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Retrospective on U.S. Health Risk Assessment: How Others Can Benefit*

Dennis J. Paustenbach **

Introduction

As broadly defined, risk assessment can be used to predict the likelihood of many unwanted events, including industrial explosions, workplace injuries, failures of machine parts, natural catastrophes, injury or death from an array of voluntary activities, diseases, natural causes, life-style or others.¹ Thus, an extraordinary number of publications on risk assessment deal with a wide range of topics.²

Health risk assessment, however is a separate and distinct discipline which uses toxicology data collected from animal studies and human epidemiology, combined with information about the degree of exposure, to quantitatively predict the likelihood that a particular adverse response will be seen in a specific human population.³ The assessment of toxicology data to predict health risks is not entirely new;⁴ the risk-assessment process has been used by agencies for

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¹ *Societal Risk Assessment: How Safe is Safe Enough?* (Richard C. Schwing & William A. Albers Jr., eds. 1980); Christopher F. Wilkinson, *Risk Assessment and Regulatory Policy*, 1 *Comments Toxicol.* 1 (1987); Richard Wilson & Edmund A.C. Crouch, *Risk Assessment and Comparisons: An Introduction*, 236 *Science* 267 (1987); Paul Slovic, *Perception of Risk*, 236 *Science* 280 (1987); Ben J. Wattenberg, *The Good News is the Bad News is Wrong* (1984) and W. Kip Viscusi, *Fatal Tradeoffs: Public and Private Responsibilities for Risk* (1992).

² Dennis J. Paustenbach, *The Risk Assessment of Environmental Hazards: A Textbook of Case Studies* (1989).

³ *Id.* and National Academy of Sciences (NAS), *Science and Policy in Risk Assessment* (1994).

⁴ Carol S. Weil, *Statistics Versus Safety Factors and Scientific Judgement in the Evaluation of Safety for Man*, 21 *Toxicol. Appl. Pharmacol.* 454 (1972) and William W. Lowrance, *Of Acceptable Risk* (1976).

almost 40 years, most notably within the U.S. Food and Drug Administration (FDA).⁵ However, the difference between assessments performed in the 1950's and 1960's and those performed in the 1980's and 1990's is the incorporation of a complex and quantitative exposure assessment. With the emergence of quantitative methods, risk-assessment models can better estimate the probability that a specific adverse effect will occur over a wide range of doses.⁶

Since 1980, many environmental regulations and some occupational health standards have, at least in part, been based on the results of low-dose extrapolation models and exposure assessments.⁷ For example, risk-assessment methodologies have been used to set standards for pesticide residues, food additives, pharmaceutical agents, drinking water, soil and ambient air, as well as exposure limits for contaminants found in indoor air, consumer products and other media.⁸ Risk managers increasingly rely on risk assessments to decide whether a broad array of environmental risks are significant or trivial, an important task since over 300 of about 5,000 chemicals routinely used in industry have been labelled carcinogens as a result of animal studies.⁹ Risk assessment has become prominent in both the U.S. and

⁵ Arnold J. Lehmann & O. Garth Fitzhugh, *100 Fold Margin of Safety*, 18 Q. Bull. Assoc. Food Drug Off. U.S. 33 (1954); Michael L. Dourson & Jerry F. Stara, *Regulatory History and Experimental Support of Uncertainty (Safety Factors)*, 3 Regul. Toxicol. Pharmacol. 224 (1983); Joseph V. Rodricks, *Origins of Risk Assessment in Food-Safety Decision-Making*, 7 Am. Coll. Toxicol. 539 (1989) and U.S. Department of Health and Human Services, *Determining Risks to Health: Federal Policy and Practice* (1986).

⁶ Paustenbach, *supra* note 2.

⁷ Ian C. Munro & Daniel R. Krewski, *Risk Assessment and Regulatory Decision-making*, 19 Food Cosmet. Toxicol. 549 (1981); Peter W. Preuss & A. M. Ehrlich, *The Environmental Protection Agency's Risk Assessment Guidelines*, 37 J. Air Pollut. Control Assoc. 7841 (1987); Joseph V. Rodricks, Susan M. Brett & Grover C. Wrenn, *Significant Risk Decisions in Federal Regulatory Agencies*, 7 Regul. Toxicol. Pharmacol. 307 (1987) and Center for Risk Analysis, *Historical Roots of Health Risk Assessment* (1994).

⁸ Center for Risk Analysis, *supra*; Dennis J. Paustenbach, *Health Risk Assessments Opportunities and Pitfalls*, 14 Colum. J. Environ. Law 379-410 (1989); Executive Office of the President, *Regulatory Program of the U.S. Government, April 1, 1990 to March 31, 1991* (1991) and Carnegie Commission on Science, Technology, and Government, *Risk and the Environment, Improving Regulatory Decision Making* (1993).

