in addressing the most important potential local hazards first.

REFERENCES

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). 1990. Toxicological Profile for Asbestos (Draft for Public Comment). U.S. Public Health Service, Atlanta, Ga.

AMERICAN LUNG ASSOCIATION, et al. 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082-C,-113. Washington, D.C. (April 12, 1994).

AMERICAN MINING CONGRESS. 1994. Comments on TRI proposal. EPA Docket #OPPTS- 400082-C,-l 12. Washington, D.C. (April 12, 1994).

ARIZONA MINING ASSOCIATION. 1994. Comments on the TRI proposal. EPA Docket #OPPTS-400082-C,-067A. Washington, D.C. (April 12, 1994).

BUREAU OF NATIONAL AFFAIRS (BNA). 1993. Daily Environment Report No. 217, A-3 (November 12, 1993).

CHEMICAL SPECIALTIES MANUFACTURERS ASSOCIATION (CSMA). 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082-C ,-133. Washington, D.C.

CONSUMER PRODUCT SAFETY COMMISSION. 1988. Memorandum, Possible Consideration of Fibrous Glass. Washington, D.C. (December 30, 1994).

[65] (Exxon 1994, 2)

COORS BREWING COMPANY. 1994. Comments on TRI proposal. EPA Docket #OPPTS- 400082-Q-065. Washington, D.C. (April 8, 1994).

DOW CHEMICAL COMPANY. 1994. Comments on TRI proposal. EPA Docket #OPPTS- 400082-C,-086. Washington, D.C. (April 12, 1994).

EDISON ELECTRIC INSTITUTE (EEI). 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082-C,-087A. Washington, D.C. (April 12, 1994).

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994. Addition of certain chemicals; Toxic chemical release reporting; Community right-to-know (Proposed rule). Fed. Reg. 59(8):1788.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993. Regulatory Impact Analysis of the Proposed addition of Various Chemicals and Chemical Categories to the EPCRA Section 313 List of Toxic Chemicals. Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1988. Health Hazard Assessment of Nonasbestos Fibers (Final Draft). Washington, D.C.

EXXON CHEMICAL AMERICAS. 1994. Comments on TRI proposal. EPA Docket #OPPTS- 400082-C,-148. Washington, D.C. (April 11, 1994).

THE FERTILIZER INSTITUTE. 1994. Comments on TRI proposal. EPA Docket #OPPTS- 400082-C,-128. Washington, D.C. (April 12, 1994).

FISHER, L.J., Assistant Administrator, EPA Office of Pesticides and Toxic Substances. 1991. Testimony before the Subcommittee on Superfund, Ocean and Water Protection of the Senate Environmental and Public Works Committee, 10-11. (June 27, 1991).

GENERAL ELECTRIC COMPANY. 1994. Comments on TRI proposal. EPA Docket #OPPTS- 400082-C,-127. Washington, D.C. (April 11, 1994).

HOUSE OF REPRESENTATIVES. 1986. Joint Explanatory Statement of the Committee of Conference. H.R. Conf. Rep. No. 962, 99th Cong., 2d Sess.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (I ARC). 1994. I ARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Man-made mineral fibres and radon. Vol. 43. 300 pp. Lyon, France.

MERCK & Co., Inc. 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082-C ,-110. Washington, D.C. (April 11, 1994).

NATIONAL ACID PRECIPITATION ASSESSMENT PROGRAM (NAPAP). 1992. Report to Congress. Washington, D.C.

NATIONAL RESOURCES DEFENSE COUNCIL (NRDC). 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082-C ,-178. Washington, D.C. (April 11, 1994).

NORTH AMERICAN INSULATION MANUFACTURERS ASSOCIATION (NAIMA). 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082. Washington, D.C. (April 11, 1994).

UOP, Inc. 1994. Comments on TRI proposal. EPA Docket #OPPTS-400082-C ,-131. Washington, D.C. (April 12, 1994).

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, PUBLIC HEALTH SERVICE, NATIONAL TOXICOLOGY PROGRAM (NTP). 1994. Seventh annual report on carcinogens. National Institute of Environmental Health Science. Research Triangle Park, N.C.

12
RADON IN DRINKING WATER

Introduction

The Safe Drinking Water Act (SDWA) requires the Environmental Protection Agency (EPA) to establish standards for contaminants in drinking water which may cause adverse health effects. Section 1412(b) of the 1986 Amendments to the SDWA required EPA to regulate eighty-three contaminants, including radon, by June 1989. On July 18, 1991, EPA proposed a drinking water standard for radon of 300 picocuries per liter (pCi/L).[1] The proposed standard is based on the capability of technology to reduce radon levels in water to less than 100 pCi/L and on detection limits for radon in water. The estimated risk at the proposed standard, $2x10^{-4}$ (2 in 10,000), is slightly above the range that EPA generally considers acceptable. Drinking water standards for radon have not yet been promulgated because of the controversial nature of the proposal and continued congressional and Science Advisory Board involvement. EPA is under a court-ordered deadline of April 30, 1995, to issue a final standard for radon. A recent draft internal EPA memorandum suggested that 200 pCi/L would be the most "legally defensible" standard under the SDWA.

Science Policy Issues Addressed in This Case Study
➢ Assumption of low-dose linearity for risk extrapolation ➢ Use of surrogate data to estimate risks of nonlung cancers associated with ingestion of radon in drinking water ➢ Assumed values for exposure variables used in quantitative exposure and risk assessment

The assessment of risks associated with exposures to radon in drinking water is highly uncertain. Relevant science policy issues addressed in this case study include: (1) the assumption of low-dose linearity for risk extrapolation, (2) the use of surrogate data to estimate risks of nonlung cancers associated with ingestion of radon in drinking water, and (3) the choice of assumed values for exposure variables to be used in the quantitative exposure and risk assessment for radon in drinking water. The impact of

[1] A *curie* is a unit for measuring radioactivity that represents $3.7x10^{10}$ nuclear disintegrations per second. A picocurie (pCi) is one trillionth of a curie, or 0.037 nuclear disintegrations per second. *Picocurie per liter* (pCi/L) is a measure of concentration. A liter is a measure of volume and can refer either to air or water.

each of these assumptions on the risk assessment is illustrated through discussion of the original and revised risk assessments that EPA published in support of the proposed drinking water standard for radon.

Health Concerns Associated With Radon

Radon is an odorless gas that results from the radioactive breakdown of uranium in soil, rock, or water. Radon is found all over the United States, [2]albeit with a significantly nonuniform distribution, and is present in ambient air. Radon emanates from the soil and may enter buildings through cracks or openings in the floor and walls, accumulating in enclosed spaces. "Radon" refers both to radon and its radioactive decay products, or progeny, which are thought to cause the health effects associated with radon exposure.[3]

Residential exposures to radon first emerged as a public health issue in 1984, when an engineer at a nuclear power plant set off the radiation detector on his way into the plant.[4] His house was subsequently found to contain elevated concentrations of radon. Thus, the potential for radon to pose a potential health risk in homes was recognized. EPA launched the Radon Action Program, designed to assist states in dealing with radon problems in homes, in September 1985[5] and printed *A Citizen's Guide to Radon* in 1986.[6] In 1987, EPA published estimates of lung cancer mortality that ranked indoor radon on a par with skin cancer from exposure to sunlight.[7]

Epidemiologic studies of highly exposed underground uranium miners demonstrate an increased risk of lung cancer, predominantly among miners who smoked.[8] These miners are also believed to have been exposed to high levels of radon. Some ecological [9] studies of residents exposed to low levels of radon have shown an association between exposure and lung cancer, whereas others have not. Of eleven ecological studies, five demonstrated a positive association between radon exposure and lung cancer in both sexes; one found an increase in men but not in women; four did not indicate an

---

[2] Environmental Protection Agency [EPA] 1992, 3)

[3] (Alliance for Radon Reduction 1992, 1)

[4] (0ffice of Technology Assessment [OTA] 1993, 148)

[5] (Guimond 1986)

[6] The updated and revised second edition of *A Citizen's Guide to Radon* (Publication 402-K92-001) was published in 1992 and is available from the U.S. Government Printing Office.

[7] (EPA 1987)

[8] (National Research Council [NRC] 1988, 29)

[9] Ecological studies are limited in their utility and explanatory power because they rely on broad, average measures of exposure or use surrogate measures for exposure. Ecological studies explore associations between occupation or environment and disease by focusing on the group—rather than the individual—as the unit of comparison. Disease rates among groups, generally defined by geographic location, are compared. Ecological studies can identify possible problems, but cannot test hypotheses (e.g., is lung cancer associated with indoor radon?) (Mausner and Kramer 1985, 304-305).

association, and one reported a negative association.[10] Case-control studies, which provide more definitive information than ecological studies, also have shown contradictory results in household residents. Two very large case-control studies are under way in Iowa and Missouri.[11]

Because definitive information regarding the risk of radon at low levels in homes is unavailable, the best that can be done is to extrapolate from the epidemiological studies of underground uranium miners. Extrapolation from the high exposures experienced by the miners to the lower levels typical of residential exposures requires a science policy decision regarding the shape of the dose-response curve. Assuming a linear, nonthreshold, dose-response model, the current estimate is that inhalation of indoor radon causes approximately 13,600 deaths each year, with a credible range of 6,740 to 30,600.[12] EPA has estimated that reducing indoor air radon concentrations in all residences to no more than 4 pCi/L would result in 2,200 fewer lung cancer deaths each year, [13] representing about 17 percent of the cases currently attributed to indoor radon.

Proposed Maximum Contaminant Level for Radon

Radon and other radionuclides in drinking water were targeted for regulation by EPA in an advanced notice of proposed rulemaking (ANPRM) issued on September 30, 1986.[14] Congress explicitly directed in the 1986 SDWA Amendments that eighty-three contaminants, including radon, be regulated by 1989. Finally, on July 18, 1991, EPA proposed Maximum Contaminant Level Goals (MCLGs) and Maximum Contaminant Levels (MCLs) for several radionuclides, including radon.[15] EPA stated that the "primary health hazard posed by radon in water is due to its volatilization from water during household water use, and enrichment of indoor air radon levels, thereby contributing to increased risk of lung cancer," and that "[radon] is prevalent in drinking water from groundwater wells and ... contribute[S] to the very substantial risks posed by radon in the environment overall."[16]

The MCLG for radon was proposed at zero, and the MCL was proposed at 300 pCi/L. The proposed MCL was based on the capability of aeration to reduce radon concentrations in water to below 100 pCi/L and on the ability to reliably detect concentrations as low

[10] (OTA 1993, 150) summarizing (Samet 1989).

[11] (OTA 1993, 152)

[12] (EPA 1994a, Ml)

[13] (EPA 1994a, 112) Of these 2,200 averted lung cancer deaths, 1,600 would occur in smokers and 600 would occur in nonsmokers.

[14] (EPA 1991, 33053) The citation for the 1986 ANPRM is 51 FR 34836.

[15] (EPA 1991)

[16] (EPA 1991, 33098-33099)

as 300 pCi/L in water.[17] Thus, the technical feasibility of measuring radon levels in and removing radon from water—rather than the risk associated with the MCL or an evaluation of the risks associated with radon from other sources—formed the basis for the proposed MCL.

