Health Risk Assessments: Opportunities and Pitfalls

Dennis J. Paustenbach*

I. INTRODUCTION

To fulfill my role in this symposium, I will discuss the regulated community's thoughts regarding current approaches to health risk assessments conducted by regulatory agencies within the United States. It might be more appropriate to say that I will discuss some of the scientific shortcomings which have crept into the practice of risk assessment and how regulatory agencies and scientists are working to overcome them. These shortcomings, more often than not, force risk assessments to overstate the likely human health risks associated with exposure to low levels of environmental pollutants.[1]

Environmental consulting firms typically serve the regulated community and its lawyers, solving problems involving contaminated soil, contaminated groundwater, airborne emissions, or a need for an operating permit. Generally, the chemicals are carcinogens, developmental or reproductive toxicants, or are highly persistent in the environment. The firms are frequently at odds with a regulatory agency. Also, they are often involved in litigation over the degree of necessary clean-up. More often than not, personal injury claims have been filed which allege that health has been or is likely to be affected due to exposure to contaminated soil, air, or water. The consulting firm's role is to assist corporations and their attorneys by developing a more thorough, balanced and therefore, credible health risk assessment than that put forward by the government or a plaintiff's attorney.

* Vice-President, McLaren Environmental Engineering, Inc., and head of the ChemRisk Division, Alameda, Ca. An earlier version of this article was presented as a paper at the Symposium on Risk Assessment presented by the Environmental Law Committee of the Association of the Bar of the City of New York on February 4, 1988 in New York City.

1. Ames, *Six Common Errors Relating to Environmental Pollution*, 7 REG. TOXICOL. & PHARM. 379, 380 (1987).

II. THE NEED FOR RISK ASSESSMENTS

Risk assessment has been a topic of intense interest during the 1980's.[2] The development of a human or ecological risk assessment can be a complex undertaking which requires the assimilation and interpretation of large quantities of scientific and medical data.[3] Although a number of definitions have been offered in the literature, it is acceptable to say that risk assessments are a way of using existing toxicity, epidemiology, environmental fate, and exposure information to describe the likely health hazard in terms that are useful to risk managers. The National Academy of Science recommended that risk assessment be considered "the characterization of the potential adverse health effects of human exposure to environmental hazards."[4] Risk assessments should represent an objective analysis of all the relevant information and should characterize the likelihood that a particular level of exposure to a given contaminant will produce a specific effect in humans or wildlife.

During the early years of the environmental movement (1960 to 1975), regulatory agencies often made decisions largely based on political pressures, social concern, and the availability of money or technology. This approach persisted for perhaps ten years until the late 1970's when it was recognized that there were too many chemicals and problems to attack in such a subjective and uneven manner.[5] Quantitative risk assessments were heralded as the solution to this problem. It was anticipated that such an objective analysis would help risk managers interpret and prioritize the implications of hundreds of toxicity studies. It became apparent that the risk assessment process assumed an important role in meeting society's need to establish an objective and standardized procedure to evaluate complex sets of scientific data.

2. *See e.g.*, Ames, *supra* note 1; Munro and Krewski, *Risk Assessment and Regulatory Decision Making*, 19 FD. COSMET. TOXICOL. 549 (1981); NATIONAL RESEARCH COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS (National Academy Press, 1983); Ames, *Dietary Carcinogens and Anticarcinogens*, 221 SCIENCE 1256 (1983); Ames, Magaw & Gold, *Ranking Possible Carcinogenic Hazards*, 236 SCIENCE 271 (1987); Office of Science and Technology Policy, *Chemical Carcinogens; A Review of the Science and its Associated Principles*, 50 Fed. Reg. 10,372 (1985); Office of Technology Assessment, Assessment of Technologies for Determining Cancer Risks From the Environment (June 1981).

3. *See* Paustenbach, *A Survey of Health Risk Assessment*, in THE RISK ASSESSMENT OF ENVIRONMENTAL AND HUMAN HEALTH HAZARDS: A TEXTBOOK OF CASE STUDIES 29 (D.J. Paustenbach ed. 1989).

4. NATIONAL RESEARCH COUNCIL, *supra* note 2, at 18.

5. Ruckelshaus, *Science, Risk, and Public Policy*, 221 SCIENCE 1026, 1027 (1983).

One benefit of risk assessment is that the truly important problems can be identified and prioritized, which in turn helps risk managers make decisions that are reasonable and cost effective.

Risk assessments appeal to regulators and the courts because they assemble and interpret all the pertinent information.[6] Assessments appear more relevant to judges and juries than the results of single or multiple toxicity tests because the significance of the substances' physical properties, acute and chronic toxicity, metabolism, interspecies differences, environmental fate, degree of human exposure, and background concentrations are all considered.[7] A risk assessment benefits the non-scientist decisionmaker by discussing and interpreting the interactions of these many factors in an understandable manner.

Interestingly, health risk assessments are not an entirely recent activity. Various examples date back almost 3,000 years.[8] They have been used by regulatory agencies for at least thirty years, most notably within the U.S. Food and Drug Administration (FDA).[9] Many of our existing environmental and occupational health standards have been, at least in part, based on the results of low-dose extrapolation models and exposure assessments. In addition, the dose extrapolation models used today were originally developed in the 1960's by radiation biologists concerned with the cancer hazard posed by exposure to medical x-rays and nuclear fallout.[10] More recently, risk assessment methodologies have been used to set standards for chemical carcinogens including pesticide residues, drinking water guidelines, ambient air standards, as well as exposure limits for contaminants found in indoor air, the workplace, consumer products, and other settings.[11]

6. Preuss & Ehrlich, *The Environmental Protection Agency's Risk Assessment Guidelines*, 37 J. AIR POLL. CONTROL A. 784 (1987).

7. Paustenbach, *supra* note 3, at 29.

8. *Id.*, at 32-40.

9. *See, e.g.*, Rodricks, *Origins of Risk Assessment in Food Safety Decision Making* 7, J. AM. COLL. TOXICOL. 539 (1989); Lehmann and Fitzhugh, *100 Fold Margin of Safety*, 18 Q. BULL. A. FOOD & DRUG OFF. U.S. 33 (1954); LEHMANN, APPRAISAL OF THE SAFETY OF CHEMICALS IN FOODS, DRUGS AND COSMETICS (Assoc. of Food and Drug Officials of the United States, Topeka, KS., 1959).

10. *See* Rodricks, *Origins of Risk Assessment*, *supra* note 9.

11. *See* Paustenbach, *supra* note 3.

Beginning in about 1984, risk assessments began to be used in personal injury cases involving exposure to toxic chemicals. The objective was to estimate the possible level of human exposure prior to the onset of the alleged injury. When the exposure estimates were shown to be relatively precise and reasonable, they were instrumental in refuting or supporting medical opinions involving causation.

Risk assessments were welcomed by Congress, environmental groups, industry, and the public because these groups expected them to organize and interpret what appeared to be an unmanageable amount of information. It was hoped that risk assessments would provide an objective approach to identifying and prioritizing hazards, as well as, help determine causation in toxic tort litigation. Regrettably, something went wrong. Few scientists, including those employed by industry, have been completely satisfied with the way risk assessments have been conducted by government agencies or their contractors.

III. CRITICISMS OF HEALTH RISK ASSESSMENTS

Scientists, engineers and attorneys have identified a number of shortcomings with what has become a typical approach for regulatory agencies conducting health risk assessments. These criticisms involve all four portions of the risk assessment process: hazard identification, dose-response assessment, exposure assessment and risk characterization.[12] Perhaps the primary concern has been that the rigidity built into regulatory assessments, caused by pressure to repeatedly adopt conservative assumptions, often does not allow all of the scientific information to be considered.[13] One consequence of this rigidity is that these assessments predict health risks much higher than those which are likely to

12. *See* NATIONAL RESEARCH COUNCIL, *supra* note 2, at 21, for a figure outlining the elements of risk assessment and risk management.

13. *See, e.g.*, Paustenbach, Shu & Murray, *A Critical Examination of Assessments of the Health Risks Associated with TCDD in Soil*, 6 REG. TOXICOL. & PHARM. 284 (1986); Turnbull & Rodricks, *Assessment of Possible Carcinogenic Risk to Humans Resulting From Exposure to Di(2-ethylhexyl)phthlate (DEHP)*, 4 J. AM. C. TOXICOL. 111 (1985); Food Safety Council, *Quantitative Risk Assessment*, in FOOD SAFETY ASSESSMENT 137, 159 (1980); Park & Snee, *Quantitative Risk Assessment: State-of-the-Art for Carcinogenesis*, 37 AM. STATISTICIAN 427, 428 (1983); Maxim & Harrington, *A Review of the Food and Drug Administration Risk Analysis for Polychlorinated Biphenyls in Fish*, 4 REG. TOXICOL. & PHARM. 192 (1984); SIELKEN, *The Capabilities, Sensitivity, Pitfalls, and Future of Quantitative Risk Assessment*, in ENVIRONMENTAL HEALTH RISKS: ASSESSMENT AND MANANGEMENT 95 (R.S. McColl ed. 1987).

exist. Another problem is that such evaluations have often focused only on the maximally exposed individual (MEI) rather than the typical person. As a result, many assessments do not yield results which apply to the vast majority of people in the community; the primary concern of risk managers.

One criticism of risk assessment was recently raised by Dr. Barry Commoner, a well-known environmental spokesperson, at a gathering of EPA employees. He was reported to have said, "The environment will not be protected by the current practice of finding an acceptable level of harm from an environmental pollutant and then issuing rules allowing industry to pollute to that level."[14] Such a characterization of the risk assessment process is not accurate and is likely to prevent a useful approach from maturing into the scientific tool that is clearly needed by regulators and the public.