⁹ Bruce N. Ames, Renae Magaw & Lois S. Gold, *Ranking Possible Carcinogenic Hazards*, 236 Science 271 (1987); Bruce N. Ames & Lois S. Gold, *Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis*, 249 Science 970 (1990);

Canada because it was seen as better than prior attempts to make decisions from volumes of toxicology and epidemiology data collected over the past 40 years.¹⁰

In 1980, for example, the U.S. Supreme Court considered the results of risk assessment to conclude that more stringent regulation of benzene was unwarranted unless it lowered significant risks,¹¹ but the challenge of deciding which risks are significant faces legislators and regulators worldwide. The practice of risk assessment has helped illustrate that decisions about industrial and agricultural practices in nearly any country in some circumstances can adversely affect the health of people and the environment elsewhere. For example, the destruction of the rain forests in South America or changes in the ozone layer in Antarctica are believed to influence the climate in North America and Europe. To help insure that the most important environmental hazards are tackled ahead of lesser ones, it would be useful if all countries had a consistent and objective approach to assessing environmental risks so that political or social pressures were not given much weight.¹²

Health Risk Assessment: A Brief History

The origin of health risk assessment, in its most basic form, can be traced back to that of early humans. When early man recognized that wildlife represented a source of food when edible plants were not available, primitive risk assessors weighed the hazard of being mauled

Bruce N. Ames & Lois S. Gold, *Comparing Synthetic to Natural Chemicals is Essential for Perspective in "Risk Assessment,"* *Risk Analysis* (1993); Bruce N. Ames & Lois S. Gold, *Environmental Pollution and Cancer: Some Misconceptions in Phantom Risk: Scientific Inference and the Law*, 153 (K.R. Foster, D.E. Bernstein, & P.W. Huber, eds. 1993); Joseph V. Rodricks, *Calculated Risks* (1992); Terry Yosie, *How Risk Assessments Are Used in the Federal Government*, 21 *Environ. Sci. Technol.* 526 (1987) and Frank A. Young, *Risk Assessment: The Convergence of Science and the Law*, 7 *Regul. Toxicol. Pharmacol.* 179 (1987).

¹⁰ NAS, *Risk Assessment in the Federal Government: Managing the Process* (1983); NAS, *supra* note 3; William Ruckelshaus, *Risk, Science, and Democracy*, 1(3) *Sci. & Tech.* 19 (1985) and Donald Barnes, *What Should We Do Now?* 11 *Environ. Toxicol. Chem.* 729 (1992).

¹¹ Industrial Union Dept., *AFL-CIO v. Am. Petroleum Institute*, 448 U.S. 607 (1980) and John D. Graham, Laura C. Green & Marc J. Roberts, *In Search of Safety: Chemicals and Cancer Risks* 80-114 (1988).

¹² U.S. Environmental Protection Agency (EPA), *Credible Science; Credible Solutions* (1992).

by a wild animal, which they hoped to kill and eat, versus the benefit of thwarting starvation. The historical record does not permit us to know how well early humans balanced this risk-benefit relationship; however, it is safe to assume that those who failed to successfully conduct these assessments fared poorly.

A thoughtful review of the history of risk analysis has been published.¹³ In it, the authors noted that perhaps the world's first professional risk assessors were the Asipu people who lived in the Tigris-Euphrates valley about 3,200 B.C. According to Covello and Mumpower,¹⁴ their primary function was to serve as consultants for risky, uncertain or difficult decisions. For risky ventures such as a proposed marriage arrangement or a suitable building site, the Asipu would identify the important dimensions of the problem, identify alternative actions and collect data on the likely outcomes of each alternative. The best available data from their perspective were signs from the gods, which the priest-like Asipu were especially qualified to interpret. After an analysis of benefits and costs of each alternative was completed, the Asipu would recommend to their client the most favorable alternative, etched upon a clay tablet.

The similarities between the practices of modern risk assessors and those of ancient Babylon underscore the historical concerns of society regarding the problems of risk and appreciation of cause and effect relationships in everyday life. By the 16th to 18th Centuries, the basis for the current approach to health risk assessment was established, including a sensitivity to the importance of exposure and response. During the early decades (1900–1940) of the 20th Century, qualitative understanding of health risk assessment improved as health scientists and factory managers learned of the hazards of occupational exposure to the more than 300 chemicals then routinely used in the workplace.¹⁵

The emergence of modern health risk assessment can be traced to about 1975. Since then, the considerable knowledge gained from scientists in many disciplines has been slowly transferred to

¹³ Vincent T. Covello & Jerry Mumpower, *Risk Analysis and Risk Management: An Historical Perspective*, 5 *Risk Anal.* 103 (1985).