EPA presented the following rationale for the proposed MCL: [18]

- Radon in drinking water can be treated centrally, whereas radon in air cannot.
- Radon removal from water is efficient and inexpensive, especially when compared to other drinking water contaminants and treatments.
- EPA was required to develop an MCL for radon in drinking water by Congress, but has no legal authority over air in private homes.
- The proposed MCL for radon would avert more cancers (80 per year) 19than the promulgated MCLs for vinyl chloride (27 cancers per year) and ethylene dibromide (72 cancers per year).

EPA determined that averting an estimated eighty cancer deaths annually (less than 0.6 percent of the estimated 13,600 annual lung cancer deaths associated with radon exposures) at a cost of $2.9 million per cancer death averted (approximately $4 per household per year for large water systems)[20] was a "substantial" benefit at a "low cost."[21]

Cancer risks at the proposed MCL of 300 pCi/L were estimated to be $2x10^{-4}$, which is slightly above the range (10^{-6} to 10^{-4}) that EPA considers acceptable.[22] The risk assessment included three pathways: (1) lung cancer risk associated with inhalation of Volatilized radon progeny, (2) internal organ cancer risk associated with inhalation of radon, (3) and internal organ cancer risk associated with ingestion of radon.[23]

- Lung cancer risk associated with inhalation of radon progeny was based on a linear extrapolation of risk from the epidemiologic studies of miners that

---

[17] (EPA 1991, 33082) EPA followed the statutory mandate of the SDWA in establishing the MCL as close as feasible to the MCLG. Feasible is defined in the act to be the best that can be achieved using the "best technology, treatment techniques and other means which ... are available (taking cost into consideration)." Neither the statutory language nor the EPA's interpretation of the SDWA precludes consideration of the cost-effectiveness of requiring additional increments of technology in setting MCLs. See (EPA 1991, 33080).

[18] (EPA 1991, 33099)

[19] Of these averted eighty cancer deaths, sixty were expected to occur in smokers, and twenty were expected to occur in nonsmokers.

[20] (EPA 1991, 33082, 33101) Costs for small water delivery systems were estimated to be up to $170 per household per year.

[21] (EPA 1991, 33099)

[22] (EPA 1991, 33058, 33080, 33082)

[23] See (EPA 1991, 33075-33076).

predict a risk of 360 lung cancer deaths (lcds) per 10^6 working level months (WLM) [24]of exposure to inhaled radon. The lifetime risk of lung cancer associated with inhalation of radon progeny volatilizing from drinking water was estimated to be 4.9x1 O^{-7} per pCi/L_{water}[25]

- Using standard models, lifetime risk of cancer to internal organs (other than the lung) associated with inhalation of radon was estimated to be $2x10^{-8}$ per pCi/L_{water}.
- Experimental and epidemiologic data do not link exposure to ingested radon to increased cancer. Therefore, the risk estimate of cancer to internal organs associated with ingestion of radon in drinking water was based on organ dose estimates26 derived from biokinetics studies in humans using the noble gas xenon as a surrogate for radon 27 and data from atomic bomb survivors. The lifetime risk due to ingestion of radon was estimated to be $1.5x10^{-7}$ per pCi/L_{water}.

Science Policy Issues Associated With the MCL Proposal

The classification of radon as a known human carcinogen is based on the observation of increased lung cancers in underground uranium miners, who were exposed to myriad radioactive components and other hazardous materials and who were likely to smoke. Increased risks of cancer in miners are associated with cumulative exposures of approximately 40 WLM.[28] Lifetime residential exposure to radon is approximately equivalent to 0.25 WLM per year.[29] Epidemiologic studies have not clearly demonstrated an increased cancer risk associated with radon levels typically found in residences.[30] Epidemiologic studies have limited population sizes and residential exposures are not particularly high, so epidemiologic studies may not be able to confirm or refute risks at typical residential exposure levels.[31] A science policy decision is required to extrapolate the risks observed in highly exposed miners to residents exposed to much lower levels.

[24] A working level month is the standard measure of occupational exposures to radon and is equivalent to the exposure to 100 pCi/L radon in air for 170 hours.

[25] In other words, drinking water containing 1 pCi/L radon would give rise to volatilized radon progeny concentrations that would increase the probability of developing lung cancer by 4.9x1 O^{-7} over a lifetime.

[26] (Crawford-Brown 1990)

[27] (Correia et al. 1988)

[28] (EPA 1994a, 7-25)

[29] (EPA 1991, 33075)

[30] See (OTA 1993, 149).

[31] (NRC 1994, 62-71)

- **Science policy issue.** Available epidemiologic data indicate increased risks of lung cancer in highly exposed underground uranium mine workers, but lung cancer incidence data for low-level exposures are inconclusive.
- **Science policy decision**. Lung cancer risks at low exposures to radon may be estimated by extrapolation of observed lung cancer cases at much higher exposures.

Citing scientific consensus that ionizing radiation is a nonthreshold carcinogen, EPA considers the linear, nonthreshold, dose-response model to be the most appropriate for estimating the carcinogenic risk of radon. The Science Advisory Board (SAB) Radiation Advisory Committee endorsed the use of a linear, nonthreshold, dose-response model.[32] if ongoing epidemiologic studies fail to support the risk estimates derived using this model, the default assumption of low-dose linearity could be called into question.[33]

The National Research Council (NRC) Committee on Health Risks of Exposure to Radon (BEIR VI) recently reviewed the information regarding carcinogenic risks of radon that has been produced since publication of their earlier report. The BEIR VI committee concluded that it is now "desirable and feasible to proceed with ... a comprehensive reanalysis of health risks associated with radon."[34] The need for a reanalysis is supported by the committee's conclusion that "new evidence could lead to the development of a risk model for radon and lung cancer that would be substantially different from that developed by the BEIR IV committee."[35] The committee called for a thorough review of case-control and ecological epidemiologic studies focused on determining risks to residents. Furthermore, the committee suggested that the miner data be re-evaluated and a new biologically driven risk model be developed. The committee anticipates completing the reassessment by the end of 1996.[36]

In risk assessment, data that directly address an exposure of concern are frequently unavailable. For example, there are no direct epidemiologic or laboratory data on which to base a risk estimate for *ingestion* of radon in drinking water. In instances such as these, it is necessary to identify other data that can be used to estimate the exposures and risks that are of interest. The suitability of the surrogate data for this purpose is determined by a science policy decision.

- **Science policy issue.** Adequate data are not available with which to estimate the risk of nonlung cancers associated with ingestion of radon in drinking water.

---

[32] (EPA 1994a, 7-25)

[33] See also the following for discussions of the uncertainty surrounding current risk extrapolations for radon: (Cohen and Cohen 1980; Guilmette et al. 1991; Harley 1989).

[34] (NRC 1994, 1-2)

[35] (NRC 1994, 3)

[36] (NRC 1994, 4-7)

- **Science policy decision.** Biokinetic data concerning a surrogate element and extrapolation of risk estimates from atomic bomb survivors provide an acceptable estimate of the risk attributable to ingested radon.

EPA used an indirect method to estimate ingestion risks. This method involved use of a study of the disposition of a surrogate, xenon, in human tissues following ingestion because radon-specific animal or human data were lacking. Further, extrapolation of acute, high-energy gamma exposures and associated risks observed in Japanese atomic bomb survivors to chronic, low-level alpha particle exposures was necessary because there were no data from animal studies of long-term ingestion of water containing radon.[37] Sources of uncertainty associated with the indirect method include: [38]

- The ingestion risk estimate postulates stomach cancers and leukemias resulting from ingestion of radon, but there is no evidence linking ingested radon with gastrointestinal cancers or leukemia.
- The xenon surrogate modeling, upon which the internal radiation dose estimates are based, was taken from a paper that was not peer-reviewed.
- Use of atomic bomb survivor data is questionable because radon and atomic bombs release different types of radiation (alpha particles vs. gamma rays and neutrons, respectively).
- Bombs deliver a one-time, intense, external radiation exposure, whereas continuous ingestion of radon in drinking water would deliver a long-term, low- level exposure.

Because of these uncertainties, the validity of the risk estimates based on the surrogate methodology has been called into question.

Another critical element in estimating risks associated with exposure to radon is the choice of assumed values for various exposure variables. Each of these assumptions directly influences the resulting exposure and risk assessment. For example, an individual assumed to consume 2 L/day of drinking water will be exposed to twice as much of a contaminant as one who is assumed to drink 1 L/day, other things being equal. The careful construction of exposure scenarios and the use of appropriate values for exposure variables require a series of science policy decisions.

- **Science policy issue**. Given that direct exposure data do not exist, how should exposures to radon in drinking water be estimated?
- **Science policy decision.** Appropriate values can be assumed for exposure variables and combined in such a way that the resulting exposures represent acceptable upper-bound estimates of likely exposures.

---

[37] (EPA 1994a, 2-3; Science Advisory Board [SAB] 1993a, 3)

[38] See (OTA 1993, 159-160) for a discussion of comments on the reassessment.

Because radon is a volatile gas, EPA stated that only water freshly drawn and directly consumed would contain appreciable amounts of radon. EPA assumed a direct drinking water ingestion rate of 0.7 L/day [39] and that 20 percent of the radon would volatilize while drawing and drinking the water.[40] These exposure assumptions are less conservative than those typically applied for other volatile contaminants in drinking water. Assumptions for inhalation exposures also were less conservative than the standard defaults: (1) people were assumed to spend 75 percent of their time indoors, (2) an equilibrium factor of radon with its progeny of 0.5 was assumed, and (3) 10,000 pCi/L radon in water was assumed to contribute 1 pCi/L in air.[41]

The Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) reviewed the overall risk assessment for radon in drinking water and suggested that the risks might be overstated by a factor of ten. CIRRPC cited the following alternative assumptions which, if used, would result in a dramatic reduction of the risk attributable to radon in drinking water: [42]

- Assumption of equal sensitivity to the carcinogenic effects of radiation (rather than EPA's unsupported assumption that people under twenty years of age are three times more likely to develop lung cancer from radon exposure) would reduce the estimated risk by 40 percent.
- Use of an average value of 37,000 to 1 for the radon water-to-air transfer factor would reduce risk estimates by a factor of 3.7.
- Use of an equilibrium ratio between radon and progeny concentrations of 0.4, which is supported by the available data, would reduce risk estimates by 20 percent.
- Use of a revised comparative dose estimate suggesting that effective residential exposures at a given level of radon are lower than those experienced by underground uranium miners would reduce residential risk estimates by 30 percent.

Of the suggestions above, only the last was incorporated into EPA's revised risk assessment.

Benefits and Costs of the Proposed Radon MCL

Adoption of the proposed MCL would limit increases in ambient indoor air concentrations, which generally range from 1 to 2 pCi/L,[43] to no more than 0.03 pCi/L. EPA has estimated that 5 percent of radon in indoor air in homes served by

[39] For comparison, the standard assumption for all water-containing beverages and foods is 2 L/day.