It is true that one use of risk assessment is to identify levels of emissions which would not pose a significant human or environmental risk, based upon the degree of human exposure, and the associated risk. The need for such analyses came about because regulators learned that it was theoretically impossible, as well as impractical and unnecessary, to reduce the emissions of all chemicals to zero or undetectable levels.[15] The plea that we must stop pollution at the source and not allow industry to pollute up to certain levels is too simplistic. One reason that we cannot eliminate "all" emissions is that we can now identify quantities as small as one part per quadrillion (ppq). With detection of such low levels possible, agencies would have to declare even the most healthy diet and the cleanest air to be potentially hazardous if exposure to measurable levels of carcinogens were deemed unacceptable. For example, the ambient air in the north woods of Maine contains detectable levels of polycyclic aromatics which are responsible for the pine odor, but which are carcinogenic in animals. Similarly, although perhaps it is in conflict with what the public has been told, naturally occurring carcinogens present in vegetables pose a cancer hazard perhaps 10,000 times greater than that posed by the pesticide residues in our diet.[16]

14. *EPA Critic Enters the Lion's Den and is Showered by Wild Applause*, N.Y. Times, Jan. 15, 1988, at B6, col. 4.

15. *See* Preuss & Ehrlich, *supra* note 6 (discussing the detailed and expansive risk assessment techniques developed at EPA).

16. Ames, *Dietary Carcinogens*, *supra* note 2, at 1258.

Although the elimination of exposure to all non-naturally occurring substances (xenobiotics) may seem a worthwhile objective, attempts to set regulations at such levels appear to be foolish, and would certainly not be the best use of America's limited resources. If there is any doubt about the finite quantity of financial resources available in the United States, and virtually every other country, one needs only to follow the current debate regarding the age criteria for deciding when to stop treating patients who could be cured and/or functional after medical treatment but are perhaps too old to justify the expense.[17]

Some public interest groups have taken the position that risk assessments allow too much variability in the implementation of legislation in an already "loose" regulatory environment. It has been claimed that setting acceptable risk levels for environmental emissions is inappropriate since persons can be placed at risk even though they receive no direct benefit. Although these are important issues, they all appear to be based on some level of misrepresentation or misunderstanding. The fact is that risk assessments should help standardize the way we regulate chemicals, thus reducing the arbitrariness which has sometimes been present. Furthermore, living in proximity to others, especially in a technological society, by definition, exposes some people to risks not of their own making.

Widespread acceptance of risk assessment will occur when there is better understanding of the process by all parties or when a better alternative is identified. Regulatory agencies cannot arbitrarily decide that it is acceptable for the public to be exposed to significant (*e.g.*, 10^{-3} or greater) levels of risk. For example, for environmental risks to be deemed acceptable by regulatory agencies, they usually need to be negligible or de minimis (*e.g.*, of such little importance as to be of no concern). Determining whether a risk is significant is influenced by a number of factors including the number of persons exposed, the likelihood and degree of exposure, and the certainty of the biologic data.[18] I am optimistic that, because chemists can now detect the presence of contaminants at concentrations less than one ppq, the public has come to

17. *Ethicist Draws Fire with Proposal for Limiting Health Care to Aged*, Wall St. J., Jan. 22, 1988, at 23, col. 1.

18. *See, e.g.*, Travis, Richter, Crouch, Wilson & Klema, *Cancer Risk Management*, 21 ENVTL. SCI. & TECH. 415, 419 (May 1987) (a review of federal regulatory decisions, which concludes that there is a consistency to the agencies' regulatory decisions).

recognize that measurable exposure to a chemical carcinogen or a reproductive toxicant does not necessarily mean the associated risk is unacceptable. If this were the case, people would not ingest alcohol, diet soda, coffee, tea, orange juice or mineral water since each contains measurable, albeit small, quantities of carcinogens.

Research of the past few years has been useful in identifying the levels of risks which the public finds acceptable. We have learned that the acceptability of a risk is a judgment that each person must reach: what is an acceptable risk to one person may be thoroughly unacceptable to another.[19] We have learned that most persons are comfortable with accepting certain levels of involuntary risks if they are very small. For example, risks in the vicinity of 1 in 1,000,000 (the chance of being struck and killed by lightning) seems to be acceptable to nearly all persons. As expected, the cost of reducing risks to such a level is not trivial. For this and other reasons, many environmental regulatory decisions allow involuntary risks to be as great as 1 in 10,000; especially if the number of exposed persons is small. The cost to lower the risk can be very high and the true risk may actually be far less than that predicted in a conservative risk analysis.[20]

My experience indicates that the strengths and weaknesses of each portion of a risk assessment need to be understood if an objective and fair resolution of environmental issues is to occur. The various elements of a risk assessment play a pivotal role in identifying appropriate clean-up levels and in helping to resolve personal injury cases in a fair manner.

IV. Pitfalls in Risk Assessment

The risk assessment process has four basic steps: hazard identification, dose-response assessment, exposure assessment and risk characterization.[21] In light of the economic impact that environmental regulations can have on a firm or the community, these pitfalls need to be recognized.

19. *See* W. Lowrance, Of Acceptable Risk 92 (1976).

20. *See* Travis, Richter, Crouch, Wilson & Klema, *supra* note 18, at 419; Rodricks, Brett & Wrenn, *Significant Risk Decisions in Federal Regulatory Agencies*, 7 Reg. Toxicol. and Pharm. 307, 315 (1987); Travis & Hattermer-Frey, *Determining Acceptable Levels of Risk*, 22 Envtl. Sci. & Tech. 873, 875 (1988).

21. *See* National Research Council, *supra* note 12.

FIGURE 1

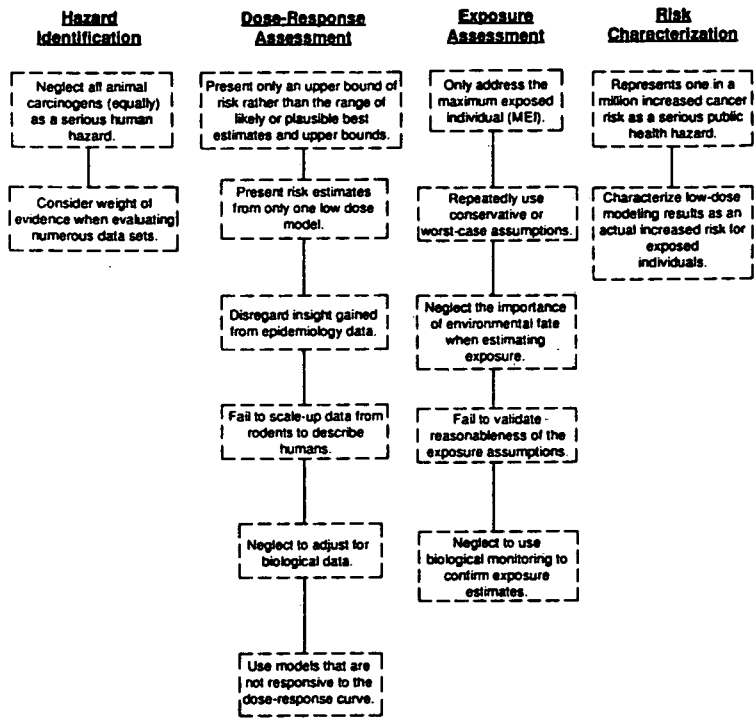


FIGURE 1: Examples of possible pitfalls in conducting or presenting health risk assessments.

A. *Hazard Identification*

In the hazard identification step of the risk assessment, there has been a tendency to consider all animal carcinogens as posing an equally serious human health hazard. In fact, carcinogens vary dramatically in their carcinogenic and/or mutagenic potency. Specifically, a weak carcinogen may require a dose 10,000,000 fold greater than that of a potent carcinogen to produce the same degree of carcinogenic response.[22] In addition, the susceptibility between species, the slope of the dose-response curve for the various toxic endpoints, pharmacokinetics, the epidemiological experience and the mechanism of action all need to be considered when attempting to predict the potency of a chemical in humans.

22. Ames, *Dietary Carcinogens supra* note 2, at 1261.

The importance of the above factors cannot be overstated since they may well explain why six hundred chemicals have been found to produce tumors in animal studies yet less than twenty are known to be human carcinogens.[23] Even after accounting for the statistical shortcomings of most epidemiological studies, it is clear that not all carcinogens pose an equivalent human hazard. The same can be said of developmental and reproductive toxicants. The challenge is to determine to what degree we need to limit exposure to each of these toxicants to insure that the risk to humans is negligible.[24]

The criteria by which the risk assessor determines that a chemical poses a significant carcinogenic or developmental threat to humans involves consideration of at least six factors.[25] For carcinogens, most of the important parameters have been identified and discussed in numerous published papers.[26] At least the following parameters should be considered when determining that an animal carcinogen may pose a human cancer hazard: number of animal species affected, the number and types of tumors occur-

23. Ames, *supra* note 1.

24. *See e.g.*, Rodricks, Brett & Wrenn, *supra* note 20, at 315; Travis & Hattermer-Frey, *supra* note 20, at 875-76; L. LAVE, ED. QUANTITATIVE RISK ASSESSMENT IN REGULATION (The Brookings Institute 1982) 153 (using estimation of lung cancer deaths caused by coke oven emissions as an example); Nichols & Zeckhauser, *The Perils of Prudence: How Conservative Risk Assessments Distort Regulation*, 8 REG. TOXICOL. & PHARM. 61 (1988) (arguing that current conservative assessment techniques leads to unnecessary overestimation of risks).