¹⁴ *Id.*

¹⁵ *Id.* and Hunter's Diseases of Occupation (P. A. Raffle et al., eds. 1987).

environmental regulators, who often take a lead role in formulating improvements in various risk assessment methods.¹⁶ For example, nearly two dozen guidance documents (about 5,000 pages) on how risk assessments should be conducted have been written by the U.S. Environmental Protection Agency (EPA) since 1986. Unfortunately, as EPA standardized the process, assessments often became too inflexible to properly characterize the more likely risks. Specifically, most regulatory attempts to standardize assessment methods have introduced several levels of conservatism because such assessments have, for the sake of public safety, been structured to over-estimate true risks.¹⁷

The Debate on the Appropriateness of Risk Assessment

Risk assessment, by its very nature, is a process whereby the magnitude of a specific risk is characterized so that decision makers can conclude whether the potential hazard is sufficiently great that it needs to be managed or regulated.¹⁸ Therefore, before deciding to conduct

¹⁶ Dennis J. Paustenbach, *A Survey of Health Risk Assessment*, in *The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies* 27 (D. J. Paustenbach, ed. 1989).

¹⁷ Albert L. Nichols & Robert J. Zeckhauser, *The Perils of Prudence: How Conventional Risk Assessments Distort Regulations*, 8 *Regul. Toxicol. Pharmacol.* 61 (1988); Dennis J. Paustenbach et al., *The Current Practice of Health Risk Assessment: Potential Impact on Standards for Toxic Air Contaminants*, 40 *J. Air Waste Mgt. Assoc.* 1620 (1990); Dennis J. Paustenbach et al., *Recent Developments on the Hazards Posed by 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Soil: Implications for Setting Risk-Based Cleanup Levels at Residential and Industrial Sites*, 36 *J. Toxicol. Environ. Health* 103 (1992); Dennis J. Paustenbach, *Important Recent Advances in the Practice of Health Risk Assessment: Implications for the 1990's*, 10 *Regul. Toxicol. Pharm.* 204 (1989); Brent L. Finley & Dennis J. Paustenbach, *The Benefits of Probabilistic Exposure Assessment: Three Case Studies Involving Contaminated Air, Water, and Soil*, 14 *Risk Anal.* 53 (1994); Brent Finley et al., *Recommended Distributions for Exposure Factors Frequently Used in Health Risk Assessment*, 14 *Risk Anal.* 533 (1994); Neil C. Hawkins, *Conservatism in Maximally Exposed Individual Predictive Exposure Assessments: A First-Cut Analysis*, 14 *Regul. Toxicol. Pharm.* 107 (1991); David E. Burmaster & Paul D. Anderson, *Principles of Good Practice for the Use of Monte Carlo Techniques in Human Health and Ecological Risk Assessments*, 14 *Risk Anal.* 477 (1994); Terie L. Copeland et al., *Comparing the Results of a Monte Carlo Analysis with EPA's Reasonable Maximum Exposed Individual: A Case Study of a Former Wood Treatment Site*, 18 *Regul. Toxicol. Pharm.* 275 (1993) and Terie L. Copeland et al., *Use of Monte-Carlo Techniques to Understand the Conservatism in California's Approach to Assessing Air Toxics*, *J. Air Waste Mgmt. Assn.* (1994).

¹⁸ Ellen K. Silbergeld, *Five Types of Ambiguity: Scientific Uncertainty in Risk Assessment*, 4 *Haz. Waste Haz. Matls.* 139 (1987) and Ellen K. Silbergeld, *Risk*

such analyses, one must concede that some level of risk can be deemed acceptable; that is, a risk-benefit balance can be found.¹⁹

Although many in society are concerned about the uncertainty and variability of assessment processes used in today's environmental decision making, the public can take solace in the fact that new and better information concerning the uptake and metabolism of toxins is continually being developed, the degree of exposure and the likelihood that an adverse effect will occur at a specific dose. Nonetheless, it is true that chemical hazards are not, and may never be, completely eliminated when decisions are based on a risk assessment. For this reason, some nations, including Germany, Sweden and others, have traditionally regulated chemicals to reduce emissions and exposure to the lowest level achievable using engineering controls or to impose a ban, raising yet another set of risk and technology issues. Also, an approach can be problematic in that it diverts financial resources that might be used to address other risks such as AIDS or to provide immunization programs.

Reducing health risks to levels that are "as low as reasonably achievable" (ALARA) or requiring the use of the "best available technology" (BAT) can produce significant reductions in the degree of exposure, but either policy has two possible shortcomings. First, adopting an ALARA or BAT approach can be costly and may not result in an appreciable overall benefit (reduction of risk) to society.²⁰ Second, a reliance on banning may not ensure that a significant or even measurable level of risk reduction will occur.²¹ History demonstrates that banning chemicals may well eliminate one risk, but often this hazard is replaced by another and the financial sacrifice is often not to the overall benefit of society. For example, chemical substitutions, as in

Assessment: The Perspective and Experience of the U.S. Environmentalists, 101 *Environ. Health Persp.* 100 (1993).