[40] (EPA 1991, 33067)

[41] (EPA 1991, 33075)

[42] (Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) 1992)

[43] (EPA 1991, 33081)

groundwater is attributable to radon in drinking water. [44] Adoption of the MCL has been estimated to reduce the public's overall exposure to radon by 1 percent.[45]

EPA estimated that adoption of a 300 pCi/L MCL would avert eighty of the estimated 200 theoretical cancers attributed to radon in drinking water each year.[46] This estimate was later revised to eighty-four averted deaths per year.[47] Of the approximately 200 deaths attributed to radon in drinking water each year, 80 percent are thought to be due to lung cancer and 85 percent of these may involve synergism with smoking. [48] With eighty averted cancers annually, the proposed MCL for radon is estimated to avert more cancers than any other chemical regulated under the SDWA.[49] Mitigation of all radon in residences to no more than 4 pCi/L would avert an estimated 2,200 cancer deaths each year.[50] A similar reduction in lung cancer deaths would result directly from a 3 percent decline in smoking.[51]

EPA estimated that approximately 25,000 facilities serving an estimated 27 million people would have to treat their water to meet the radon MCL. EPA estimated that meeting the MCL would require $1.6 billion in capital costs and $180 million in annual operating costs. These total costs correspond to $2.9 million per averted cancer death.[52] For large systems (>10,000 connections), implementation costs were estimated to be $4 per household per year. For small systems (25 to 100 connections), annual household costs were estimated to be $170.[53] Since 85 percent of groundwater systems serve fewer than 500 people,[54] it would appear that the costs of meeting the radon MCL would be concentrated on small systems.

The American Water Works Association (AWWA) estimated that capital costs required to meet the proposed MCL would exceed $12 billion. The Association of California Water Agencies (ACWA) estimated that 9,420 water facilities in California would incur total capital costs of $2.7 to $3.7 billion and $520 to $710 million in annualized costs. The annual cost per cancer case averted in California would be $65 to $87 million. Both the AWWA and ACWA charged that EPA's cost estimates were too low because EPA had

---

[44] (EPA 1991, 33099)

[45] (Alliance for Radon Reduction 1992, it)

[46] (EPA 1991, 33101)

[47] (EPA 1994a, M2)

[48] (EPA 1991, 33076) Radon risk is ten times greater in smokers than in nonsmokers.

[49] (EPA 1991, 33099)

[50] (EPA 1994a, 112)

[51] (Alliance for Radon Reduction 1992, ii)

[52] (EPA 1991, 33099, 33101)

[53] (EPA 1991, 33082)

[54] (EPA 1991, 33067)

underestimated the occurrence of radon in groundwater, the number of treatment facilities affected by the proposed standard, and the unit costs of treatment facilities.**55**

Criticism of the Proposed MCL and Revised Risk Estimates

The proposed MCL for radon generated extensive interest in the environmental and regulated communities, as evidenced by the many comments received by EPA, which are briefly summarized below.[56]

- The Natural Resources Defense Council and Friends of the Earth argued that the quantitation limit of 300 pCi/L was too high, that lower levels are easily attainable, and that the risk at the proposed MCL ($2x10^{-4}$) is too high, especially when compared to those for other regulated carcinogens in drinking water.
- Water suppliers wondered whether eighty statistical lives would really be saved each year and were concerned about an MCL that is based on detection limits, which could leave the door open for ever more stringent standards as analytical capabilities improve. Water suppliers also estimated that considerably larger populations would be affected by the proposed MCL and that treatment costs would be much greater as well. Further, they contend that EPA's cost estimates were unrealistic because EPA had underestimated the occurrence of radon in groundwater, underestimated unit treatment costs, assumed that all water systems could rely on a single centralized treatment facility, and assumed an interest rate of 3 percent.
- State-level health and environmental departments claimed that the proposed MCL would impose significant financial and administrative burdens on local public water systems and state administrative agencies.
- Federal agencies and departments also submitted comments. The Navy suggested an MCL of 1,000 pCi/L because ambient radon air concentrations pose a greater risk than radon in drinking water. Several other agencies questioned the reasonableness of regulating a very minor contributor to total radon risk.

The continued controversy over the promulgation of an MCL for radon stems in part from the inconsistency in the way EPA regulates—and has attempted to regulate—radon.[57] The Science Advisory Board criticized EPA's approach to regulating radon in drinking water because it did not focus "limited resources to the more important risks" and stated:

---

[55] (Alliance for Radon Reduction 1992, 16-18; OTA 1993, 161-162)

[56] For a more thorough discussion of the comments received, see (OTA 1993, 158-162; Alliance for Radon Reduction 1992, 12-19).

[57] See (OTA 1993, 146).

> *Radon in drinking water is a very small contributor to radon risk except in rare cases and the committee suggests that the Agency focus its efforts on primary rather than secondary sources of risk.*[58]

The 1988 Indoor Radon Abatement Act established the national goal of achieving indoor radon concentrations no greater than outdoor concentrations,[59] which average from 0.1 to 0.5 pCi/L.[60] EPA suggests that homeowners take action when indoor radon concentrations exceed 4 pCi/L,[61] but volatilization of radon from drinking water at the proposed MCL was estimated to increase indoor concentrations by no more than 0.03 pCi/L.[62] Thus, the proposed MCL would appear to focus resources and efforts on a negligible portion of the total risk attributable to radon in residences.

The SAB expressed concerns about several issues which it felt the EPA had not addressed: [63]

- Uncertainties associated with the selection of models, parameters, and final risk estimates were not adequately evaluated.
- High radon exposures at the point of use, such as in a shower, were not adequately evaluated.
- Regulation of radon in drinking water could introduce additional risks from the disposal of treatment by-products.
- Regulation and removal of radon from drinking water could result in occupational exposures at treatment facilities.

Congress, prodded by the SAB, intervened on October 6, 1992, and ordered EPA to reexamine its risk and cost estimates in the Chafee-Lautenberg Amendment to EPA's Appropriations Bill. The Chafee-Lautenberg amendment directed EPA to conduct a revised risk assessment that considered exposures and risks to radon from water and air. Costs of controlling exposures from various pathways and the costs to households and communities were also to be examined. Senator Chafee believed it unreasonable to regulate a small risk due to the ingestion of radon in drinking water when Congress had not directed that the greater risk associated with radon in indoor air be regulated.[64]

In response to the Congressional mandate, EPA produced a revised risk assessment[65] that addressed some of the uncertainties. However, the risk results were similar to

---

[58] (SAB 1992)

[59] (Alliance for Radon Reduction 1992, 4)

[60] (EPA 1991, 33099)

[61] See (EPA 1992).

[62] Assuming a water-to-air transfer factor of 10,000 to 1 for volatilized radon.

[63] Compiled from SAB reports transmitted to the EPA Administrator on January 9 and January 29, 1992.

[64] See (OTA 1993, 158).

[65] (EPA 1993)

those previously released, and some questions raised by the SAB and Congress went unanswered. EPA originally had estimated that 74 percent of the total risk was due to radon that had volatilized from drinking water, but the revised risk assessment suggested that ingestion contributed 52 percent of the total. The bases for the revised risk estimates are described below.

- The National Academy of Sciences reviewed the relative dose estimates of radon decay products in mines and homes and reduced the risk factor for residential exposures from 360 led per 106 WLM to 224 led per 106 WLM. The individual lifetime lung cancer risk for inhalation of volatilized radon progeny was decreased by 39 percent to $3.0x10^{-7}$ per pCi/L_{water}.[66]
- The lifetime risk associated with inhalation of radon was not revised and remained $2x10^{-8}$ per pCi/L_{water}.[67]
- The lifetime ingestion risk estimate was changed based on revised organ-specific risks per unit radiation and revised dose estimates for radiation-induced cancers. The lifetime cancer risk for ingestion of radon in drinking water was increased by a factor of 2.3 to $3.5x10^{-7}$ per pCi/L_{water}.[68]

Although the individual pathway risk estimates were revised, the total risk estimate remained virtually unchanged, increasingly slightly to $6.8x10^{-7}$ per pCi/L_{water}. Table 12-1 summarizes and compares the original and revised risk estimates for radon in drinking water. All revisions to the risk estimates were based on changes in parameters and exposure assumptions used in the original models. However, the revised risk estimate did not account for the greatest sources of uncertainty in the risk assessment (*i.e.*, the linear extrapolation of risk observed in miners to low doses for inhalation risk and the use of surrogate dose data and atomic bomb survivor data to estimate ingestion risks).

Table 12-1. Comparison of Original and Revised Lifetime Risk Estimates for Radon in Drinking Water

Exposure Pathway	Lifetime Cancer Risk Per pCi/L in Water	
	Original	**Revised**
Inhalation of radon progeny due to radon released from water	$4.9x10^{-7}$ (74%)	$3.0x1\ O^{-7}$ (44%)
Inhalation of radon gas released from water to indoor air	$0.2x10^{-7}$ (3%)	$0.2x10^{-7}$ (4%)
Ingestion of radon gas in direct tap water	$1.5x10^{-7}$ (23%)	$3.5x10^{-7}$ (52%)
Total from all pathways	$6.6x10^{-7}$	$6.8x10^{-7}$

[66] (EPA 1993, 3-2—3-5) See also (National Academy of Sciences [NAS] 1991). This is the only change advocated by CIRRPC that EPA used in the revised risk assessment.

[67] (EPA 1993, 3-1-3-2)

[68] (EPA 1993, 3 11-3 19)

The ingestion risk assessment continues to be controversial because of the use of surrogate data and modeling. The revision of risk due to ingestion of radon elicited several negative comments, including some from Dr. Crawford-Brown, whose work EPA had used to develop the ingestion risk assessment. Because of uncertainties in the modeling and extrapolation, reviewers have suggested that the revised ingestion risk may be overstated by a factor of 100.[69]

The SAB gave EPA high marks for its general approach in the revised risk assessment.[70] However, estimates of exposed populations, risks due to ingested radon, and capital cost estimates elicited concern. The SAB again noted that radon in drinking water contributes only a small fraction of total radon exposure and reiterated the suggestion that relative risk reduction approaches were appropriate for addressing radon in air and water. The SAB found EPA's uncertainty analysis to be lacking, especially with regard to the uncertainty about the ingestion risk estimate, which was believed to be considerably more uncertain than implied. The SAB urged qualitative uncertainty discussions where quantitative treatment was not possible.

Final EPA Risk Assessment for Radon in Drinking Water

In 1994, EPA issued the final version of its risk assessment and uncertainty analysis, *Report to the U.S. Congress on Radon in Drinking Water—Multimedia Risk and Cost Assessment of Radon.*[71] This report, mandated by the Chafee-Lautenberg Amendment, was required to: [72]

- Report on the risk of adverse human health effects associated with exposure to various pathways of radon;
- Report on the costs of controlling or mitigating exposure to radon;
- Report on the costs for radon control or mitigation experienced by households and communities, including costs experienced by small communities; and
- Consider the risks posed by the treatment or disposal of waste produced by water treatment.

The distributional risk estimates provided in the *Report to Congress* are summarized in Table 12-2, which demonstrates the range of uncertainty in the risk estimates. In estimating benefits associated with the proposed MCL, EPA used the "best"[73] estimates of risk in Table 12-2 rather than high-end estimates. EPA often uses central rather than

[69] See (OTA 1993, 159-160) for a discussion of comments on the reassessment.