25. Critical factors in the hazard identification of chemical carcinogens and developmental toxicants:

CARCINOGENS	DEVELOPMENTAL TOXICANTS
- Number of different species affected	- Number of animal speciel affected
- Number of different types of neoplasms in one or more species	- Difference between species
- Spontaneous incidence in appropriate control group neoplasms induced in treated groups	- Relevancy of route of administration
- Dose-response relationship	- Multiplicity and nature of developmental effects among litters
- Malignancy of induced neoplasms	- Number of litters or fetuses being affected
- Genotoxicity, measured in an appropriate battery of tests	- Rare vs. common malformations
	- Ratio of adult and developmental NOEL or LOEL

Adapted from Squire, *Ranking Animal Carcinogens: A Proposed Regulatory Approach*, 214 SCIENCE 877, 878 (1981); Johnson, Christian, Dansky & Gabel, *Use of the Adult Developmental Relationship in Prescreening for Developmental Hazards*, 7 TERATOGENESIS, CARCINOGENESIS, & MUTAGENESIS 273 (1987); Wang & Schwetz, *An Evaluation System for Ranking Chemicals with Teratogenic Potential*, 7 TERATOGENESIS, CARCINOGENESIS & MUTAGENESIS 133, 134 (1987).

26. *See, e.g.*, Munro & Krewski, *supra* note 2; Paustenbach, *supra* note 3; Sielken, *supra* note 13.

ring in the animals, the dose (relative to the acute toxic dose) at which the animals are affected, the dose/response relationship, and the genotoxicity of the chemical.[27] For the developmental toxicants, guidance has been provided by a number of researchers.[28] The primary factors are similar to those for carcinogens and include: the number of species affected, severity of the effect and the relationship of the dose which affects the mother compared to that which affects the offspring.[29]

During the past few years, regulatory agencies often placed an emphasis on any piece of data that supported the fact that a chemical posed a carcinogenic or developmental hazard, and little weight on data that suggested the chemical failed to cause these problems. Extraordinary confidence was placed on studies which indicated that a chemical may pose a particular hazard, irrespective of the study's quality. This approach was considered prudent and health protective. Recently, the scientific community and most regulatory agencies have come to recognize that not all data are equal, and that only data of similar quality should be judged equally. We have also learned through experience that it should not be necessary to spend huge sums of money to repeatedly conduct high quality toxicity studies simply to refute one or two poorly controlled ones. Further, when the conclusions reached from high quality data are overwhelming, spurious data must be de-emphasized or discarded. This philosophy, known as a "weight of evidence" approach, has been applied primarily to the hazard identification segment of risk assessment, but is also applicable to the exposure and dose-response assessment segments.[30]

27. Squire, *Ranking Animal Carcinogens: A Proposed Regulatory Approach*, 214 SCIENCE 877-78 (1981); *See also* EPA, *Guidelines for Carcinogenic Risk Assessment*, 51 Fed. Reg. 33,992, 34,000 (1986); California Department of Health Services, Guidelines for Carcinogenic Risk Assessment and Their Scientific Rationale A-12 - A-14 (1986).

28. *See, e.g.*, Johnson, Christian, Dansky & Gabel, *Use of the Adult Developmental Relationship in Prescreening for Developmental Hazards*, 7 TERATOGENESIS, CARCINOGENESIS, & MUTAGENESIS 273 (1987); Kimmel & Gaylor, *Issues in Qualitative and Quantitative Risk Analysis for Developmental Toxicology*, 8 RISK ANALYSIS 15 (1988); Johnson, *Cross-Species Extrapolations and the Biologic Basis for Safety Factor Determinations in Developmental Toxicology*, 8 REG. TOXICOL. & PHARM. 22 (1988); Wang & Schwetz, *An Evaluation System for Ranking Chemicals with Teratogenic Potential*, 7 TERATOGENESIS, CARCINOGENESIS & MUTAGENESIS 133 (1987).

29. Wang & Schwetz, *supra* note 28, at 135.

30. EPA Dioxin Task Force, A Cancer Risk-Specific Dose Estimate for 2, 3, 7, 8-TCDD 3 (1987) (External Review Draft).

The following statements from the 1986 EPA Cancer Guidelines[31] summarize their approach to applying the weight of evidence test:

> The overall scheme for categorization of the weight of evidence of carcinogenicity of a chemical for humans uses a three-step process. (1) The weight of evidence in human studies or animal studies is summarized; (2) these lines of information are combined to yield a tentative assignment to a category; and (3) all relevant supportive information is evaluated. Relevant factors to be included along with the tumor information from human and animal studies include structure-activity relationships; short-term test findings; results of appropriate physiological, biochemical, and toxicological observations; and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause one to adjust the overall categorization of the weight of evidence.

This scheme is a good first attempt at bringing more reason to the hazard identification process. One advantage of the weight of evidence approach is that when new information is available, it is considered and weighed fairly against the old.

B. *Dose-Response Assessment*

Perhaps the most uncertain portion of assessments of chemical carcinogens is the low-dose extrapolation assessment. For this reason, it offers a plethora of opportunities for technical improvement and for better communication of the uncertainties to the risk manager. At best, science has a limited ability to use the results of standard rodent bioassays to understand the human cancer hazard posed by typical levels of exposure.[32] The main reason is that we do not yet fully understand all of the various possible mechanisms of action for carcinogens. Accordingly, we must rely on a model or theory to estimate the human response to environmental pollutants since they are generally exposed to doses at least one-thousand-fold below the lowest animal dose

31. EPA Guidelines, *supra* note 27, at 34,000.

32. Ames, *Dietary Carcinogens supra* note 2, at 1261; *See also* Anderson, *Quantitative Risk Assessment and Occupational Carcinogens*, 3 APPL. IND. HYG. 267, 268 (1988); Conolly, Reitz, Clewell & Andersen, *Biologically Structured Models and Computer Simulation: Application to Chemical Carcinogenesis*, 2 COMMENTS TOXICOL. 305 (1988); Crump, *An Improved Procedure for Low-Dose Carcinogenic Risk Assessment from Animal Data*, 5(5) J. ENVTL. PATH. TOX. 339 (1984); Crump & Howe, *The Multistage Model with a Time-Dependent Dose Pattern: Applications to Carcinogenic Risk Assessment*, 4 RISK ANALYSIS 163 (1984) (all of these articles present and discuss models to extrapolate animal data to the human situation).

tested.[33] Although rarely accounted for in the dose-response models, such doses may well be easily handled by the protective biologic mechanisms in humans.[34]

The reason for conducting a dose-response assessment is to understand what response might occur, if any, one-hundred to one-thousand-fold below the lowest dose tested in rodents (since these are the levels to which humans are typically exposed). Because it would require the testing of thousands of animals to observe a response at such low doses, mathematical models are used to predict the response. To understand the level of uncertainty in the dose extrapolation process and the typical regulatory use of low-dose models, the dose-response curve must be understood. In the example shown in Figure 2, 100% of the animals responded at a dose of 100 milligrams per kilogram per day (mg/kg-day), 50% responded at 50 mg/kg-day, and 5% of the animals developed the response at 5 mg/kg-day. None of the animals were affected at a dose of 1 mg/kg-day, and this is called the no observed adverse effect level (NOEL). Therefore, 5 mg/kg-day constituted the lowest observed effect level (LOEL). As shown, the experimental data range over only a factor of 100; between 1 and 100 mg/kg-day. The challenge, which can contain a high degree of uncertainty, is to estimate what might occur (if anything) in humans exposed to doses perhaps as low as 0.001 mg/kg-day.

There are at least six serious pitfalls into which scientists can slip during the conduct of a dose-response assessment (Figure 1). The first pitfall is to present only the upper-bound risk from the cancer models rather than identifying the range of likely or best estimates, as well as the upper bounds of the risk. The objective of the bounding techniques is to attempt to account for the statistical uncertainty in the results of the animal tests. However, the degree of potential conservatism of the bounding procedure and the fact that zero risk is as likely as the upper-bound value of risk is rarely reported in risk characterizations. The result is that the risk manager rarely is fully aware of the breadth of equally plausible risk estimates. For example, the cancer risk associated with

33. Ames, *supra* note 1, at 382 ("[E]xtrapolating linearly from the enormous doses of rat tests to low-dose human exposure may be much too pessimistic even for those carcinogens which are mutagens.")

34. *Id.*, at 381; BUS & GIBSON, *Body Defense Mechanisms to Toxicant Exposure*, in 3B PATTY'S INDUSTRIAL HYGIENE AND TOXICOLOGY 143 (J. Lewis and L. Cralley eds. 1985).

FIGURE 2

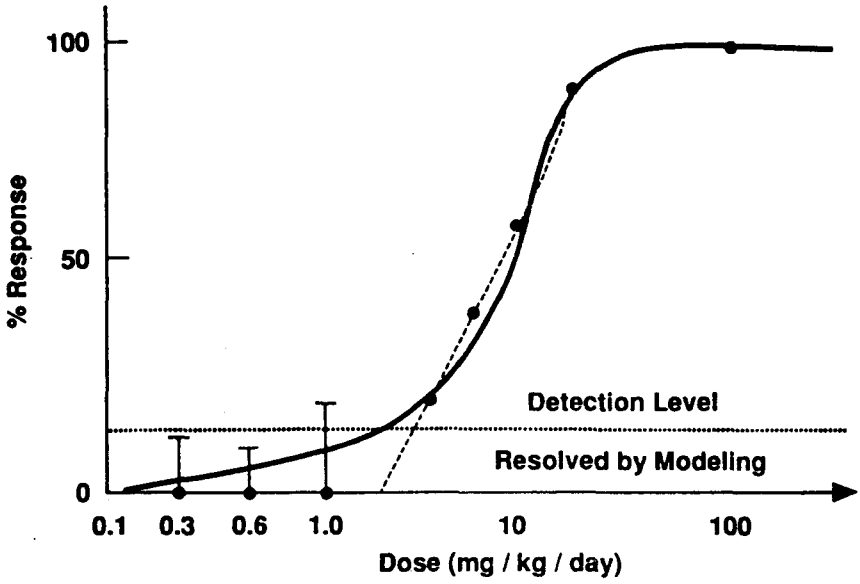


FIGURE 2: A dose-response curve from a carcinogenicity study. The solid line is a best fit of the eight data points identified in the test. The three lowest data points indicate that at these doses, no increased incidence in tumors was observed in the test animals. The error bars on the three lowest doses indicate the statistical uncertainty in the test results since a limited number of animals were tested (n = 100). In an effort to derive risk estimates that are unlikely to underestimate the risk, the models usually derive risk estimates based on the estimated upper bound of the response, rather than the best estimate.