¹⁹ Aaron Wildavsky, *Searching for Safety* (1991); Thomas B. Starr, *Risk Management, Assessment, and Acceptability*, 5 *Risk Anal.* 97 (1985); Richard Zeckhauser & William K. Viscusi, *Risk Within Reason*, 248 *Science* 559 (1990); Seymour Friess, VIII *Risk Assessment; Historical Perspectives in Drinking Water and Health* 3 (1987); Stephen Breyer, *Breaking the Vicious Circle: Towards Effective Risk Regulation* (1994) and Rae Zimmerman, *Social Equity and Environmental Risk*, 13 *Risk Anal.* 649 (1993).

²⁰ Dennis J. Paustenbach, *Jousting with Environmental Windmills*, 13 *Risk Anal.* 13 (1993).

²¹ Francine Laden & George M. Gray, *Toxics Use Reduction: Pro and Con*, 4 *Risk* 213 (1993).

the case of saccharin and Nutrasweet[®], may raise new uncertainties about other risks to health. In an ideal world, the costs of decisions concerning risk reduction should be weighed against the benefits of applying the same resources to reduce other important risks such as adequate medical care for all citizens or immunization.²² However, no one has yet determined how to distribute limited financial resources optimally between very different portions of the U.S. budget dealing with, e.g., education, space engineering or the military.

Improving the Practice of Risk Assessment

Risk assessment has (by convention) been separated into four subdisciplines: hazard identification, dose-response assessment, exposure assessment and risk characterization.²³ This has been called the "risk assessment paradigm." Hazard identification is the first and most easily recognized step in risk assessment. It is the process of determining whether exposure to an agent could (at any dose) cause an increase in the incidence of adverse health effects in humans or wildlife. Dose-response evaluations define the relationship between the dose of an agent and the probability of a specific adverse effect in laboratory animals. Exposure assessment quantifies the uptake of xenobiotics from the environment by any combination of oral, inhalation and dermal routes of exposure. The most important part of an assessment, risk characterization, summarizes and interprets the information collected from previous activities and identifies the limitations and the uncertainties in risk estimates.²⁴

Nearly twenty years of U.S. experience have taught scientists a great deal about how to perform each step in risk assessment more efficiently and accurately.²⁵ With the ongoing and accelerating application of

²² Graham, Green & Roberts, *supra* note 11; Wattenberg, *supra* note 1; Viscusi, *supra* note 1; Wildavsky, *supra* note 19; Benjamin J. O'Keefe, *Shooting Ourselves in the Foot* (1985); George M. Gray & John D. Graham, *Risk Assessment and Clean Air Policy*, 10 *J. Policy Anal. & Mgmt.* 286 (1991); John D. Graham, *Harnessing Science for Environmental Regulation* (1991) and Michael Gough, *How Much Cancer Can EPA Regulate Anyway?* 10 *Risk Anal.* 1 (1990).

²³ NAS, *supra* note 10 and NAS, *supra* note 3.

²⁴ Preuss & Ehrlich, *supra* note 7 and NAS, *supra* note 3.

²⁵ Paustenbach, *supra* note 17, Finley et al., *supra* note 17, Copeland et al., *supra* note 17, Robert L. Sielken, *Some Issues in the Quantitative Modeling Portion of Cancer Risk Assessment*, 5 *Regul. Toxicol. Pharm.* 175 (1985); Thomas B. Starr &

risk analyses worldwide, the time is ideal to adopt many improvements to risk assessment that have been identified which could significantly advance the usefulness of risk assessment in the twenty-first century.

Hazard Identification

We have learned a great deal about how U.S. regulatory agencies might better have conducted the hazard-identification process over the past ten to twenty years, and many possible improvements are discussed here (Table 1).²⁶ For example, we need not consider all