[70] (SAB 1993b)

[71] (EPA 1994a)

[72] (EPA 1994a, 1-3)

[73] Although based on conservative science policy assumptions, a "best" estimate in this case represents the most likely estimate. A high-end estimate would not be likely to understate the risk.

high-end estimates of risk when epidemiologic data are available. Had EPA used high-end risk estimates, the estimated risks attributable to radon in drinking water would have been approximately three times higher than those used to support the proposed MCL.

Table 12-2. Lifetime Risk Estimates for Exposures to Radon in Drinking Water[74]

	Inhalation of Radon Progeny (per pCi/L_{water})	Ingestion of Radon (per pCi/L_{water})
Low Estimate	$1.4x10^{-7}$	$3.9x10^{-8}$
"Best Estimate"	$3.0x10^{-7}$	$3.5x10^{-7}$
Median	$3.9x10^{-7}$	$1.7x10^{-7}$
High Estimate	$1.4x10^{-6}$	$7.2x10^{-7}$

EPA published revised cost estimates in the Report to Congress. After evaluating additional data, EPA estimated that 27,294 water systems containing a total of 41,136 treatment sites and serving a population of 19 million would be required to install equipment to meet the MCL.[75] EPA increased the sophistication of its cost estimates and incorporated many of the suggestions offered by water associations, the SAB, and other commenters. Total annual costs to meet the MCL were revised to $272 million. On a per-household basis, this corresponds to $242 in systems serving fewer than 100 people and $5 in the largest systems.[76] The average cost per cancer case averted is $3.2 million, ranging from $1.2 million in large systems to $7.9 million in small systems.[77] Thus, it is clear that costs increase substantially as the number of households served decreases to below 100. Despite these revisions, there still is considerable disagreement about the cost estimates, as evidenced by the AWWA estimates, which are approximately an order of magnitude higher.[78]

The *Report to Congress* includes cost estimates for a variety of radon levels and for different size systems.[79] This information would be useful for a risk manager who is charged with deciding what level to select for the MCL. Unfortunately, the report is not written so that trade-offs among cost, risk, uncertainty, and alternatives (e.g., mitigating airborne radon versus controlling radon in drinking water) are explained or even

[74] Derived from (EPA 1994a, 1-9)

[75] (EPA 1994a, 4-2)

[76] (EPA 1994a, 4-14-15)

[77] (EPA 1994a, 5-1-5-2)

[78] (EPA 1994a, 4-17)

[79] See Chapters 1 and 4 in (EPA 1994a).

invited. Both total costs and number of lives saved are graphed as functions of MCL level, [80]but the graphs are not combined so that the average cost per life savedcan be appreciated as a function of the MCL. Because information such as this is not included in the report, it seems that the *Report to Congress* is meant to justify the proposed MCL of 300 pCi/L rather than to encourage debate and discussion about where the MCL might best be set.

Furthermore, the discrepancy between spending $700,000 per life saved by mitigating household airborne radon and $3.2 million per life saved through controlling radon in drinking water is not discussed, explained, or justified. The SAB examined these EPA cost estimates and stated that the "wide discrepancy between the cost-effectiveness of mitigating waterborne radon versus soil gas radon underscores the minor role that waterborne radon plays in the overall health hazard."[81] This comment echoes several other SAB statements regarding the need to direct resources and efforts to achieving the greatest risk reduction.

Future Regulatory Action

EPA is under a court-ordered deadline to promulgate a final rule for radionuclides in drinking water by April 30, 1995.[82] A proposal to set the final MCL at 200 pCi/L was written in an internal EPA draft memorandum, dated late May, 1994, by Robert Perciasepe, Assistant Administrator for Water.[83] Perciasepe contended that an MCL of 200 pCi/L is the most "legally defensible" under the current SDWA and would have "significant risk reduction benefits ... a sound scientific foundation, and [would meet] the statutory criteria for feasibility."[84] Staff from the EPA Office of Water stated that recent data demonstrate that an MCL of 200 pCi/L is "feasible."[85] In an apparent effort to put pressure on Congress, Perciasepe opted not to take a multimedia approach to radon regulation [86] because the SDWA is focused on a single medium. Perciasepe said that a multimedia approach would be "especially attractive for both cost effectiveness and comparative risk reasons,"[87] and he has noted that the administration and Congress

[80] See Figures 3 and 4 on pages xiii and xiv in (EPA 1994a).

[81] (SAB 1993c, 2)

[82] (EPA 1994b, 21089-21090)

[83] (Bureau of National Affairs (BNA) 1994a)

[84] (BNA 1994a, A-9)

[85] (BNA 1994b)

[86] The SAB and other critics of the original proposed MCL have consistently argued that a failure to employ a multimedia approach to radon regulation will result in the misallocation of resources dedicated to reducing radon-induced cancer deaths. In other words, money will be spent on meeting the MCL even though more cancer cases could be avoided with the same level of expenditure in household radon mitigation programs.

[87] (BNA 1994a, A-9)

are working on authorization of a multimedia approach for radon.[88] He further urged Congress to consider multimedia risk reduction issues when reauthorizing the SDWA.[89]

Congress is considering various alternatives for reauthorization of the SDWA. Full cost-benefit analysis and comparative risk analysis, rather than simple cost-effectiveness considerations, could be integrated into the standard setting mechanisms at EPA. This would allow EPA to consider more fully risk and cost trade-offs when setting MCLs. An emphasis on the net benefits and cost savings that could be achieved through a multimedia approach to radon regulation might lead to significant changes in the SDWA. In the near term, however, EPA responses to the Chafee-Lautenberg Amendment and congressional response to the *Report to Congress* are likely to influence the radon MCL.

The Senate passed a SDWA reauthorization bill that contains a provision to adopt an alternative contaminant level for radon. The alternative contaminant level would be set such that radon volatilizing from drinking water would increase indoor air concentrations to between 50 and 100 percent of the national average outdoor radon concentration. Public water supplies in states or areas where programs to reduce radon in indoor air are implemented may comply with the alternative contaminant level rather than the MCL. However, because the House of Representatives has not yet acted, [90]it is not clear that a reauthorization bill will be presented to the President this year. The Senate also passed an appropriations bill that effectively prevents EPA from promulgating drinking water standards for radon before October 1, 1995.[91] However, this provision is not in the House version of the appropriations bill.

Evaluation

The proposed MCL for radon illustrates how an expensive regulation can be justified on the basis of limited science and use of several science policy assumptions. This case study demonstrates that EPA did not use maximally conservative estimates and approaches in calculating the risk attributable to radon in drinking water. Had typical default assumptions been used, the estimated number of lives averted with adoption of the MCL would have increased, thereby increasing the anticipated benefits of the regulation. The considerable uncertainty regarding the risk assessment, however, is underscored by more realistic alternative assumptions that would have reduced the published risk estimates by a factor of ten or more. For radon in drinking water, EPA has produced risk estimates that are neither the most nor least conservative. However, this middle-of-the-road risk assessment does not address key questions of science policy, such as whether very low levels of radon pose any potential risk at all.

---

[88] (BNA 1994b, A-7)

[89] (BNA 1994a, A-9)

[90] Regulation of radon is one of the issues contributing to the stalemate of SDWA rewrite legislation in the House Energy and Commerce Subcommittee on Health and the Environment.

[91] (Alliance for Radon Reduction 1994)

The focus on cost-effectiveness under the Safe Drinking Water Act does not allow for the appropriate consideration of exposures and risks from other sources. Thus, despite widespread dismay that EPA is proposing to devote considerable resources to addressing

a small portion of the total risk due to radon, EPA is subject to an antiquated, media-specific law that effectively precludes multimedia approaches and relative risk considerations.

REFERENCES

ALLIANCE FOR RADON REDUCTION. 1994. Personal communication from Joe Findaro, Esq. Washington, D.C. (August 9, 1994).

ALLIANCE FOR RADON REDUCTION. 1992. Radon in Drinking Water: A White Paper. Alliance for Radon Reduction, Washington, D.C.

BUREAU OF NATIONAL AFFAIRS (BNA). 1994a. Daily Environment Report No. 106, A-9-A10 (June 6, 1994).

BUREAU OF NATIONAL AFFAIRS (BNA). 1994b. Daily Environment Report No. 112, A-6-A-7 (June 14, 1994).

COHEN, A.F., and B.L. COHEN. 1980. Tests of the linearity assumption in the dose-effect relationship for radiation-induced cancer. Health Physics 38:53-69.

COMMITTEE ON INTERAGENCY RADIATION RESEARCH AND POLICY COORDINATION (CIRRPC). 1992. Letter from Dr. Alvin L. Young, Chair of CIRRPC, to Dr. Donald A. Henderson, Associated Director for Life Sciences, Office of Science & Technology Policy, Washington, D.C., dated May 21, 1992.

CORREIA, J.A., S.B. WEISE, R.J. CALLAHAN, and H.N. STRAUS. 1988. The Kinetics of Ingested Radon in Humans Determined from Measurements with Xe-133. Massachusetts General Hospital, Boston, Mass. Report to the Environmental Protection Agency under cooperative agreement CR810942.

CRAWFORD-BROWN, D.J. 1990. A Calculation of Organ Burdens, Dose and Health Risks from Rn-222 Ingested in Water (Draft). Report to the Office of Drinking Water, Environmental Protection Agency, Washington, D.C.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994a. Report to the United States Congress on Radon in Drinking Water—Multimedia Risk and Cost Assessment of Radon. Office of Water, Washington, D.C. EPA/811-R-94-001.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1994b. Regulatory agenda; National primary drinking water regulation: Radionuclides. Fed. Reg. 59(79):21089-21090.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1993. Uncertainty Analysis of Risks Associated with Exposure to Radon in Drinking Water. Office of Radiation and Indoor Air, Washington, D.C. Dated January 29, 1993.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1992. A Citizen 's Guide to Radon (Second edition)—The Guide to Protecting Yourself and Your Family from Radon. Washington, D.C. Publication 402-K92-001.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1991. National primary drinking water regulations; radionuclides (Notice of proposed rulemaking). Fed. Reg. 56(138):33050—33127.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1987. Unfinished Business: A Comparative Assessment of Environmental Problems: Appendix I. Cancer Risk Work Group, Washington, D.C.

GUILMETTE, R.A. et al. 1991. Risks from radon progeny exposure: What we know, and what we need to know. Ann. Rev. Pharmacol. Toxicol. 31:569-601.

GUIMOND, R.J. 1986. Indoor radon: The federal approach. EPA Journal 12(August):5.

HARLEY, N.H. 1989. Environmental lung cancer risk from radon daughter exposure. Chapter 18 in D.J. Paustenbach (ed.), The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies. New York: John Wiley & Sons.

MAUSNER, J.S., and S. KRAMER. 1985. Epidemiology—An Introductory Text. Philadelphia: W.B. Saunders Company.

NATIONAL ACADEMY OF SCIENCES (NAS). 1991. Comparative Dosimetry of Radon in Mines and Homes. Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on Health Effects of Exposure to Radon (BEIR VI). 1994. Health Effects of Exposure to Radon: Time for Reassessment? Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL (NRC), Committee on the Biological Effects of Ionizing Radiation (BEIR IV). 1988. Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Washington, D.C.: National Academy Press.

OFFICE OF TECHNOLOGY ASSESSMENT (OTA). 1993. Researching Health Risks. U.S. Congress, Washington, D.C.