exposure to chloroform in drinking water has been reported to be as high as one in ten thousand using the upper bound estimate of the multi-stage model. However, using the same model, the best or maximum likelihood estimate of the risk is about one in a million and the lower bound estimate is zero. Therefore, the plausible range of risk is as high as one in ten thousand and as low as zero. When biological factors are considered, such as its lack of genotoxicity, the carcinogenic risk associated with the levels of chloroform in chlorinated drinking water is most likely to be negligible.[35]

Reliance on the results of only one mathematical model is the second potential pitfall in the dose-response assessment. To the

35. REITZ, QUAST, STOTT, WATANABE & GEHRING, *Pharmacokinetics and Macromolecular Effects of Chloroform in Rats and Mice: Implications for Carcinogenic Risk Estimation*, 1980 WATER CHLORINATION 983, 991.

surprise of many scientists and attorneys, there are at least six different modeling approaches that may need to be considered when estimating the risks at low doses. These models include the probit, multihit, multistage, Weibull, one-hit, and, when possible, the Moolgavkar - Knudson - Venzon (MKV) biologic-based approach. Nearly all of them can yield results which are plausible.[36] Although it has been claimed that models which lack low dose linearity are not appropriate for carcinogens, the scientific support for this assertion is not compelling, especially for chemicals which are not genotoxic. Except for those chemicals which are known to be initiators or mutagens, no single statistical model can be expected to accurately predict the low-dose response with greater certainty than another.[37] One approach is to present the best estimate of the risk from the two or three models which are considered equally reasonable, as well as, the upper and lower-bound estimates from those models. The estimates should be accompanied by a rationale as to why one model appears more reasonable for that particular chemical or data set. The model's responsiveness to the data or the most likely response due to biologic considerations should be the criteria for selection.

Adoption of this approach would give decisionmakers the benefit of access to pertinent data and an understanding of the uncertainty in the results. Sielken has described how such an approach might be implemented and has identified criteria for conducting a dose-response assessment.[38] If there is a biological or statistical reason to favor one model over another, then the weight of evidence approach should be used to select the most justifiable value. Such an approach was recently attempted by the EPA in its reevaluation of dioxin (TCDD).[39] The diversity of views between various regulatory agencies and scientists within the United States and in other countries on safe levels of exposure to TCDD is illustrated in Figure 3.

Some generalizations can be made about low-dose models. It is noteworthy that the various models will usually fit the rodent data

36. FOOD SAFETY COUNCIL, *supra* note 13, at 159; Park & Snee, *supra* note 13, at 428.

37. *See, e.g.*, Turnbull & Rodricks, *supra* note 13; Maxim & Harrington, *supra* note 13; Sielken, *supra* note 13, at 105.

38. Sielken, *Some Issues in the Quantitative Modeling Portion of Cancer Risk Assessment*, 5 REG. TOXICOL. & PHARM. 175 (1985) (listing and discussing 20 criteria for evaluating the dose response extrapolation in a cancer bioassay)

39. See *supra*, note 30.

FIGURE 3

Weight of Evidence Evaluation
Dioxin (1988)
(upper bound dose at 1 in a million risk)

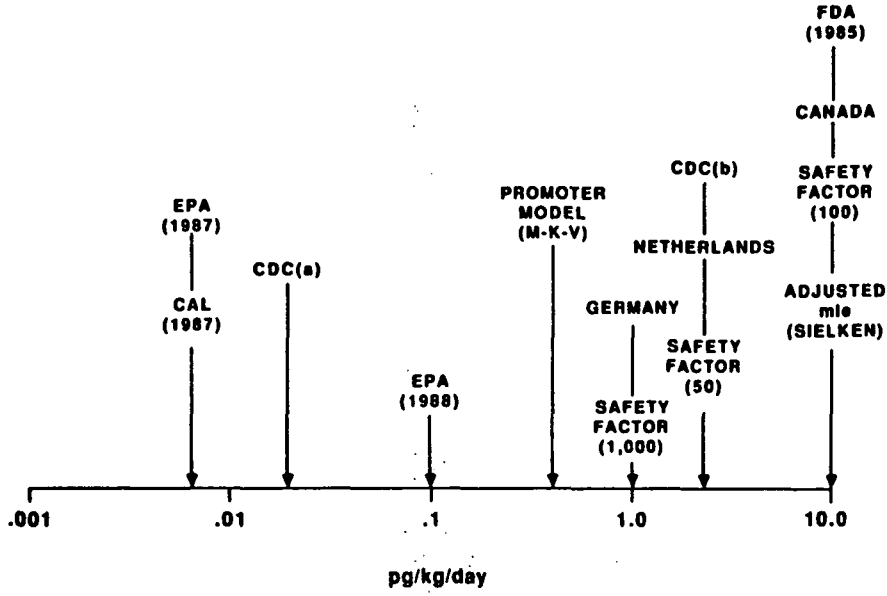


FIGURE 3: Application of the weight of evidence approach should improve each phase of the risk assessment process. Recently, the U.S. EPA evaluated all the various national and international health guidelines for dioxin in an effort to select the most appropriate one to use in the coming years in the United States. As shown here, equally creditable scientific bodies can occasionally have very different views about what constitutes a safe level of human exposure to a chemical. Adapted from ENVIRONMENTAL PROTECTION AGENCY, A CANCER RISK-SPECIFIC DOSE ESTIMATE FOR 2,3,7,8-TCDD (1988) (Draft), at 4.

in the observable dose region, but that they vary in the unobserved, but all important, low-dose region (Figure 4). It should also be recognized that the results of the six most commonly used low-dose models usually vary in a predictable manner.[40] In general, although not in all cases, the one hit and linearized

40. The results of low-dose extrapolation models usually vary in the following predictable manner:

MODEL	PREDICTED RISK
Linear	highest
One-Hit	↑
Multistage	|
Weibull	|
M.K.V.	|
Multi-Hit	|
Logit	|
Probit	lowest

FIGURE 4

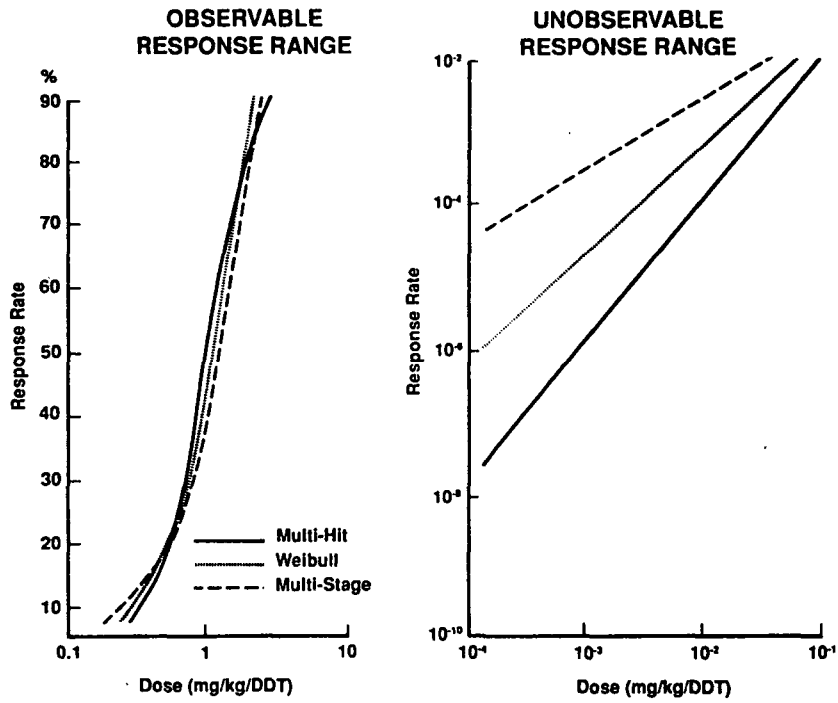


FIGURE 4: The fit of most dose-response models to data in the observable range is generally similar. However, due to the differences in the assumptions upon which the equations are based, the risk estimates at low doses can vary dramatically between the different models.

multi-stage models will predict the highest risk and the probit model will predict the lowest.[41] The results vary in a predictable manner because the models are based on different mathematical equations which are expected to describe the chemical's likely behavior in the low dose region.

Over the past fifteen years, mathematicians and toxicologists have not been able to present a compelling reason to choose one extrapolation model over another, so regulatory agencies arbitrarily adopted the one that usually predicted the highest risk *i.e.*, the linearized multi-stage model (to insure that they were above accusation that they were not protective of the public health). The statistical underpinnings of the multi-stage model, the one

41. Munro & Krewski, *supra* note 2, at 554.

most widely accepted, are the best documented of the various models. However, like the other statistical models it can not make use of most of the biologic information on a substance. Hopefully, toxicologists now know enough about the likely mechanism of carcinogenicity of enough chemicals to provide sufficient insight to select the most appropriate form of the multistage model, or several different models or approaches, to identify an acceptable level of human exposure.[42] For example, a substantial number of scientists (although certainly not all of them) believe that there are at least three mechanisms by which chemicals may produce a carcinogenic response: repeated cytotoxicity, promotion, and initiation. Butterworth has suggested that at least eight different classes of carcinogens exist.[43] These distinctions are important since the appropriate model for estimating the cancer risk for humans exposed to low doses of a cytotoxicant or promotor should be markedly different than that for an initiator.[44]

In general, the scientific underpinnings of the dose-response models are based on our understanding of the cancer process caused by exposure to ionizing radiation and chemicals that are initiators.[45] Both types of agents may well have a nearly linear or a linear response in the low dose region. However, promoters and cytotoxicants need not have a linear dose response curve. Scientific data increasingly suggest that they would be expected to be very non-linear at low doses and, more importantly, probably have a genuine or practical threshold (a dose below which no response [risk] would be present).[46] The increased acceptance of this postulate is evidenced by EPA's recent position that the linearized multi-stage model is inappropriate for dioxin, thyroid type carcinogens, NTA, and, presumably, similar non-genotoxic

42. *Id*, at 556; BUTTERWORTH & SLAGA, NONGENOTOXIC MECHANISMS IN CARCINOGENESIS (1987); WEISBERGER & WILLIAMS, *Chemical Carcinogens*, in CASARETT AND DOULL'S TOXICOLOGY 84, 134 (Doull, Klaassen & Amdur eds. 3d ed. 1986). *See also* Butterworth, *Nongenotoxic Carcinogens*, 7 CIIT ACTIVITIES 1 (Dec. 1987).