Raymond B. Buck, *The Importance of Delivered Dose in Estimating Low-Dose Cancer Risk for Inhalation Exposure to Formaldehyde*, 4 *Fund. Appl. Toxicol.* 740 (1984); Melvin E. Andersen, *Quantitative Risk Assessment and Chemical Carcinogens in Occupational Environments*, 3 *Appl. Ind. Hyg.* 267 (1991); Melvin E. Andersen et al., *Physiologically Based Pharmacokinetic Modeling with Dichloromethane, Its Metabolite, Carbon Monoxide, and Blood Carboxyhemoglobin in Rats and Humans*, 108 *Toxicol. Appl. Pharmacol.* 14 (1991); J. Ashby et al., *A Scheme for Classifying Carcinogens*, 12 *Regul. Toxicol. Pharm.* 270 (1990); Frederick Y. Bois, Lauren Zeise & Thomas N. Tozer, *Precision and Sensitivity Analysis of Pharmacokinetics Models for Cancer Risk Assessment: Tetrachloroethylene in Mice, Rats, and Humans*, 102 *Toxicol. Appl. Pharmacol.* 300 (1990); Kenneth T. Bogen, *Risk Extrapolation for Chlorinated Methanes as Promoters vs. Initiators of Multistage Carcinogenesis*, 15 *Fund. Appl. Toxicol.* 536 (1990); Kenneth T. Bogen, *Cell Proliferation Kinetics and Multistage Cancer Risk Models*, 81 *J. Natl. Cancer Inst.* 267 (1989); David E. Burmaster & Karl von Stackelberg, *Using Monte Carlo Simulations in Public Health Risk Assessments: Estimating and Presenting Full Distributions of Risk*, 1 *J. Expos. Anal. Environ. Epid.* 491 (1991); Suresh H. Moolgavkar, Anup Dewanji & David J. Venzon, *A Stochastic Two-Stage Model for Cancer Risk Assessment: The Hazard Function and the Probability of Tumors*, 8 *Risk Anal.* 383 (1988); Samuel M. Cohen, E.M. Garland & Leon B. Ellwein, *Cancer Enhancement by Cell Proliferation*, 374 *Prog. Clin. Biol. Res.* 213 (1992); J. Huff & J. Haseman, *Long-Term Chemical Carcinogenesis Experiments for Identifying Potential Human Cancer Hazards: Collective Database of the National Cancer Institute and National Toxicology Program (1976-1991)*, 96 *Environ. Health Persp.* 23 (1991); W. Gary Flamm & Lois D. Lehman-McKeeman, *The Human Relevance of the Renal Tumor-Inducing Potential of D-Limonene in Male Rats: Implications for Risk Assessment*, 13 *Regul. Toxicol. Pharm.* 70 (1991); Rory B. Connolly et al., *A Biologically-Based Risk Assessment Strategy for Inhaled Formaldehyde*, 4 *Comments Toxicol.* 269 (1992); Gary Goodman & Richard Wilson, *Quantitative Prediction of Human Cancer Risk from Rodent Carcinogenic Potencies: A Closer Look at the Epidemiological Evidence for Some Chemicals Not Definitely Carcinogenic in Humans*, 14 *Regul. Toxicol. Pharm.* 118 (1991) and Robert A. Squire, *Ranking Animal Carcinogens: A Proposed Regulatory Approach*, 214 *Science* 877 (1981).

²⁶ Huff & Haseman, *supra*; Squire, *supra*; Robert C. Barnard, Robert J. Moolenaar & Donald E. Stevenson, *IARC and HHS Lists of Carcinogens: Regulatory Use Based on Misunderstanding of the Scope of Purposes of the Lists*, 9 *Regul. Toxicol. Pharm.* 81 (1989); Robert C. Barnard, *Some Regulatory Definitions of Risk: Interaction of Scientific and Legal Principles*, 11 *Regul. Toxicol. Pharm.* 201 (1990); James Huff, Joseph Haseman & David Rall, *Scientific Concepts, Value, and Significance of Chemical Carcinogenesis Studies*, 31 *Ann. Rev. Pharm. & Toxicol.* 621 (1991); Byron E. Butterworth, *A Review of Mechanisms of Carcinogenesis*

animal carcinogens as posing an equally serious human hazard because we now know that carcinogens vary dramatically in their carcinogenic and/or mutagenic potency.²⁷ Some carcinogens, e.g., ethylene oxide, are mutagenic at low doses in every *in vitro* and *in vivo* test, while others, e.g., the dioxins and cyclodienes, are potent carcinogens but are not mutagenic or genotoxic in any of these tests.²⁸ Weak carcinogens, e.g., saccharin, may require a dose 10-million-fold greater than for potent carcinogens, e.g., aflatoxin, to produce the same response in animals.²⁹ In short, many factors including tumor type, species, metabolism, pharmacokinetics, mechanism of action and the epidemiological experience all need to be considered when attempting to predict whether a specific chemical poses a significant hazard to humans at doses to which they might reasonably be exposed.³⁰

This helps explain why more than 400 chemicals have been found in animal studies to produce tumors, yet fewer than twenty are known human carcinogens.³¹ Even after accounting for the typical epidemiology shortcomings, it is clear that some, if not many, rodent carcinogens do not pose an equivalent cancer hazard in humans.³² Although it is plausible that some carcinogens may pose a greater

(1994); Byron E. Butterworth & Thomas Slaga, *Nongenotoxic Mechanisms in Carcinogenesis* (Banbury Report No. 25 1987) and Byron E. Butterworth, *Consideration of Both Genotoxic and Nongenotoxic Mechanisms in Predicting Carcinogenic Potential*, 239 *Mutat. Res.* 117 (1990).

²⁷ Ames, Magaw & Gold, *supra* note 9; Ames & Gold, *supra* note 9; Bruce C. Allen, Kenny S. Crump & Annette M. Shipp, *Correlation Between Carcinogenic Potency of Chemicals in Animals and Humans*, 8 *Risk Anal.* 531 (1988) and John Ashby & Raymond W. Tennant, *Definitive Relationships Among Chemical Structure, Carcinogenicity, and Mutagenicity for 301 Chemicals Tested by the U.S. NTP*, 257 *Mutat. Res.* 229 (1991).

²⁸ Gary M. Williams & John H. Weisburger, *Chemical Carcinogenesis*, in Casarett and Doull's *Toxicology: The Basic Science of Poisons* 127 (4th ed. M. D. Amdur, J. D. Doull & C. D. Klaassen, eds. 1991).