SAMET, J.M. 1989. Review: Radon and lung cancer. J. Natl. Cancer Inst. 81:745-757.

SCIENCE ADVISORY BOARD (SAB). 1993a. SAB Review of Multimedia Risk and Cost Assessment of Radon in Drinking Water (EPA-SAB-EC-LTR-93-010), July 30, 1993.

Environmental Protection Agency, Washington, D.C.

SCIENCE ADVISORY BOARD (SAB). 1993b. An SAB Report: Multi-media Risk Assessment for Radon—Review of Uncertainty Analysis of Risks Associated with Exposure to Radon. Environmental Protection Agency, Washington, D.C. EPA-SAB-RAC-93-014.

SCIENCE ADVISORY BOARD (SAB). 1993c. An SAB Report: Review of Issues Related to the Cost of Mitigating Indoor Radon Resulting from Drinking Water. Environmental Protection Agency, Washington, D.C. EPA-SAB-DWC-93-015. 240

SCIENCE ADVISORY BOARD (SAB). 1992. Letter to William K. Reilly, EPA Administrator, dated January 29, 1992, re: Reducing risks from radon: Drinking water criteria documents. Environmental Protection Agency, Washington, D.C.

13
CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Many risks to human health and the environment are "unprovable."

Some risks to human health and the environment are provable. Provable risks can be measured or observed directly and include actuarial risks such as those associated with highway or air travel accidents. In contrast, other risks—such as those associated with low-doses of radiation or exposure to chemicals in the environment—are often too small to be measured or observed directly with existing scientific methods and available resources. Additionally, specific health and environmental effects are often difficult to attribute to specific causes because other competing causes cannot be excluded with reasonable certainty. Such risks are unprovable. However, the fact that a risk is unprovable does not mean that it does not exist. Provable risks can be calculated, whereas unprovable risks can only be estimated through the risk assessment process. Although unprovable risks may be estimated and expressed in probabilistic terms, they are at best educated guesses and do not constitute knowledge or uncontroverted fact. In other words, the ability to produce a numerical estimate of an unprovable risk does not mean that the risk is proven.

Science policy issues are unavoidable in, and science policy decisions are essential to, the regulatory risk assessment process.

Risks are unprovable because of significant gaps and uncertainties in scientific knowledge, data, and method. When risk assessment is used to estimate unprovable risks, these gaps and uncertainties become science policy issues. Both risk assessors and risk managers make science policy decisions in order to bridge the gaps and uncertainties. Thus, science policy decisions enable the estimation of unprovable risks.

Science policy decisions, particularly when compounded, lead to conservative risk assessment results.

By design, many science policy decisions lead to risk assessment results that are more likely to overstate than to understate risks. In other words, compensation for the lack of knowledge in the risk assessment process is intended to be protective of public health. Risk assessment results are even less likely to underestimate risk when, as is generally the case, a series of conservative science policy decisions is involved. There is nothing wrong with such science policy decisions and risk assessments unless the nature and extent of the science policy decisions made are not fully disclosed to policy makers, risk managers, the media, and the public.

The existence and extent of science policy in risk assessment are rarely fully and fairly disclosed.

The numerical results of risk assessments tend to be emphasized while discussions of the role of science policy in generating the risk assessment results tend to be de-emphasized. For example, given that many risks are unprovable, there is some probability that, in fact, they are zero. For unprovable risks, science policy decisions enable the estimation of nonzero risks. However, this fact rarely, if ever, is clearly presented in a risk assessment. The lack of disclosure causes risk assessment results to be communicated essentially as fact. Such communication is misleading. Lack of full and fair disclosure of the role of science policy in risk assessment is not the fault of regulators alone. Media communication of risk information tends to omit discussions of science policy because such discussions: (1) do not fit into sound bites; (2) tend to detract from the sensationalism of the risk information; or (3) are not simple to communicate, and subtleties are lost.

Science policy decisions are responsible for regulatory programs and regulatory impacts that are justified on the basis of risk assessment

For regulatory activities and programs that involve or depend upon risk assessment, the science policy decisions made generally determine the existence, extent, and continued credibility of the regulatory activities and programs. As illustrated by the case studies in this report, science policy decisions have been instrumental in determining that:

- Used oil should not be classified as a hazardous waste subject to regulation under Subtitle C of the Resource Conservation and Recovery Act;
- Unleaded gasoline is not carcinogenic to humans;
- Fluoridated drinking water is not carcinogenic, and drinking water should continue to be fluoridated as a public health measure; and
- Commercial uses of asbestos could be banned under the Toxic Substances Control Act.

In the future, science policy decisions will be used to help determine whether:

- Glass wool, food additives, nitrogen dioxide, sulfur dioxide, nitrate ion, phosphorus compounds, and other chemicals will be added to the Toxics Release Inventory;
- Workplace indoor air quality will be regulated;
- Drinking water standards for radon will be made more stringent; and
- Remediation of Superfund sites contaminated with trichloroethylene will continue to be as stringent as currently required.

As in the risk assessment process, science policy and other assumptions play a significant role in the estimation of benefits and costs associated with regulatory programs.

When risks can only be estimated, the benefits of regulatory programs to reduce those risks also can only be estimated, are not verifiable, and depend on science policy-based assumptions. Similarly, cost assessments often depend on assumptions, are uncertain, and cannot constitute uncontroverted fact. An important distinction between estimates of costs and benefits is in the certainty of their existence. Because it is not possible to prove with certainty the existence of unprovable risks, the existence of benefits from regulatory programs also cannot be proven. In contrast, while there is uncertainty involved in cost assessments, such uncertainty is associated with the magnitude of the estimated costs, not their existence.

Science policy decisions can be made so as to result in desired regulatory outcomes.

The case studies of fluoride in drinking water, asbestos in consumer products, unleaded gasoline, and used oil are examples of decisions where science policy-based assumptions help to justify desired regulatory outcomes.

- In the case of fluoride in drinking water, the weight-of-evidence science policy decision that fluoride was not carcinogenic in humans supported the continued fluoridation of water, a highly valued and desirable public health measure. This science policy decision also helped maintain the credibility of the Public Health Service, which has been promoting the use of fluoride since the 1940s.
- In the case of asbestos in consumer products, the science policy decision to consider only the estimated cancer risk from asbestos brake products and not to consider the potentially offsetting safety risk from the use of nonasbestos brake product substitutes helped justify EPA's decision to promulgate a ban on commercial uses of asbestos.
- In the case of unleaded gasoline, the science policy decision that mechanisms of carcinogenicity varied between rodents and humans provided the basis for concluding that unleaded gasoline is not carcinogenic to humans. This science policy decision helped maintain the credibility of EPA's program to remove lead from gasoline.
- In the case of used oil, the science policy decision that used oil is not a hazardous waste facilitates used oil recycling. Labeling of used oil as a hazardous waste would have resulted in a burdensome cradle-to-grave regulatory scheme for used oil that might have undermined recycling efforts and increased pollution from illegal or improper disposal of used oil.

For the foreseeable future, science policy will remain the key to all regulatory programs that rely on quantitative risk assessment.

Although a great deal of scientific knowledge has been developed over the last twenty years, existing knowledge still cannot answer all the questions we can put to it. Advances in knowledge are not likely to come fast enough to address the onslaught of genuine and manufactured, known and hypothetical, and significant and insignificant risks faced by regulatory agencies, the regulated community, and the public. Although continued scientific research is highly valued, from a practical point of view, regulatory agencies rarely enjoy the luxury of time to wait for new research to aid them in regulatory decisions. Hence, science policy decisions will continue to be relied upon by regulators. For policy makers and risk managers who are aware of the tendency of risk assessors to make conservative science policy decisions, regulatory decisions are easier, because they know their decisions are not likely to be made on the basis of underestimated risk.

Recommendations

Policy makers, risk managers, the media, and the public should be made aware of the role of science policy in risk assessment and subsequent risk management decisions.

Although risk assessors are likely to be aware of science policy issues and decisions, the same cannot be said for policy makers, risk managers, the media, and the public. Risk assessors often fail to emphasize the existence and extent of science policy in risk assessment. Where the role of science policy is not explicitly explained, risk estimates may be erroneously communicated to policy makers, risk managers, the media, and the public as uncontroverted fact. Because these groups are unaware of the role of science policy, they often fail to inquire about its impact on risk assessment. Either failure may result in regulatory decisions that are made on an uninformed basis to an uninformed, misled, or unnecessarily alarmed public. Risk assessors should ensure that such miscommunication does not occur. Policy makers, risk managers, and the media should inquire about the existence and extent of science policy.

The federal government should institute a mandatory training and continuing education program on regulatory risk assessment and risk management for policy makers, risk managers, risk assessors, and their staffs.

Decisions based on risk assessment affect the health and of safety people, the condition of the environment, the operation of the federal, state, and local governments, and the operation of industries and businesses. Remarkably, no formal training in risk assessment or risk management is required of the policy makers, risk managers and risk assessors and their staffs who participate in the making of these weighty regulatory decisions. In contrast, physicians, attorneys, policemen, firefighters, plumbers and electricians, among others, are required to undergo substantial training, apprenticeship,

and licensing before engaging in their respective occupations. Although professional societies exist, and regulatory agencies sponsor seminars and workshops from time to time, there is no system in place which attempts to achieve a minimal level of competence in the area of risk assessment and risk management among all policy makers, risk managers, risk assessors, and their staffs. It is quite likely that a mandatory training and continuing education program that explicitly discusses science policy as a matter of policy rather than fact would: (1) improve awareness and understanding of science policy throughout the federal government; (2) result in more effective, efficient, and timely regulatory programs; and (3) pay for itself in a short period of time.

Communication of risk assessment results should emphasize the role of science policy.

Because risk assessments for unprovable risks are educated guesses, risk assessment results should never intentionally or inadvertently be presented as fact. Full disclosure of the role of science policy should accompany risk estimates wherever presented, including Federal Register notices, executive summaries of regulatory documents, press releases, and other public and media communications. Disclosure is ineffective if it is inaccessible, comprehensive, explicit, and understandable. Disclosure should attempt to address the following questions:

- Is the risk of concern provable, and can it be calculated? If the risk is unprovable, is it because the risk is too small to be detected with current scientific methods or because competing risk factors cannot be sufficiently distinguished?
- If the risk is unprovable, or provable but incalculable, what are the gaps and uncertainties in scientific knowledge and data that preclude the calculation of risk?
- What science policy decisions have been made to bridge these gaps and uncertainties? For unprovable risks, what science policy decisions have been made that concern the existence of the risk?
- Could alternative science policy decisions have been considered? What would the impacts have been on the risk assessment of these alternative decisions?
- What are the implications for regulation of the science policy decisions made as well as the alternatives? Do alternative science policy decisions reduce or eliminate the basis for regulation? Does consideration of substitution risks or lifecycle risks affect the basis for regulation?

Answers to these questions will facilitate understanding of the likelihood that a risk exists and its potential magnitude. Improved understanding will enable: (1) policy makers and risk managers to decide on a more fully informed basis whether and what resources should be expended to address the risk; and (2) the public and media to debate the issue on a more fully informed basis.

Risk assessment guidelines may help provide a framework for the use of science policy in risk assessment, but only if such guidelines are flexible and complied with in good faith.