43. BUTTERWORTH & SLAGA, *supra* note 42.

44. *Id.*; Weisburger & Williams, *supra* note 42, at 134; Anderson, Clewell, Gargas, Smith & Reitz, *Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride*, 87 TOXICOL. & APP. PHARM. 185 (1987).

45. E.J. CALABRESE, PRINCIPLES OF ANIMAL EXTRAPOLATION 518-20 (1983); NATIONAL RESEARCH COUNCIL, THE EFFECTS ON POPULATION OF EXPOSURE TO LOW LEVELS OF IONIZING RADIATION 21-23 (National Academy Press 1980).

46. Squire, *supra* note 27; Paynter, Burin, Jaeger & Gregorio, *Goitrogens and Thyroid Follicular Cell Neoplasia: Evidence for a Threshold Process*, 8 REG. TOXICOL. PHARM. 102 (1988) (commenting on research indicating a threshold for thyroid follicular neoplasia).

chemicals.[47] For these types of chemicals, a threshold model, the MKV model or one of the other biologically-based models appears to be more appropriate.[48] The extrapolation process is improved further if a physiologically-based pharmacokinetic model (PB-PK) has also been used to correctly calculate the delivered dose and scale-up the rodent data to humans.[49]

The third pitfall in the dose-response assessment is to disregard the insight gained from epidemiological data. Traditionally, it has been claimed that epidemiologic studies are almost never as statistically robust as the animal studies and, therefore, are not very useful.[50] Acceptance of this assertion seems inappropriate because epidemiological studies can establish the degree of confidence that should be placed in the results of low-dose extrapolation models.[51] For example, in 1982 it was claimed that workers exposed for 8 hrs/day for 40 years to the OSHA standard for ethylene dibromide (20 ppm) incurred a risk of 999 in 1,000 of developing cancer due exclusively to this level of occupational exposure.[52] However, epidemiological studies of the actual can-

47. EPA, *supra* note 30, at 3; ANDERSON & ALDEN, *Risk Assessment for Nitrilotriacetic Acid (NTA)*, in THE RISK ASSESSMENT OF ENVIRONMENTAL AND HUMAN HEALTH HAZARDS: A TEXTBOOK OF CASE STUDIES 390, 422 (D.J. Paustenbach ed. 1989); Paytner, *supra* note 46.

48. *See, e.g.*, Krewski, Brown & Murdoch, *Determining "Safe" Levels of Exposure: Safety Factors or Mathematical Models?* 4 FUND. APP. TOXICOL. S383, S391-2 (1984); Moolgavkar, *The Multistage Theory of Carcinogenesis and the Age Distribution of Cancer in Man*, 61 J. NAT'L CANCER INST. 49 (1978); Moolgavkar & Venzon, *Two-Event Models for Carcinogenesis: Incidence Curves for Childhood and Adult Tumors*, 47 MATH. BIOSCIENCES 55 (1979); Ellwein & Cohen, *A Cellular Dynamics Model of Experimental Bladder Cancer: Analysis of the Effect of Sodium Saccharin in the Rat*, 8 RISK ANALYSIS 215 (1988); Moolgavkar, Dewanji & Venzon, *A Stochastic Two-Stage Model for Cancer Risk Assessment: The Hazard Function and the Probability of Tumor*, 8 RISK ANALYSIS 383 (1988).

49. Andersen, *Incorporating Pharmacokinetics and Risk Assessment Into the Setting of Occupational Exposure Limits: The Stodinger Lecture*, 3 *Appl. Ind. Hyg.* 10 (1988); Andersen, Clewell, Gargas, Smith & Reitz, *supra* note 44; D'Souza & Boxenbaum, *Physiological Pharmacokinetic Models: Some Aspects of Theory, Practice and Potential*, 4 TOXICOL. INDUS. HEALTH 151 (1988).

50. Office of Science and Technology Policy, *supra* note 2, 10,375, 10,421; LAYARD & SILVERS, *Epidemiology in Environmental Risk Assessment*, in THE RISK ASSESSMENT OF HUMAN AND ENVIRONMENTAL HEALTH HAZARDS: A TEXTBOOK OF CASE STUDIES 157, 160 (D.J. Paustenbach, ed. 1989); *Dioxin Risk to Humans is Minimal*, Pesticide & Toxic Chemical News, Oct. 26, 1988, at 24.

51. LAYARD & SILVERS, *supra* note 50, at 160; Pesticide & Toxic Chemical News, *supra* note 50 (providing four suggestions by Dr. Vernon N. Houk of the Center for Disease Control, "[c]oncerning epidemiology that would be useful" for risk assessment); See also Dinman & Sussman, *Uncertainty, Risk, and the Role of Epidemiology in Public Policy Development*, 25 J. OCCUP. MED. 511, 514-5 (July 1983) (a test of a Proposed Epidemiologic Study Scoring Method)

52. *Adequate Standards or Cancellation, Rep. Miller Says of EDB*, Pesticide & Toxic Chemical News, July 13, 1983, at 26.

cer incidence in workers did not show an increase in the cancer rate even though they had been exposed to concentrations as high as 20 ppm for about fifteen to twenty-five years.[53] When epidemiological data are available, it seems scientifically inappropriate to blindly accept the results of mathematical models which analyze only rodent data without giving serious consideration to the human experience.[54] At the very least, epidemiological data can help bracket the range of reasonable risks associated with certain levels of exposure.[55] This "reality check" should be a part of every risk assessment, whenever possible.

Many scientists and regulators seem to have forgotten that virtually all published risk estimates for carcinogens and developmental toxicants are based on data collected in rodents which are often given doses 100 to 10,000 times greater than that to which humans are typically exposed.[56] Few people will argue that such testing is inappropriate or unnecessary for identifying potential carcinogens, but these data must be carefully interpreted before the risk to humans exposed at low doses can be estimated.[57] Among other things, it should be remembered that the rodent studies now used to predict human risk were never intended for that purpose.[58] These studies were designed to qualitatively identify potential human hazards, not to quantitatively estimate the human risk at low levels of exposure.[59]

Pitfall number four in dose-response assessment is the failure to carefully scale-up data from rodents to describe the human response. For purposes of risk assessment, statisticians and biolo-

53. Ames, *supra* note 1, at 380; Hertz-Picciotto, Gravitz & Neutra, *How Do Cancer Risks Predicted From Animal Bioassays Compare with the Epidemiologic Evidence? The Case of Ethylene Dibromide*, 8 RISK ANALYSIS 205 (1988).

54. LAYARD & SILVERS, *supra* note 50, at 160; Pesticide & Toxic Chemical News, *supra* note 50.

55. LAYARD & SILVERS, *supra* note 50 ("[E]pidemiology can play an important role in bracketing the risk estimates derived from animal experiments.")

56. Havendar, *Peanut Butter Sandwich Deadlier Than Muffins Containing EDB*, Wall St. J., April 4, 1984, at B11, col. 1. ("According to EPA's estimates, the average person consumes 5 to 10 micrograms of EDB a day...[t]hat quantity is less than a quarter-millionth of what, on a body-weight basis, the rats were given.")

57. *See, e.g.*, Sielken, *Quantitative Cancer Risk Assessments for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD)*, 25 FOOD CHEM. TOXIC. 257 (1987).

58. *Id.*

59. S.L. FRIESS, *Risk Assessment: Historical Perspectives*, in PHARMACOKINETICS IN RISK ASSESSMENT, 8 DRINKING WATER AND HEALTH 3 (National Academy Press 1987); E. EFRON, THE APOCALYPTICS. CANCER AND THE BIG LIE, 308 (1984); Barr, *Design and Interpretation of Bioassays for Carcinogenicity*, 7 REG. TOXICOL. & PHARM. 422, 423 (1987).

gists have generally assumed that at a given dose (mg/kg-day) the rodent response to a chemical will be nearly identical to the human response; even though most scientists recognize that this will often not be true. This all-important assumption is no longer necessary, and risk assessors should move aggressively to incorporate a more scientifically defensible approach. Many factors need to be considered when trying to predict how humans will respond compared to rodents.[60] First, the biologic half-life between rodents and humans can be expected to vary for virtually all chemicals.[61] Often, for a given chemical, these differences will vary in a predictable manner based simply on the body weight to surface area ratio and/or life span.[62] As a result, regulators have used correction factors based on surface area in an attempt to adjust for the pharmacokinetic differences between rodents and humans. However, due to its simplicity, the surface area per body weight approach will frequently not account for the difference in half-life; additionally, the need for a correction factor depends on whether the carcinogen is the parent chemical or a metabolite.[63] Rather than rely on simple scale-up factors, we now have the capacity to accurately adjust our risk estimates to account for these differences by using physiologically-based pharmacokinetic (PB-PK) models.[64] They represent a mathematical approach to account for the various physiological and metabolic differences between the test species and humans including body weight, metabolic capacity and products, respiration rate, blood flow, fat content, and a number of other parameters.[65] The potential benefits of this approach have been so impressive that a special sym-

60. EPA, *supra* note 27, at 33,993-34,000; Bus & Gibson, *supra* note 34; Sielken, *supra* note 37; Whittemore, Grosser, & Silvers, *Pharmacokinetics in Low Dose Extrapolation Using Animal Cancer Data*, 7 FUND. & APP. TOXICOL. 183 (1986).