²⁹ Ames & Gold (1990), *supra* note 9; Ames & Gold (1993), *supra* note 9 and Williams & Weisburger, *supra*.

³⁰ Bogen, *supra* note 25; Squire, *supra* note 25; Butterworth, *supra* note 26 and Williams & Weisburger, *supra* note 28.

³¹ Ames, Magaw & Gold, *supra* note 9; Ames & Gold (1990), *supra* note 9 and Ames & Gold (1994), *supra* note 9.

³² Connolly et al., *supra* note 25; Jack Moore, Renate Kimbrough & Michael Gough, *The Dioxin TCDD: A Selective Study of Science and Policy* (1994) and Renate D. Kimbrough, *How Toxic is 2,3,7,8-TCDD to Humans?* 30 *J. Toxicol. Environ. Health* 261 (1990).

human hazard than that suggested by rodent studies, there are few examples where appropriate animal tests were conducted.

Table 1
Lessons Learned in the U. S. Regarding
How to Improve the Conduct of Health Risk Assessment

<i>Hazard Identification</i>	<i>Dose-Response Assessment</i>	<i>Exposure Assessment</i>	<i>Risk Characterization</i>
<p>Do not consider all animal carcinogens as equally serious human hazards</p> <p>Consider "weight of evidence" when evaluating data sets to classify a chemical as a carcinogen, reproductive toxicant, etc.</p>	<p>Present upper bound of risk plus the best estimates and the bounds</p> <p>Consider risk estimates from several low-dose models</p> <p>Conduct a "reality check" using epidemiology data</p> <p>Adjust for biological differences among species using physiologically-based pharmacokinetic (PB-PK) models</p> <p>Use low-dose models to objectively rank carcinogens rather than expecting these models to accurately predict the actual cancer incidence rate</p> <p>Understand the fragility and sturdiness of low-dose models</p> <p>Use a weight of evidence approach to select best low-dose extrapolation methodology</p>	<p>Do not put too much emphasis on risk estimates for the maximally exposed individual (MEI)</p> <p>Evaluate the uptake (absorbed dose) for both the 5% and 95% persons</p> <p>Do not repeatedly use conservative or worst-case assumptions</p> <p>Incorporate Monte Carlo techniques whenever possible</p> <p>Ensure a proper statistical analysis of environmental data</p> <p>Conduct sensitivity analysis to understand fragility of dose estimates</p> <p>Understand the role of environmental fate when estimating exposure</p> <p>Validate the reasonableness of the exposure estimates</p> <p>Consider using biological monitoring to confirm exposure estimates</p> <p>Consider all indirect pathways of exposure</p>	<p>Understand that a one-in-a-million increased cancer risk is rarely a serious public health hazard</p> <p>Do not characterize low-dose modeling results as an actual increased risk (rather than a plausible upper-bound)</p> <p>Consider background levels of exposure when characterizing the degree of incremental risk</p> <p>Do not assume the solution to most environmental hazards involves remediation, destruction of the contaminated media or substitution with less toxic chemicals</p> <p>Put risk estimates into perspective</p> <p>Characterize risk using results of Monte Carlo analysis</p> <p>Conduct uncertainty and sensitivity analyses</p>

The same generalization applies to developmental and reproductive toxicants.³³ Unfortunately, most human exposure is not to a single

³³ E. Marshall Johnson et al., *Use of the Adult Developmental Relationship in Pre-*

chronic toxicant, so the complexities of potentiation, antagonism and synergy must also be considered when the simultaneous uptake of substantial amounts of various toxicants occurs.³⁴ Clearly, in light of the hundreds of industrial chemicals to which we are daily exposed, the challenge to regulators is to identify toxicants for which exposure should be limited.

As a result of knowledge gained during 1975–95, the first twenty years of health risk assessment, it has become clear that most animal carcinogens (at some dose) will probably pose a human cancer hazard. However, actual human cancer risk at very low doses remains unclear and will continue to be debated for many years.³⁵ The criteria by which a risk assessor determines that a chemical could pose a significant carcinogenic or developmental threat to humans is based on animal studies and consideration of at least six factors. For carcinogens, these include the number of animal species affected, the number and types of tumors occurring in them, the dose (relative to the acute toxic dose) at which they are affected, the dose/response relationship, and the genotoxicity of the chemical.³⁶ For developmental toxicants, the key issues in hazard identification are similar to those for carcinogens and include the number of species affected, the severity of effects, the slope of the dose-response curve and the relationship between the dose which affects the mother compared to that affecting the offspring.³⁷

Screening for Developmental Hazards, 7 *Terato. Carcin. Mutagen.* 273 (1987); E. Marshall Johnson, *A Two Tier System for Developmental Toxicity Evaluations Based on Consideration of Exposure and Effect Relationships*, 35 *Teratol.* 405 (1987) and E. Marshall Johnson, *Cross-Species Extrapolations and the Biologic Basis for Safety Factor Determinations in Developmental Toxicology*, 8 *Regul. Toxicol. Pharm.* 22 (1988).