Risk assessment guidelines can provide a framework within which regulators can make science policy decisions. Such a framework would provide the regulated community and the public with the "rules" for science policy decisions in regulatory risk assessment. Flexible guidelines would delineate the factors to be considered in developing a risk assessment and would require explanations for all judgments. Risk assessment guidelines should not establish a cookbook approach. Unless the guidelines are flexible enough to accommodate new scientific developments and specify the level of evidence required to deviate from a default assumption, efforts to develop new knowledge may be stymied or wasted. This could, in turn, inhibit advances in risk assessment. To the extent that risk assessment guidelines actually provide policy guidance, such guidance should be complied with in good faith by regulatory agency staff or it will be of little practical value. With respect to potential judicial review, although it will be difficult for a court to rule on the scientific merits of an agency science policy judgment, a court can rule whether that judgment has been explained adequately. Ultimately, the merits of the judgment will be evaluated, and the agency's credibility will be weighed in the court of public opinion as well as by the scientific community.

Precedent has been established, and agencies should be encouraged to give meaningful consideration to alternatives to the default assumptions used in risk assessment

Default science policy decisions generally are employed in risk assessment. In some cases, however, regulatory agencies have opted to use alternatives to the default science policy decisions where the alternatives are supported by scientific knowledge or data. This trend should be encouraged. To the extent possible, risk assessment guidelines should provide a timely and effective process for evaluating and implementing potential alternatives to the default science policy decisions. Such a process should include a compliance mechanism, perhaps independent from the particular regulatory agency, to ensure an objective review.

Summary

Risk assessment is a valuable tool through which regulators can gauge the existence and severity of potential risks to human health and the environment. Risk assessment cannot provide the definitive answers policy makers, regulators, the regulated community, and the public would like. Nonetheless, risk assessment based on science policy can frame the debate about whether particular potential risks should be regulated and who should bear the costs of regulation. Full and open disclosure of science policy in risk assessment can take this debate to the next level.

Only when policy makers, risk managers, the public, and the media fully understand the role of science policy decisions in risk assessment can the "real" issue in environmental and public health protection be debated. We must determine what society is willing to pay to reduce or avoid risks to human health and the environment which have been identified and estimated using science policy rather than science alone. These risks may or may not actually exist. If they do exist, they are likely to be relatively small or indistinguishable from other risks. If risks are too small or indistinguishable, it likely will not be possible to know whether regulation produced any benefit. The open debate of the value and priority of regulating these types of risks will enable, but not guarantee, policy and regulatory decisions to be made on a fully informed basis.

APPENDIX 1
GLOSSARY OF ACRONYMS AND ABBREVIATIONS

RIAP interviewed and/or collected information from individuals in a number of key public and private organizations, including (in alphabetic order):

Alliance for Radon Reduction

American Automobile Manufacturers Association

American Electronics Association

American Forest and Paper Association

American Industrial Health Council

American Insurance Association

American Iron and Steel Institute

American Petroleum Institute

ARCO

Chemical Manufacturers Association

Chemical Manufacturers Association, Chemstar Panel on Crystalline Silica

Chemical Waste Management

Competitive Enterprise Institute

Don Clay & Associates

Edison Electric Institute

E.I. du Pont de Nemours and Co.

ENVIRON Corporation

Environmental Defense Fund

Environmental Working Group

Executive Office of the President, Office of Management and Budget

The Fertilizer Institute

The George Washington University

Halogenated Solvents Industry Association

Harvard Center for Risk Analysis

Hazardous Waste Cleanup Project

Health Policy Institute

The Heritage Foundation

Jenner and Block

Ketchum Communications

Kirkpatrick & Lockhart

Local Governments for Superfund Reform

Louisiana State University, Department of Pathology

Monsanto Company

National Agricultural Chemicals Association

National Association of Home Builders

National Association of Manufacturers

National Association of Sewer Service Companies

National Coal Association

National Food Processors Association

National Paint & Coatings Association

National Research Council, Committee to Review Risk Management in DOE's Environmental Remediation Program

Natural Resources Defense Council

North American Insulation Manufacturers Association

Occidental Petroleum

Philip Morris Companies

Public Citizen, Health Research Group

Resources for the Future

Robert Wood Johnson School of Medicine

Rochester Institute of Technology Science International

Texaco

University of California at Berkeley

U.S. Air Force U.S. Army

U.S. Chamber of Commerce

U.S. Conference of Mayors

U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health and the Environment

U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Transportation and Hazardous Materials

U.S. Congress, House Committee on Public Works and Transportation, Subcommittee on Investigations and Oversight

U.S. Congress, House Committee on Science, Space and Technology, Subcommittee on Science

U.S. Congress, House Committee on Science, Space and Technology, Subcommittee on Technology, Environment and Aviation

U.S. Congress, Office of Rep. Dick Zimmer

U.S. Congress, Office of Technology Assessment

U.S. Congress, Senate Committee on Energy and Natural Resources

U.S. Congress, Senate Committee on Environment and Public Works

U.S. Congress, Senate Committee on Veterans Affairs

U.S. Department of Agriculture, Office of the Secretary

U.S. Department of Energy, Committee on Interagency Radiation Research and Policy Coordination

U.S. Department of Energy, Office of Environment, Safety and Health

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences

U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health

U.S. Department of Health and Human Services, Public Health Service, Office of Emergency Preparedness

U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration

U.S. Department of Labor, Occupational Safety and Health Administration

U.S. Environmental Protection Agency, Office of the Administrator

U.S. Environmental Protection Agency, Office of Enforcement

U.S. Environmental Protection Agency, Office of Policy Planning and Evaluation

U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances

U.S. Environmental Protection Agency, Office of Research and Development

U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response U.S. Environmental Protection Agency, Science Advisory Board

U.S. Navy

Vulcan Materials, Chemicals Division

Wiley, Rein and Fielding

World Bank

WMX, Inc.

APPENDIX 2
GLOSSARY OF
ACRONYMS AND ABBREVIATIONS

A/C	Asbestos/cement
ACWA	Association of California Water Agencies
ADA	American Dental Association
ADME	Absorption, distribution, metabolism, and elimination
AFL-CIO	American Federation of Labor-Congress of Industrial Organizations
AIHC	American Industrial Health Council
AIRS	Aerometric Information Retrieval System
AM	After market
AMA	American Medical Association
ANPRM	Advanced notice of proposed rulemaking
ARAR	Applicable or relevant and appropriate requirement
ASME	American Society of Mechanical Engineers
ATSDR	Agency for Toxic Substances & Disease Registry
AWWA	American Water Works Association
BAT	Best available technology
BHA	Butylated hydroxyanisole
BMD	Benchmark dose
BME	Body mass equivalence
BRS	Biennial Report System
CAA	Clean Air Act
CAG	EPA Cancer Assessment Group
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFC	Cholorfluorocarbon
CFSAN	FDA Center for Food Safety and Applied Nutrition
CIGA	Compound inducing a-2p.-globulin accumulation

CIRRPC	Committee on Interagency Radiation and Research and Policy Coordination
CMA	Chemical Manufacturers Association
CPSC	Consumer Product Safety Commission
CRAM	NRC Committee on Risk Assessment Methodology
CSMA	Chemical Specialties Manufacturers Association
CUS	Chemical Update System
CWA	Clean Water Act
DCA	Dichloroacetic acid
DHHS	U.S. Department of Health and Human Services
DIY	Do it yourselfers
DOE	U.S. Department of Energy
EDTA	Ethy lene-diam ine-tetra-acetate
EEI	Edison Electric Institute
EH	DOE Office of Environment, Safety and Health
EM	DOE Office of Environmental Restoration and Waste Management
EPA	U.S. Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act of 1986
ETS	Environmental tobacco smoke
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
f/ml	fiber per milliliter
FR	Federal Register
gplg	grams per leaded gallon
GRAS	Generally recognized as safe
H.R. ####	U.S. House of Representatives bill ####
HSTD	Highest subtoxic dose
HSWA	Hazardous and Solid Waste Amendments
HWCP	Hazardous Waste Cleanup Project
HWTC	Hazardous Waste Treatment Council
IAQ	Indoor air quality
IARC	International Agency for Research on Cancer
IBM	International Business Machines

IRIS	Integrated Risk Information System
lcd	Lung cancer death
LMS	Linearized Multistage Model
m	milli (one-thousandth)
MCL	SDWA Maximum contaminant level
MCLG	SDWA Maximum contaminant level goal
MEI	Maximally exposed individual
minTD	Minimally toxic dose
mg/kg/d	milligram(s) per kilogram of body weight per day
MTD	Maximum tolerated dose
NAIMA	North American Insulation Manufacturers Association
NAO	Nonasbestos organic
NAPAP	National Acid Precipitation Assessment Program
NAS	National Academy of Sciences
NESHAP	National emissions standards for hazardous air pollutants
NIEHS	National Institute of Environmental Health Sciences
NPDES	CWA National Pollutant Discharge Elimination System
NPL	National Priorities List
NRC	National Research Council
NRDC	Natural Resources Defense Council
NTP	National Toxicology Program
OEM	Original equipment market
OIRA	OMB Office of Information and Regulatory Affairs
OMB	Office of Management and Budget
OSHA	Occupational Safety and Health Administration
OSHAct	Occupational Safety and Health Act
OSTP	Office of Science and Technology Policy
OTA	U.S. Congress Office of Technology Assessment
PAH	Polynuclear aromatic hydrocarbon
PBPK	Physiologically based pharmacokinetics
PCBs	Polychlorinated biphenyls
PCE	Tetrach loroethy lene
pCi/L	picocurie per liter

PHS	U.S. Public Health Service
PPb	parts per billion
ppm	parts per million
RAF	EPA Risk Assessment Forum
RCRA	Resource Conservation and Recovery Act
RFI	Request for Information
RIA	Regulatory impact analysis
RIAP	Regulatory Impact Analysis Project, Inc.
RME	Reasonable maximum exposure
S. ###	U.S. Senate bill ###
SAB	EPA Science Advisory Board
SAE	Surface area equivalence
SARA	Superfund Amendments and Reauthorization Act
SDWA	Safe Drinking Water Act
SMCL	SDWA secondary maximum contaminant level
SNL	Sandia National Laboratories
SSTS	Section 7 Tracking System
TCA	Trichloroacetic acid
TCE	Trichloroethylene
TCLP	Toxicity characteristic leachate procedure
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
UCL	Upper confidence limit
UORA	Used Oil Recycling Act
u.s.c.	United States Code
TSCA	Toxic Substances Control Act
VSD	Virtually safe dose
WLM	Working level month
P	micro (one-millionth)

APPENDIX 3
GLOSSARY OF TERMS

Absorbed dose. The amount of a substance penetrating the exchange boundaries of an organism after contact.

Acute exposure. One dose or multiple doses occurring within a short time (24 hours or less).

Acute hazard or toxicity. See Health hazard.

Adenoma. A benign neoplasm of epithelial tissue in which tumor cells form glands or gland-like structures.

Administered dose. The mass of a substance given to an organism and in contact with an exchange boundary (e.g., gastrointestinal tract) per unit body weight per unit time (e.g., mg/kg/day).

Aeration. To pass air through a liquid. Aeration can be used to remove volatile contaminants (e.g., radon) from water.