61. Biological half-life of selected chemicals (days):

SUBSTANCE	MOUSE	RAT	HAMSTER	GUINEA PIG	MONKEY	HUMAN
Carbon Tetrachloride	0.10	0.25	0.35	-	0.46	0.50
Dioxin	15.0	31.0	15.0	31.0	455.00	2800.00

62. Whittemore, Grosser & Silvers, *supra* note 60; Ramsey & Anderson, *A Physiologically Based Description of the Inhalation Pharmacokinetics of Styrene in Rats and Humans*, 73 TOXICOL. & APP. PHARM. 159 (1984).

63. D'Souza & Boxenbaum, *supra* note 49; HART & FISHBEIN, *Interspecies Extrapolation of Drug and Genetic Toxicity Data*, in TOXICOLOGICAL RISK ASSESSMENT 3 (Clayson, Krewski & Munro eds. 1985).

64. D'Souza & Boxenbaum, *supra* note 49.

65. *Id.*

posia was held by the National Academy of Sciences to discuss PB-PK models and encourage their use.[66]

The fifth, and possibly most important pitfall is failure to alter the risk estimates by considering biological information such as the time it takes for a tumor to appear, metabolic differences between species, and whether the chemical is genotoxic.[67] Generally, irrespective of the type of carcinogenic response, regulatory agencies will use a single curve fitting procedure to estimate the human risk. The result is usually based on three data points from a two-year rodent study.[68] The shortcomings associated with ignoring biological information are numerous. For example, nitrilotriacetic acid (NTA) produced kidney tumors in rodents, but only following very high doses. It was ultimately shown that at high doses, NTA produced chronic progressive nephrosis (CPN) due to repeated cytotoxity. The repeated toxic effects produced sufficient irritation to form bladder tumors.[69] However, at doses to which humans might be exposed, the tumors would not be expected to form. After a good deal of study, it was agreed that although the cancer models predicted a significant risk at low doses, no human risk was likely at the anticipated level of exposure.[70] This is one of many examples which illustrates that no matter how well the animal dose-response data are statistically analyzed, it is a serious pitfall to predict human health risks from rodent data without considering all the relevant biological data.

It is increasingly clear that numerous mechanisms are at work in the multi-step process of chemical carcinogenesis. Heretofore, we have divided chemical carcinogens into two broad classes: genotoxicants and nongenotoxicants. At one time, it was believed that all carcinogens were genotoxicants, chemicals which directly alter the DNA. Some believe that genotoxicants may act through point mutations, insertions, deletions, or changes in chromosome structure or number. These can be measured as chemical reactivity with the DNA, mutagenesis, induction of DNA repair, or cyto-

66. KREWSKI, MURDOCH & WITHEY, *The Application of Pharmacokinetic Data in Carcinogenic Risk Assessment*, in PHARMACOKINETICS IN RISK ASSESSMENT, 8 DRINKING WATER & HEALTH 441, 442 (National Academy Press 1987) (this volume was a result of the National Academy of Sciences symposia).

67. Sielken, *supra* note 38; Butterworth & Slaga, *supra* note 42.

68. Krewski, Brown & Murdoch, *supra* note 48.

69. *Id.*; Butterworth, *Nongenotoxic Carcinogens*, 7 CHEM. INDUS. INST. OF TOXICOL. ACTIVITIES 2 (1987).

70. ANDERSON & ALDEN, *supra* note 47.

genetic effects in bacterial or mammalian cell culture assays as well as in the whole animal. Conversely, nongenotoxic chemicals are those that lack genotoxicity as a primary biological activity.[71] While these agents may secondarily yield genotoxic events as a result of toxicity, such as hyperplasia (excessive cellular growth), their primary action does not involve reactivity with the DNA. Because at low doses nongenotoxicants may not produce toxicity, the primary reason for excessive cell turnover, many scientists expect them to possess a threshold dose below which no cancer hazard would be present. This is in contrast with genotoxicants which may have some risk, albeit small, even at very low doses.[72]

Pitfall six is the use of models which do not or are not capable of responding to the dose-response curve. As discussed by Sielken,[73] it does not seem appropriate to use models which are minimally responsive to the very costly information collected in standard lifetime rodent studies. By considering only one low-dose model, or by conducting only one statistical test for selecting the form of the model, we limit our ability to learn from the rodent data. One way to avoid this shortcoming is to conduct simulations of the model's responsiveness to alternative, but similar, data sets to insure that the extrapolation is reasonable. Some regulatory agencies, however, believe that too little is known about what might happen at low doses to change to less conservative approaches.[74]

What is meant by the phrase "responsive to the data?" Two terms are frequently used in this regard: fragile and insensitive. Fragile usually means that the model over-responds to the data while insensitive means that the risk estimates vary little irrespective of the rodent's response. The following example should illustrate the potential problem. Assume that two identical animal studies were conducted: one in New York and one in San Francisco. In each lab, there are one hundred test animals (fifty per sex were exposed to two doses and a control). At the conclusion, there was no increased tumor incidence in the females at any dose in either lab. However, in the males, we find that one additional

71. Butterworth, *supra* note 69.

72. *Id.*

73. Sielken, *supra* note 13; Sielken, *A Response to Crump's Evaluation of Sielken's Dose-Response Assessment of TCDD*, 26 FOOD CHEM. TOXICOL. 80 (1988).

74. California Department of Health Services, *supra* note 27; Crump, *A Critical Evaluation of a Dose-Response Assessment for TCDD*, 26 FOOD CHEM. TOXICOL. 79 (1988).

rat in San Francisco, at the 3 mg/kg-day dose, has a tumor compared to the test group in New York.[75] The controls had no increased incidence of this tumor type. To scientists, the biological difference between these results is insignificant; that is, the results are equivalent. To estimate the risk of having this chemical in our diet at a dose one thousand fold below the lowest dose tested in rodents, a model needs to be used.

Applying the multistage model, the one most frequently used in the United States, we find a significant difference in the maximum likelihood estimates (MLE) due only to the difference of one rat between the two studies. For example, as shown in our hypothetical animal study, at a dose of 0.01 mg/kg-day, the San Francisco data would suggest a risk of one in ten thousand whereas the New York data would predict that the excess risk was only two in one million.[76] Frequently, such a difference in the potential cancer risk represents the difference between whether a chemical is banned or its use encouraged. Interestingly, the UCL's on the added risk for both studies are about the same, that is 3/10,000, and this is almost 100 fold greater than that suggested by the MLE of the New York data. The point is that scientists should not be constrained by the insensitivities of the UCL methodology nor the responsiveness of the MLE; rather decisions should be heavily influenced, if not dictated, by biologic factors and good scientific judgment. Clearly, both lawyers and risk managers must be aware of the potential for a mathematical model to inadvertently over-state or underestimate the significance of the data which, at times, may have a dramatic effect on the regulatory decision.

75. An example of how low dose extrapolation models may over-respond:

RESULTS OF TESTING

	RESPONSE	
DOSE (mg/kg-day)	SAN FRANCISCO	NEW YORK
0	0/50	0/50
3	2/50	1/50
10	10/50	10/50

76. MLE RISK ESTIMATES

	RISK	
DOSE (mg/kg-day)	SAN FRANCISCO	NEW YORK
3	4/100	2/100
1	1/100	1/20,000
0.1	1/1,000	1/200,000
0.01	1/10,000	1/2,000,000

C. *Exposure Assessment*

Over the past five years, a good deal of emphasis has been placed on improving the first two steps of the risk assessment process, hazard identification and dose-response assessment. However, most health risk assessments of waste sites and other hazards which precipitate personal injury litigation are plagued by serious problems in the exposure assessment phase of the analyses. Indeed, this is the most easily mishandled of the four portions of the assessment. This is a tragedy because exposure assessment is the portion likely to be understood by the jury, the government, and the judges.

Although there have been numerous claims that exposure assessment is exceedingly difficult and uncertain, this portion contains no greater uncertainty than other steps in the process. As discussed previously, it is possible for different dose-response models to predict risks which span one to four orders of magnitude: a significant range of uncertainty. Admittedly, there are a large number of factors to consider when estimating exposure, and it is a complicated procedure to estimate the transport and distribution of a chemical which has been released into the environment. Nonetheless, the available data indicate that scientists can do an adequate job of estimating the concentration of chemicals in the environment and the resulting uptake by exposed persons if they account for the many factors that must be considered.[77]

There are at least four major pitfalls in the exposure assessment process to which one should be sensitive. First, the typical or average person, rather than the theoretical maximum exposed individual (MEI), should be the focus of a health risk assessment. Although the risk for those potentially exposed to particularly high levels needs to be understood, too much emphasis has been

77. EPA, ESTIMATING EXPOSURES TO 2,3,7,8-TCDD, 205 (1988) (Draft); Eschenroeder, Jaeger, Ospital & Doyle, *Health Risk Analysis of Human Exposures to Soil Amended With Sewage Sludge Contaminated With Polychlorinated Dibenzodioxins and Dibenzofurans*, 28 VET. HUM. TOXICOL. 435 (Oct. 1986); Paustenbach, *Important Recent Advances in the Practice of Health Risk Assessment: Implications for the 1990's*, REG. TOXICOL. PHARM. (in press) (1989); LEUNG & PAUSTENBACH, *Assessing Health Risks in the Workplace: A Case Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin*, in THE RISK ASSESSMENT OF ENVIRONMENTAL HAZARDS: A TEXTBOOK OF CASE STUDIES 689, 691 (D.J. Paustenbach ed. 1989); Bogen & Spear, *Integrating Uncertainty and Interindividual Variation in Environmental Risk Assessment*, 7 RISK ANALYSIS 427 (1987).

placed on the MEI.[78] Instead, the typical person should be the primary emphasis of the analyses even though the risk to others should also be understood. The distinction is important. If, for example, a regulatory agency bases its decision on the results of an assessment assuming that a person eats about 100 grams of fish every day of his or her lifetime (99th percentile), yet the average American eats only eighteen grams of fish per day (lifetime average), the analysis should reflect the fact that ninety-nine of 100 persons are not represented by the corresponding risk estimate.[79] To help minimize the potential for misunderstanding, it is recommended that the number of exposed persons at each of the anticipated dose levels be presented, along with the most likely and upper estimates of exposure. This has been done in only a limited number of assessments. Using an exhibit like Table 1, the risk manager or the court can readily understand the severity of the risk for each segment of the population. Provided with this information, it can then be decided whether large or small sums of money need to be expended to reduce the health risks.