³⁴ Daniel Krewski, Todd Thorslund & James Withey, *Carcinogenic Risk Assessment of Complex Mixtures*, 5 *Toxicol. Ind. Health* 851 (1989); Daniel Krewski & Richard D. Thomas, *Carcinogenic Mixtures*, 12 *Risk Anal.* 105 (1992) and Ralph L. Kodell, Daniel Krewski & Jan M. Zielinski, *Additive and Multiplicative Relative Risk in the Two-Stage Clonal Expansion Model of Carcinogenesis*, 11 *Risk Anal.* 483 (1991).

³⁵ Allen, Crump & Shipp, *supra* note 27; Ashby & Tennant, *supra* note 27 and Williams & Weisburger, *supra* note 27.

³⁶ Squire, *supra* note 25; Butterworth, *supra* note 26 and Williams & Weisburger, *supra* note 28.

³⁷ Johnson et al., *supra* note 33; Ralph L. Kodell et al., *Mathematical Modeling of Reproductive and Developmental Toxic Effects for Quantitative Risk Assessment*, 11 *Risk Anal.* 583 (1991); William L. Hart et al., *Evaluation of Developmental Toxicity Data: A Discussion of Some Pertinent Factors and a Proposal*, 8 *Risk Anal.* 59

Over the past two decades, scientists have also learned not to place equal weight on all data. Regulators, for example, need to resist the temptation to emphasize any data that suggests that a chemical poses a carcinogenic or developmental hazard but put little weight on any that suggests a failure to cause such effects at environmentally relevant exposures. This approach has heretofore been considered prudently health-protective. Yet, it is not scientific, nor is it necessarily in the public's best interest.³⁸ For example, extraordinary confidence has sometimes been placed on studies suggesting that a chemical may pose a particular hazard with modest consideration of the study's quality.³⁹

During the 1990's, the scientific community and most regulators have come to accept that not all data are equal, and that only data of similar quality should be judged equally.⁴⁰ In the U.S., this is known

(1988); Rhoda Wang & Bernard A. Schwetz, *An Evaluation System for Ranking Chemicals with Teratogenic Potential*, 7 *Terato. Carcin. Mutagen.* 133 (1987) and E. Marshall Johnson, *A Case Study of Developmental Toxicity Risk Estimation Based on Animal Data: The Drug Bendectin*, in *The Risk Assessment of Environmental Hazards: A Textbook of Case Studies* 711 (D. J. Paustenbach, ed. 1989).

³⁸ See Slovic, *supra* note 1; Adam M. Finkel, *Edifying Presentation of Risk Estimates: Not as Easy as It Seems*, 10 *J. Policy Anal. Mgmt.* 296 (1991); David E. Burmaster & Robert N. Harris, *The Magnitude of Compounding Conservatism in Superfund Risk Assessments*, 13 *Risk Anal.* 131 (1993); Richard W. D'Souza & Harold Boxenbaum, *Physiological Pharmacokinetic Models: Some Aspects of Theory, Practice and Potential*, 4 *Toxicol. Ind. Health* 151 (1988); Richard Reitz et al., *Physiologically-Based Pharmacokinetic Modeling with Methylchloroform: Implications for Interspecies, High Dose/Low Dose, and Dose-Route Extrapolations*, 95 *Toxicol. Appl. Pharm.* 185 (1988); David G. Hoel, Norman L. Kaplan & Marshall W. Anderson, *Implication of Nonlinear Pharmacokinetics on Risk Estimation in Carcinogenesis*, 291 *Science* 1032 (1983); Richard H. Reitz, Melvin Andersen & Michael Gargas, *A PB-PK Model for Vinyl Chloride*, *Toxicol. Appl. Pharm.* (in review 1995); Robert C. Spear et al., *Modeling Benzene Pharmacokinetics Across Three Sets of Animal Data: Parametric Sensitivity and Risk Implications*, 11 *Risk Anal.* 641 (1991); Christopher Whipple, *Nonpessimistic Risk Assessment and De Minimus Risk as Risk Management Tools*, in *The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies* 1105 (D. J. Paustenbach, ed. 1989); D. Zilberman et al., *The Economics of Pesticide Use and Regulation*, 253 *Science* 518 (1993) and Charles T. Rubin, *The Green Crusade: Rethinking the Roots of Environmentalism* (1994).

³⁹ See Rodricks, *supra* note 9; Manfred S. von Wittenau, *Strengths and Weaknesses of Long-Term Bioassays*, 7 *Regul. Toxicol. Pharm.* 113 (1988); Bruce N. Ames, *Pesticides, Risk and Applesauce*, 244 *Science* 755 (1989); Phillip H. Abelson, *Exaggerated Carcinogenicity of Chemicals*, 256 *Science* 160 (1992) and John Barr, *Design and Interpretation of Bioassays for Carcinogenicity*, 7 *Regul. Toxicol. Pharm.* 422 (1988).