Alpha particles. Particulate ionizing radiation.

Anecdotal data. Data based on descriptions of individual cases rather than on controlled studies.

Aquifer. A water-bearing stratum of permeable rock, sand, or gravel.

Asbestosis. Pneumoconiosis produced by inhalation of asbestos fibers. A chronic disease characterized by diffuse interstitial pulmonary fibrosis, often accompanied by thickening and sometimes calcification of the pleura.

Attributable risk. The difference between risk of exhibiting a certain adverse effect in the presence of a toxic substance and that risk in the absence of the substance.

Benign. Not malignant; remaining localized. A benign tumor does not form metastases and does not invade and destroy adjacent normal tissue. See Malignant.

Bioaccumulate. Accumulation of toxic chemicals in living things.

Bioassay. The determination of the carcinogenic potency or toxicity of a test substance by noting its effects in five animals.

Bioavailability. The degree to which a drug or other substance becomes available to the target tissue after administration or exposure.

Biokinetics. Study of growth changes and movements that developing organisms undergo.

Biotransformation. The transformation of chemical compounds within a living organism.

Body mass equivalence (BME). Equivalent dose per unit of body weight is assumed to have the same effect on all species.

Body surface area equivalence (BAEV Equivalent dose per square meter of body surface area is assumed to produce that same effect on all species.

Carcinogen. An agent capable of inducing a cancer response.

Carcinogenesis. The origin or production of cancer, veiy likely a series of steps. The carcinogenic event so modifies the genome and/or other molecular control mechanisms in the target cells that these can give rise to a population of altered cells.

Case-control study. An epidemiologic study that looks back in time at the exposure history of individuals who have a health effect (cases) and at a group who do not (controls) to ascertain whether they differ in proportion exposed to the chemical under investigation.

Chronic effect. An effect that is manifest after some time has elapsed from initial exposure. See also Health hazard.

Chronic exposure. Multiple exposures occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime.

Chronic hazard or toxicity. See Health hazard.

Chronic study. A toxicity study designed to measure the (toxic) effects of chronic exposure to a chemical.

Cohort study. An epidemiologic study that observes subjects in differently exposed groups and compares the incidence of symptoms. Although ordinarily prospective in nature, such a study is sometimes carried out retrospectively, using historical data.

Confounder. A condition or variable that may be a factor in producing the same response as the agent under study. The effects of such factors may be discerned through careful design and analysis.

Control group. A group of subjects observed in the absence of agent exposure or, in the instance of a case-control study, in the absence of an adverse response.

Cost-benefit analysis. A methodology that examines whether or not a given activity or project has more benefits than costs. The systematic identification of all costs and benefits associated with a project, regulation, or policy decision, including a full analysis of how those costs and benefits are distributed across different groups in society. Ranges of costs and benefits are developed, and summary statistics are presented.

Cost-effective analysis. The calculation of different alternatives arrayed along a scale relating costs to achievement (i.e., more pollution reduction).

Critical effect. The first adverse effect, or its known precursor, that occurs as the dose rate increases.

Dental caries. Cavities.

Dental fluorosis. An increased porosity of the tooth enamel caused by excess fluoride reaching developing teeth. Dental fluorosis can range from very mild, which is barely visible, to severe, which features pronounced pitting and discoloration.

Detection limit. The lowest amount that can be distinguished from the normal "noise" of an analytical instrument of method.

Developmental toxicity. The study of adverse effects on the developing organism (including death, structural abnormality, altered growth, or functional deficiency) resulting from exposure prior to conception (in either parent), during prenatal development, or postnatally up to the time of sexual maturation.

Dose-response evaluation. The process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of a contaminant administered or received and the incidence of adverse health effects in the exposed population. From the quantitative dose-response relationship, toxicity values are derived that are used in the risk

characterization step to estimate the likelihood of adverse effects occurring in humans at different exposure levels.

Dose-response relationship. A relationship between the amount of an agent (either administered, absorbed, or believed to be effective) and changes in certain aspects of the biological system (usually toxic effects), apparently in response to that agent.

Dysphagia. Difficulty in swallowing.

Endpoint. A response measure in a toxicity study.

Epidemiology. The study of disease in human populations.

Eutrophication. Nutrient enrichments of a body of water which lead, in turn, to excessive growth of algae and then depletion of dissolved oxygen as dead algae are consumed by decomposers. Algal blooms may result from addition of nutrients, whose scarcity is normally limiting. Phosphate is frequently the limiting nutrient in aquatic ecosystems.

Excess lifetime risk. The additional or extra risk incurred over the lifetime of an individual by exposure to a toxic substance.

Exposure. Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure assessment. The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure event. An incident of contact with a chemical or physical agent. An exposure event can be defined by time (e.g., day, hour) or by incident (e.g., eating a single meal of contaminated fish).

Exposure pathway. The course a chemical or physical agent takes from a source to an exposed organism. An exposure pathway describes a unique mechanism by which an individual or population is exposed to chemicals or physical agents at or originating from a site. Each exposure pathway includes a source or release from a source, an exposure point, and an exposure route.

Exposure point. A location of potential contact between an organism and a chemical or physical agent.

Exposure route. The way a chemical or physical agent comes in contact with an organism (i.e., by ingestion, inhalation, dermal contact).

Extra risk. The added risk to that portion of the population that is not included in measurement of background tumor rate.

Extrapolation. An estimation of a numerical value of an empirical (measured) function at a point outside the range of data which were used to calibrate the function. Quantitative risk estimates for carcinogens are generally low-dose extrapolations based on observations made at higher doses.

False negative. Said to occur when a test fails to detect a response that is actually present.

False positive. Said to occur when a test appears to detect a response that is actually absent.

Fibrosis. The formation of tissue containing fibroblasts, as well as fibers and fibrils of connective tissue, in a reparative or reactive process.

Filtrate. Material that has passed through a filter.

Gamma rays. Short-wavelength, high-frequency electromagnetic ionizing radiation.

Gavage. The introduction of material into the stomach through a tube.

Generally recognized as safe (GRAS). GRAS indicates that there is a reasonable certainty in the minds of scientists that a particular food ingredient is not harmful under its intended conditions of use as designated by the FDA.

Genotoxic. Material that interacts with and alters DNA.

Geometric mean. The n* root of the product of n numbers. For example, the geometric mean of (0.25, 4, and 8) is 2.

Group A carcinogen. Known human carcinogen, as classified by EPA.

Group B carcinogen. Probable human carcinogen, as classified by EPA. This group is divided into Groups B1 and B2, based on the weight of evidence from human epidemiologic studies.

Group C carcinogen. Possible human carcinogen, as classified by EPA.

Group D carcinogen. Not classifiable as to human carcinogenicity, as classified by EPA.

Group E carcinogen. Evidence of noncarcinogenicity for humans, as classified by EPA.

Hazard identification. The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defects) and whether the adverse health effect is likely to occur in humans.

Health hazard. Types of:

1. Acute toxicity. The older term used to describe immediate toxicity. Its former use was associated with toxic effects that were severe (e.g., mortality) in contrast to the term "subacute toxicity" that was associated with toxic effects that were less severe. The term "acute toxicity" is often confused with that of acute exposure.

2. Allergic reaction. Adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one.

3. Chronic toxicity. The older term used to describe delayed toxicity. However, the term "chronic toxicity" also refers to effects that persist over a long period of time, whether or not they occur immediately or are delayed. The term "chronic toxicity" is often confused with that of chronic exposure.

4. Idiosyncratic reaction. A genetically determined abnormal reactivity to a chemical.

5. Immediate versus delayed toxicity. Immediate effects occur or develop rapidly after a single administration of a substance, while delayed effects are those that occur after a lapse of some time. These effects have also been referred to as acute and chronic, respectively.

6. Reversible versus irreversible toxicity. Reversible toxic effects are those that can be repaired, usually by a specific tissue's ability to regenerate or mend itself after chemical exposure, while irreversible toxic effects are those that cannot be repaired.

7. Local versus systemic toxicity. Local effects refer to those that occur at the site of first contact between the biological system and the toxicant; systemic effects are those that are elicited after absorption and distribution of the toxicant from its entry point to a distant site.

Heritable. Capable of being inherited or of passing by inheritance.

Hyperplasia. An increase in the number of cells in a tissue or organ, excluding tumor formation, whereby the bulk of the part or organ is increased.

Immunosurveillance. The monitoring function of the immune system, whereby it recognizes and reacts against aberrant cells arising within the body.

Incidence. The number of new cases of a disease within a specified period of time.

Incidence rate. The ratio of the number of new cases over a period of time to the population at risk.

Individual risk. The probability that an individual person will experience an adverse effect. This is identical to population risk unless specific population subgroups can be identified that have different (higher or lower) risks.

Initiation. The ability of an agent to induce a change in a tissue which leads to the induction of tumors after a second agent, called a promoter, is administered to the tissue repeatedly. See also Promoter.

Intake. A measure of exposure expressed as the mass of a substance in contact with the exchange boundary per unit body weight per unit time (i.e., mg chemical/kg/day). Also termed the normalized exposure rate; equivalent to administered dose.

Integrated Risk Information System (IRIS). An EPA database containing verified RfDs and slope factors and up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS is EPA's preferred source for toxicity information for Superfund.

Interspecies dose conversion. The process of extrapolating from animal doses to equivalent human doses.

Intraperitoneal. Within the peritoneal cavity. The peritoneal cavity is formed by a serous sac consisting of a mesothelium and a thin layer of irregular connective tissue that lines the abdominal cavity and covers most of the viscera contained therein.

Intrapleural. Within the pleura. The pleura is a serous membrane enveloping the lungs and lining the walls of the thoracic cavity.

Ionizing radiation. Any radiation capable of displacing electrons from atoms or molecules, thereby producing ions.

Latency period. The time between the initial induction of a health effect and the manifestation (or detection) of the health effect; crudely estimated as the time (or some fraction of the time) from first exposure to detection of the effect.

Leach. To dissolve out by the action of a percolating liquid.

Lesion. A wound or injury. A more or less circumscribed pathologic change in the tissues.

Lifetime average daily intake. Exposure expressed as mass of a substance contacted per unit body weight per unit time, averaged over a portion of a lifetime.

Limited evidence. According to the U.S. EPA's Guidelines for Carcinogen Risk Assessment, limited evidence is a collection of facts and accepted scientific inferences that suggests that the agent may be causing an effect, but this suggestion is not strong enough to be considered established fact.

Linearized multistage model (LMS). The modified form of the multistage model where the constant q, is forced to be positive (>0) in the estimation algorithm and is also the slope of the dose-response curve at low doses. The upper confidence limit of q, (called qj) is called the slope factor.

Malignant. A neoplasm with the property of uncontrollable growth and dissemination. A malignant tumor invades surrounding tissues, is usually capable of producing metastases, is

likely to recur after attempted removal, and is likely to cause death of the host unless adequately treated. See Benign.

Maximally exposed individual (MED). The MEI is postulated to remain at a fenceline, downwind from the facility, 24 hours a day for 70 years.

Maximum contaminant level (MCL). Legally enforceable drinking water standards individually set as close as feasible to the MCLG considering best technology, treatment techniques, etc.