The next pitfall is a variation of the first one. It involves the repeated use of conservative assumptions.[80] Several published papers have discussed this issue and have demonstrated its importance.[81] The problem can be illustrated in a recent attempt to assess the dioxin hazard posed by municipal waste incinerators. An agency evaluated the theoretical cancer risk for a child who lived within a short distance (0.8 km) from the hypothetical incinerator.[82] At first review, the analysis seemed reasonable until one noted that the child ate about two teaspoons of dirt each day, that his house was down-wind of the stack, that he ate fish from a pond near the incinerator, his fish consumption was at the ninety-fifth percentile level, he drank contaminated water from the pond, he

78. The Environmental Protection Agency has proposed guidelines on exposure related measurements for risk assessments. 53 Fed. Reg. 48,830 (Dec. 2, 1988).

79. TOLLEFSON, *Methylmercury in Fish: Assessment of Risk for U.S. Consumers*, in THE RISK ASSESSMENT OF ENVIRONMENTAL HAZARDS: A TEXTBOOK OF CASE STUDIES 845, 863 (D.J. Paustenbach ed. 1989).

80. Paustenbach, Shu & Murray, *supra* note 13, at 303; MAXIM, *Problems Associated with the Use of Conservative Assumptions in Exposure and Risk Analysis*, in THE RISK ASSESSMENT OF ENVIRONMENTAL AND HUMAN HEALTH HAZARDS: A TEXTBOOK OF CASE STUDIES 526 (D.J. Paustenbach ed. 1989); Finkel & Evans, *Evaluating the Benefits of Uncertainty Reduction in Environmental Health Risk Management*, 37 J. AIR POLL. CONTROL A. 1164 (1987).

81. Paustenbach, Shu & Murray, *supra* note 13, at 303; Finkel & Evans, *supra* note 80; Maxim & Harrington, *supra* note 13.

82. EPA, *supra* note 77.

TABLE 1

Exposure to benzene soluble organics (micrograms per cubic meter of air)[b]	People in exposure group (thousands)	Lifetime probability of lung cancer[c]	Increased in lung cancer due to coke oven emissions[a]	Number of lung cancer deaths per year due to coke oven emissions
4.5	13,900	0.0335	6.37×10^{-4}	125.0
5.5	1,034	0.0344	1.49×10^{-3}	22.0
6.5	54	0.0362	2.33×10^{-3}	1.8
7.5	8	0.0360	3.18×10^{-3}	0.4
8.9	2	0.0369	4.02×10^{-3}	0.1
10.9	2	0.0389	6.04×10^{-3}	0.2

a. Estimated using the Weibull probability model.
b. Background level assumed to be 3.75 micrograms per cubic meter of air.
c. Lifetime probability 0.0329 at background exposure level.

TABLE 1: The following represents one method for presenting exposure, risk, and population data. Such an approach gives risk managers all the important information needed to make the difficult decisions about where to best allocate limited resources, rather than rely on data for the maximally exposed individual (MEI). Adapted from EPA, CARCINOGEN ASSESSMENT GROUP, PRELIMINARY REPORT ON POPULATION RISK TO AMBIENT COKE OVEN EXPOSURES, 14 (1978).

ate food grown primarily from the family garden, and he drank milk from a cow which grazed on forage at the farm. This is not quite the description of a typical person living near a municipal incinerator. Regrettably, the associated upper estimate of the risk was the only one reported in the press. Certainly, it would have been more appropriate to have studied and presented the number of persons likely to be exposed to this level, as well as the level of exposure for the typical person living within ten miles of the facility. It may also have been useful to note that few farms are located near incinerators due to the need to service large communities. Without such a presentation of the data, risk managers and the public can easily be misled and, as a result, make poor decisions.

The third pitfall is to conduct an exposure assessment without considering the environmental fate of the chemical. In general, many factors such as degradation by sunlight, soil and water microbes, and evaporation will influence the degree of human exposure. For instance, the public health hazard posed by the

potential contamination of groundwater by ethanol (alcohol) washed down the sinks of taverns and restaurants was recently evaluated. It was alleged that the disposal of this listed carcinogen might place the restaurant in violation of one of California's new laws, Proposition 65. Consequently, a risk assessment was conducted. It was soon recognized that the environmental half-life of the chemical was a critical factor in this analysis. Specifically, chemicals such as methanol, ethanol, and phenol have relatively short half-lives in most waters; only about four to eight hours. This means that soon after release the ethanol would be degraded and rendered harmless by water-borne microbes or lost through volatilization, and that virtually none of the alcohol would reach the tap water of homeowners. What had been portrayed as a potentially serious hazard was shown to be insignificant when half-life was considered.

Another pitfall is to neglect to consider using biological monitoring to validate or confirm the degree of human exposure. Over the past five years, analytical chemists have increased their ability to detect very small quantities of non-natural chemicals in blood, urine, hair, feces, breath, and fat. For many chemicals, the results would be a direct indicator of either recent or lifetime exposure to a chemical. For example, the exposure to dioxin in 2,4,5-T (Agent Orange) of veterans who served in Vietnam was recently evaluated by analyzing the amount of dioxin in their blood. This study, conducted almost fifteen to twenty years after the last day of service in Vietnam, allowed epidemiologists to conclude that the vast majority of veterans had only a modest degree of exposure to dioxin; a contaminant which has been alleged to produce numerous adverse health effects in field soldiers.[83]

The last trap is the failure to validate some of the assumptions used in the analysis or the reasonableness of the results. In an attempt to position themselves so as to be above the accusation that their assessments are not sufficiently health protective, many scientists have gone overboard in selecting certain parameters used in the calculations. One example of the problem of making assumptions without checking the reasonableness, occurred during an evaluation of the cancer hazard posed by dioxin-contaminated soot from an office building fire. The risk assessment

83. Centers for Disease Control Veterans Health Studies, *Serum 2,3,7,8-Tetrachlorodibenzo-p-dioxin Levels in US Army Vietnam-Era Veterans*, 260 J. AM. MED. A. 1249 (1988).

assumed that the office workers might be exposed to the dioxin in the soot for the entire forty years that they might work in the building and that the dioxin would be released through volatilization at a particular rate. It was calculated that persons who worked forty years in the office building would be exposed to an increased cancer risk much greater than 1 in 1,000,000, and as a result, the building was not reoccupied. Even if one agreed with the assertion that an increased cancer risk of 1 in 1,000,000 is the maximum risk to which one should be exposed, something in the analysis seemed flawed. After some study, it was shown that the assumption regarding dioxin's volatility was too conservative. Apparently, no one checked to see if the volatilization rate was reasonable. Specifically, had this assumption been accurate, the dioxin would have all been volatilized and been removed via the ventilation system only four years after reoccupation. In short, the exposure assessment assumed exposure was to occur for forty-six years even though it would not have been present after four years. The moral is that in any assessment a validation should be performed to insure that the assumptions and results are reasonable.[84]

D. *Risk Characterization*

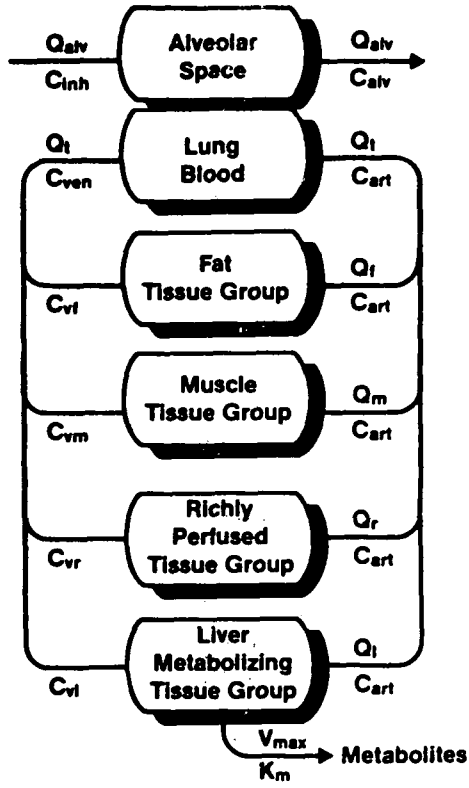
The final step in a risk assessment, risk characterization, also contains potential pitfalls.[85] Among the most frequent shortcomings is to portray the theoretical increased cancer risk of one in a million as a serious public health risk. First, it is important to remember that these usually represent the upper estimate of the potential risks, not a true estimate of risk. Indeed, as stated in nearly every risk assessment conducted by a regulatory agency, "These estimates represent an upper bound of the plausible risk and are not likely to underestimate the risk. The actual risk may be much lower, and in some cases, zero."[86] In short, unless the estimate is based on the results of a PB-PK scale-up procedure and a biologically-based model that tries to incorporate all the pertinent biologic data, the risk estimates are more applicable to a rat than a human (Figure 5).

84. Maxim, *supra* note 80.

85. Slovic, *Perception of Risk*, 236 SCIENCE 280 (1987); Wilson & Crouch, *Risk Assessment and Comparisons: An Introduction*, 236 SCIENCE 267 (1987).

86. *See, e.g.*, EPA, HEALTH ASSESSMENT DOCUMENT FOR TRICHLOROETHYLENE A-120 (1982), EPA, HEALTH ASSESSMENT DOCUMENT FOR DICHLOROMETHANE 5-94 (draft) (1983).

FIGURE 5



Where:

Q_{alv}	Alveolar ventilation rate (liters air/hr)
C_{inh}	Concentration in inhaled air (mg/liter air)
C_{alv}	Concentration in alveolar air (mg/liter air)
C_{exh}	Concentration in exhaled air (mg/liter air)
N	Blood air partition coefficient (liters air/liter blood)
Q_t	Cardiac output (liters blood/hr)
C_{art}	Concentration in arterial blood (mg/liter blood)
C_{ven}	Concentration in mixed venous blood (mg/liter blood)
V_{max}	Maximum enzymatic reaction rate (mg/hr)
K_m	Michaelis constant for enzymatic reaction (mg/liter blood)
Q_i	Blood flow rate to tissue group (liters blood/hr)
V_i	Volume of tissue group (liters i)
C_i	Concentration in tissue group (mg/liter i)
A_i	Amount in tissue group (mg)
C_{vi}	Concentration in venous blood leaving tissue group (mg/liter blood)
P_i	Tissue: blood partition coefficient (liters blood/liter i)

FIGURE 5: A physiologically-based pharmacokinetic (PB-PK) model as developed by Ramsey & Anderson, *A Physiologically-Based Description of the Inhalation Pharmacokinetics of Styrene in Rats and Humans*, 73 TOXIC'L. AND APP. PHARM. 159, at 160 (1984). These types of models allow scientists to predict how humans will respond to a chemical based on data collected in rodents. Basically, the movement and transformation of the test chemical within the rodent is described by mathematical equations. The same is done for the human. By comparing the two, one can quantitatively predict the human response. This methodology has only been used by toxicologists since 1984.

Central to the area of risk characterization is the accurate and unbiased presentation of the significance of the data. Specifically, regulatory agencies have been subject to the pitfall of stating that the results of low-dose models can actually predict the increased cancer risk for exposed individuals. As recently discussed by Dr. Frank Young,[87] the current Commissioner of the FDA, this was not the intent of such estimates:

> In applying the de minimis concept and in setting other safety standards, FDA has been guided by the figure of "one in a million." Other Federal agencies have also used a one in a million level such as the Occupational Safety and Health Administration and the Environmental Protection Agency. Both agencies rely on the one in one million increased risk over a lifetime as a reasonable criterion for separating high-risk problems warranting agency attention from negligible risk problems that do not. The risk level of one in one million is often misunderstood by the public and the media. It is not an actual risk - i.e., we do not expect one out of every million people to get cancer if they drink decaffeinated coffee. Rather, it is a mathematical risk based on scientific assumptions used in risk assessment. FDA uses a conservative estimate of risk to ensure that the risk is not understated. We interpret animal test results conservatively and we are extremely careful when we extrapolate risks to humans. When FDA uses the risk level of one in one million, it is confident that the risk to humans is virtually nonexistent.

Frequently, regulators suggest that most environmental regulations have been promulgated so as to keep the theoretical cancer risks below one in a million. In fact, the theoretical risks associated with currently enforced environmental regulations are in the vicinity of one in 100,000, not one in 1,000,000.[88] Occupational exposure limits usually have theoretical risks in the region of one in 1,000.[89]

We should also attempt to present the significance of these risks in a more understandable fashion. For example, the goal of some environmental standards, such as the maximum contaminant levels (MCL) for drinking water, is to keep the maximum plausible risk to about one in 1,000,000. What few persons rec-

87. Young, *Risk Assessment: The Convergence of Science and the Law*, 7 REG. TOXICOL. PHARM. 179, 184 (1987).

88. Travis, Richter, Crouch, Wilson & Klema, *supra* note 18, at 416-18 (a table of risk levels for 132 chemicals regulated by government agencies); Travis & Hattermer-Frey, *supra* note 20, at 875 (a table of upper-bound risk levels after regulation of 36 chemical carcinogens).

89. Rodricks, Brett & Wrenn, *supra* note 20, at 315.

ognize is that since the incidence of cancer in the population is currently about 25%, this is equivalent to insuring that the lifetime cancer risk for any person exposed to this level of contamination is not greater than 250,001 in 1,000,000 (25.0001%) rather than 250,000 in 1,000,000. If society demands this standard of care, that is its choice. However, both society and its risk managers deserve to understand the significance of the risk before deciding to spend money on one hazard versus another.

Many news releases of the past ten years seem to indicate that agencies have demanded that exposure to chemicals must be controlled to a level that risks are only in the vicinity of one in 1,000,000. However, recent work has shown that this has clearly not been the case.[90] Specifically, we have tended to allow exposure levels to be influenced by the number of exposed individuals (Figure 6).

V. Conclusion

What does all of this mean to the legal profession? If one considers all of the issues raised here, the reasons why risk assessments are important and necessary becomes clear. The process gives non-scientists the insight and knowledge needed to make more objective and rational decisions in a complex scientific arena. Assessments give regulators and courts the information needed to know whether a particular hazard poses a significant or de minimis risk.[91] The hope is that this insight will result in cost effective decisions and fair court settlements.

In toxic tort cases, risk assessments can clearly play an important role. Risk assessments can help substantiate medical opinions regarding causation, quantitatively describe the likely degree of exposure, reduce reliance on experts' professional intuitions, and neutralize subjective or unsubstantiated claims about exposure level and associated health risks. My experience is that attorneys who have been aware of the benefits of the risk assessment process have done very well in representing their clients in clean-up and personal injury litigation.[92] This has, in part, been be-

90. *See, e.g.*, Travis, Richter, Crouch, Wilson & Klema, *supra* note 18.

91. C. Whipple, *Dealing with Uncertainty About Risk in Risk Management*, in Hazards: Technology and Fairness 44, 45 (National Academy Press 1986).

92. Black, *Evolving Legal Standards for the Admissibility of Scientific Evidence*, 239 Science 1508 (1988); Mitchell, Ward & Grutsch, *Legal Standards of Causation in Chemical Exposure Litigation*, 7 Reg. Toxicol. Pharm. 206, 211 (1987).

FIGURE 6
EFFECT OF INDIVIDUAL VS. POPULATION RISK ON CHEMICAL CARCINOGEN REGULATION

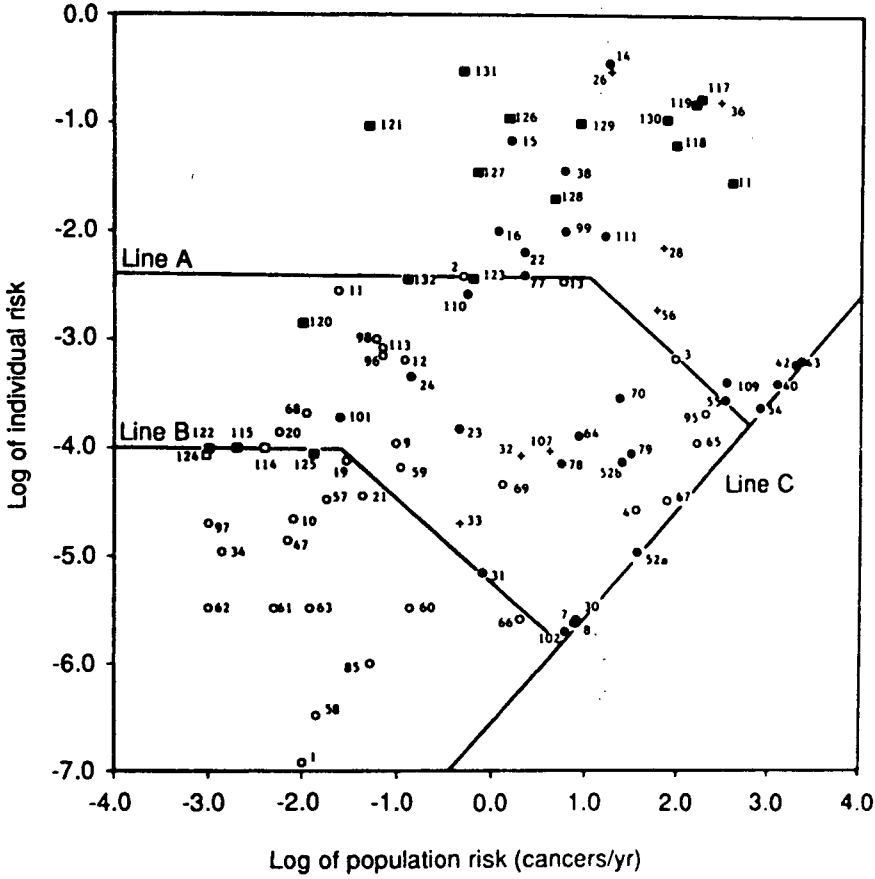


FIGURE 6. A compilation of the individual risk levels inherent in various regulatory decisions as a function of the number of exposed persons. Note that when the number of exposed persons is relatively small, the allowable level of exposure increases. From Travis, Richter, Crouch, Wilson, and Klema, *supra* note 18, at 419.

cause high quality assessments have helped juries quantitatively evaluate the reasonableness of the medical claims. An understanding of the pitfalls and shortcomings that have been identified and discussed here should give a significant advantage to attorneys and scientists who must respond to or present health risk assessments.