Maximum contaminant level goal (MCLG). The contaminant concentration in drinking water at which no known or anticipated health effects will occur. MCLGs are not legally enforceable.

Maximum tolerated dose (MTD). The largest dose that can be administered to animals in a long-term bioassay without causing signs of overt toxicity. MTD is usually defined as the dose that suppresses body weight gain slightly (i.e., no more than 10 percent) in a ninety day chronic exposure study.

Mechanism of carcinogenicity. This mechanism is a two-step process. The first step is initiation, in which a normal cell is converted to a neoplastic cell. The second step is promotion, in which the neoplastic cell develops into an overt neoplasm.

Mesothelioma. Rare neoplasms derived from lining cells of the pleura and peritoneum. The cells grow in thick sheets covering the viscera and are composed of spindle cells or fibrous tissue, which may enclose gland-like spaces lined by cuboidal cells.

Meta-analysis. Any systematic method that uses statistical analysis to integrate that data from a number of independent studies.

Metabolism. Generally refers to all the chemical reactions in all the cells of the body. As such, metabolism also refers to the chemical changes undergone by chemical contaminants or pollutants in the body.

Metastasis. The appearance of a neoplasm in parts of the body remote from the site of the primary tumor.

Methemoelobin (Met HbV The transformation product of oxyhemoglobin of the normal Fe^{2+} to Fe^{3+}. It contains oxygen in firm union with ferric iron, thus being chemically different from oxygenated hemoglobin.

Model. A mathematical function that has parameters which can be adjusted so that the function closely describes a set of empirical data. A “mechanistic” model is usually based on biological or physical mechanisms, and has model parameters that have real- world interpretation. In contrast, “statistical” or “empirical” models fit a mathematical function to data, where the mathematical function is selected for its numerical properties. Extrapolation from mechanistic models usually carries higher confidence than extrapolation using empirical models.

Morphological. Relating to the science that studies the configuration of animals and plants.

Mutagenicity. Pertaining to the ability of chemicals to cause changes in the genetic material in the nucleus of cells in ways that can be transmitted during cell division.

National emissions standards for hazardous air pollutants. Standards governing emissions of hazardous air pollutants established under Section 112 of the Clean Air Act.

Naturally occurring background levels. Ambient concentrations of chemicals that are present in the environment and have not been influenced by humans.

Necrotic lesion. Pathological death of one or more cells, or of a portion of a tissue or organ, resulting from irreversible damage. Outlines of individual cells are indistinct and affected cells

may become merged, sometimes forming a focus of coarsely granular, amorphous, or hyaline material.

Neoplasm. An abnormal tissue that grows by cellular proliferation more rapidly than normal. Neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissues and usually form a distinct mass of tissue. Neoplasms may be either benign or malignant.

Nephropathy. Any disease of the kidney. The nephron is the functional unit of the kidney.

Neutron. An uncharged elementary particle that is found in all atomic nuclei except the hydrogen nucleus.

No data. According to the U.S. EPA Guidelines for Carcinogen Risk Assessment, "no data" describes a category of human and animal evidence in which no studies are available to permit one to draw conclusions as to the induction of a carcinogenic effect.

No evidence of carcinogenicity. According to the U.S. EPA Guidelines for Carcinogen Risk Assessment, a situation in which there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies of adequate power and dose in different species.

No observed adverse effect level (NOAELT) In dose-response experiments, an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered as adverse, nor precursors to adverse effects. In an experiment with several NOAELs, the regulatory focus is primarily on the highest one, leading to the common usage of the term NOAEL as the highest exposure without adverse effect.

No observed effect level (NOEL).In dose-response experiments, an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

Noncancer health effect. A health effect other than cancer.

Noncancer risk assessment. Risk assessment for health endpoints other than cancer.

Nonpositive data. Data which do not associate an exposure with an adverse health effect.

Nuclide. Any atomic nucleus specified by its atomic number, atomic mass, and energy state.

Osteoma. A benign neoplasm consisting of osteoblastic connective tissue that form osteoid tissue and new bone, which may become veiy compact.

Osteosarcoma. The most common and malignant of bone sarcomas that arises from bone-forming cells and affects the ends of long bones. Greatest incidence found in the age group ten to twenty-five years.

Papilloma. A circumscribed benign tumor or epithelial tumor projecting from the surrounding surface.

Paradigm. The philosophical and theoretical framework of a scientific school of discipline within which theories, laws, and generalizations and the experiments performed in support of them are formulated.

Pathology. Medical science that deals with all aspects of disease but with special reference to the essential nature, the causes, and the development of abnormal

conditions, as well as the structural and functional changes that result from the disease process.

Peroxisome. A cell organelle containing enzymes that catalyze the production and breakdown of hydrogen peroxide.

Pharmacokinetics. Quantitation and determination of the time course of absorption, distribution, biotransformation, and excretion of chemicals in the body.

Physiologically based pharmacokinetics (PBPK) model. Physiologically based compartmental model used to quantitatively describe pharmacokinetics behavior. See Pharmacokinetics.

Point estimate. A single value calculated from sample observations that is used as the estimate of the population value or parameter.

Positive data. Data that associate an exposure with a adverse health effect.

Preneoplastic lesion. A lesion preceding the formation of any neoplasms, benign or malignant, that is not always precancerous.

Principal study. The study that contributes most significantly to the qualitative and quantitative risk assessment.

Progeny. Decay products, such as those produced by the radioactive decay of radon.

Promoter. In studies of skin cancer in mice, an agent that results in an increase in cancer induction when administered after the animal has been exposed to an initiator, which is generally given at a dose that would not result in tumor induction if given alone. A' cocarcinogen differs from a promoter in that it is administered at the same time as the initiator. Cocarcinogens and promoters do not usually induce tumors when administered separately. Complete carcinogens act as both initiator and promoter. Some known promoters also have weak tumorigenic activity, and some also are initiators. Carcinogens may act as promoters in some tissue sites and as initiators in others.

Promulgate. To make known or public the terms of a proposed law or regulation.

Proportionate mortality ratio (PMRT The number of deaths from a specific cause and in a specific period of time per 100 deaths in the same time period.

Prospective study. A study in which subjects are followed forward in time from initiation of the study. This is often called a longitudinal or cohort study.

Q^*_1. Upper-bound on the slope of the low-dose linearized multistage procedure.

Qualitative risk assessment. In addition to the final results of a bioassay, all other available and relevant scientific evidence considered when evaluating the potential human health and environmental hazards associated with a certain chemical or process. Sometimes referred to as a "weight-of-evidence" determination.

Quantitation. Expression as a measurement of a quantity or amount.

Quantitative risk assessment. Use of mathematical models to extrapolate animal data to estimate human risk from chemicals or processes.

Radionuclide. A radioactive nuclide

Reasonable maximum exposure (RME) An estimate defined by the EPA to be at about the 95th percentile level of exposure.

Recall bias. An assessment bias that occurs when individuals in one group are more likely to remember past effects than individuals in another of the study or control groups.

Relative risk (sometimes referred to as risk ratio). The ratio of incidence or risk among exposed individuals to incidence or risk among nonexposed individuals.

Remediation. The act or process of correcting a problem with treatment or application, such as cleaning up a hazardous waste site.

Risk. The probability of injury, disease, or death under specific circumstances. In quantitative terms, risk is expressed in values ranging from zero (representing the certainty that harm will not occur) to one (representing the certainty that harm will occur). The following are examples showing the manner in which risk is expressed: 10^{-4} = a risk of 1/10,000; 10^{-5} = a risk of 1/100,000; 10^{--6} = a risk of 1/1,000,000.

Risk assessment. The determination of the kind and degree of hazard posed by an agent, the extent to which a particular group of people has been or may be exposed to the agent, and the present or potential health risk that exists due to the agent. A methodology that examines an activity or an exposure and attempts to quantify a probability of an event or harm occurring as a result of that activity or exposure.

Risk management. A decision-making process that entails considerations of political, social, economic, and engineering information with risk-related information to develop, analyze, and compare regulatory options and to select the appropriate regulatory response to a potential chronic health hazard.

Route-to-route extrapolation. The process of estimating risk for one route of exposure using the data from another route of exposure.

Science policy decision. The policy decision made in response to the science policy issue.

Science policy issue. A gap or uncertainty in scientific knowledge, data, information, or method in the risk assessment process that requires a policy decision in order to continue conducting the risk assessment.

Scrubbers. An apparatus for removing impurities from gases.

Short-term exposure. Multiple or continuous exposures occurring over a week or so.

Skeletal fluorosis. A condition caused by excessive intake of fluorine that causes bones to become brittle, chalky structures.

Slope factor. (1) The slope of the dose-response curve in the low-dose region. An upper-bound estimate on this slope is usually used instead of the slope itself. The units of the slope factor are usually expressed as (mg/kg/day) 1. (2) A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen. (3) For radionuclides, the age-averages lifetime excess cancer incidence rate per unit intake (or unit exposure for external exposure pathways) of a radionuclide.

Squamous cell. An epithelial cell that is flat and scaly.

Standardized mortality ratio (SMR). The ratio of observed deaths to expected deaths.

Statistical significance. The determination of the probability that an association observed in a sample might occur by chance.

Subchronic exposure. Multiple or continuous exposures occurring usually over three months.

Subchronic study. A toxicity study designed to measure effects from subchronic exposure to a chemical.

Sufficient evidence. According to the U.S. EPA's Guidelines for Carcinogen Risk Assessment, sufficient evidence is a collection of facts and scientific references definitive enough to establish that the adverse effect is caused by the agent in question.

Superfund. Federal authority established by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) in 1980, to respond directly to releases or threatened releases of hazardous substances that may endanger health or welfare.

Supporting studies. Those studies that contain information that is useful for providing insight and support for the conclusions.

Systemic effects. Systemic effects are those that require absorption and distribution of the toxicant to a site distant from its entry point, at which point effects are produced. Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs, but usually demonstrate major toxicity to one or two organs. These are referred to as the target organs of toxicity for that chemical.

Target organ of toxicity. See Systemic effects.

Threshold. The dose or exposure below which a significant adverse effect is not expected. Carcinogens are thought to be nonthreshold chemicals, to which no exposure can be presumed to be without some risk of adverse effect.

Toxicity. The quality or condition of being harmful, destructive, deadly, or poisonous. Pertaining to a toxin.

Tumor progression. The sequence of changes in which a tumor develops from a microscopic lesion to a malignant stage.

Tumorigenic. Causing the formation of a tumor.

Unit risk. The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 pg/L in water, or 1 pg/m3 in air.

Upper-bound. Referring to an estimate of the plausible upper limit to the true value of the quantity. This is usually not a statistical confidence limit.

Weight-of-evidence classification. An EPA classification system for characterizing the extent to which the available data indicate that an agent is a human carcinogen. Recently, EPA has developed weight-of-evidence classification systems for some other kinds of toxic effects, such as developmental effects.

Weight of evidence for carcinogenicity. The extent to which the available biomedical data support the hypothesis that a substance causes cancer in animals or humans. See also Weight-of-evidence classification.

Working level month (WLM). The standard measure of occupational exposures to radon, defined as exposure to 100 pCi/L radon in air for 170 hours.

ISBN: 0-9643747-1-4
Regulatory Impact Analysis Project, Inc.
1155 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036
202-429-6545