⁴⁰ See von Wittenau, *supra*; Ames, *supra*; Abelson, *supra* and Barr, *supra*. See also, Barnard, Moolenaar & Stevenson, *supra* note 26; Barnard, *supra* note 26;

as the “weight-of-evidence” approach. It represents an important refinement and is applicable not only to hazard identification, but also to exposure and dose-response evaluations. One benefit of using a “weight-of-evidence” approach is that it minimizes the possibility that huge sums of money will be spent to conduct several high quality toxicity studies, only to have the results refuted by one or two poor ones.⁴¹ This approach has been embraced by many environmental agencies outside the U.S. Some of the best examples where an agency attempted to use a weight-of-evidence approach, coupled with understanding of the mechanism of action, include d-limonene,⁴² formaldehyde,⁴³ NTA,⁴⁴ methylene chloride,⁴⁵ and chloroform.⁴⁶

Dose-Response Assessments

A dose-response evaluation usually requires an extrapolation from the generally high doses administered to experimental animals, or exposures reported in occupational studies, to the exposures expected from human contact with the agent in the environment (Figure 1).

As we enter the mid-1990's, it is clear that the most uncertain aspect of chemical assessments, especially carcinogens, is the low-dose extrapolation. Although perhaps humbling, most toxicologists agree that they are limited in ability to estimate the risks associated with

Huff, Haseman & Rall, *supra* note 26; Butterworth, *supra* note 26; Butterworth & Slaga, *supra* note 26; and Butterworth, *supra* note 26; Allen, Crump & Shipp, *supra* note 27; Ashby & Tennant, *supra* note 27; Williams & Weisburger, *supra* note 28; Moore, Kimbrough & Gough, *supra* note 32; Kimbrough, *supra* note 32; references *supra* notes 33 and 34; Kodell et al., *supra* note 37; Hart et al., *supra* note 37; Wang & Schwetz, *supra* note 37; Johnson, *supra* note 37; EPA, *supra* note 39; Finkel, *supra* note 38; Burmaster & Harris, *supra* note 38; D'Souza & Boxenbaum, *supra* note 38; Reitz et al., *supra* note 38; Hoel, Kaplan & Anderson, *supra* note 38; Reitz, Andersen & Gargas, *supra* note 38; Spear et al., *supra* note 38; Whipple, *supra* note 38; Zilberman et al., *supra* note 38 and Rubin, *supra* note 38.

⁴¹ Barr, *supra* note 39; EPA, Science Advisory Board, *Unfinished Business* (1988); EPA, Science Advisory Board, *Reducing Risk: Setting Priorities and Strategies for Environmental Protection* (1990) and EPA, Science Advisory Board, *Safeguarding the Future* (1991).

⁴² Flamm & Lehman-McKeeman, *supra* note 25.

⁴³ Connolly et al., *supra* note 25.

⁴⁴ Robert L. Anderson & Charles L. Alden, *Risk Assessment for Nitrotriacetic Acid (NTA)* in *The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies* 390 (D. J. Paustenbach, ed. 1989).

⁴⁵ Andersen, *supra* note 25.

⁴⁶ Rory A Corley et al., *Development of a Physiologically-Based Pharmacokinetic Model for Chloroform*, 103 *Toxicol. Appl. Pharm.* 512 (1990).

typical levels of environmental exposure based on results of standard rodent bioassays.⁴⁷ There are many reasons why this is so. First, we do not fully understand all of the possible mechanisms of action for carcinogens.⁴⁸ Second, the doses at which we conduct the animal tests are so high that they often produce effects that would not occur at the doses to which people are exposed.⁴⁹ Third, there are usually significant differences between animals and humans with respect to the rate at which chemicals are metabolized, distributed and excreted. Fourth, the delivered dose to specific target tissues in animals will often be much higher than that delivered to human target tissues.⁵⁰ Thus, scientists must rely on a model or theory to estimate the human response at experimental doses that are often one-thousand-fold below the lowest tested animal dose as illustrated below.⁵¹

Figure 1 depicts a dose-response curve from an exceptionally thorough (8 dose groups) study. The solid line is a best fit of the eight data points identified. The three lowest 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 at each dose (n = 100). To insure that risk estimates are not underestimated, the models most frequently used by regulators are based on the upper bound of the plausible response, rather than the best estimate.

⁴⁷ Andersen, *supra* note 25; Ames, *supra* note 39; Anderson & Alden, *supra* note 44; Daniel Krewski, D. Murdoch & James R. Withey, *Recent Developments in Carcinogenic Risk Assessment*, 57 *Health Physics* 313 (1989); Lois S. Gold et al., *Rodent Carcinogens: Setting Priorities*, 258 *Science* 261 (1992) and Food Safety Council, *Quantitative Risk Assessment in Food Safety Assessment* ch. 11 (1980).

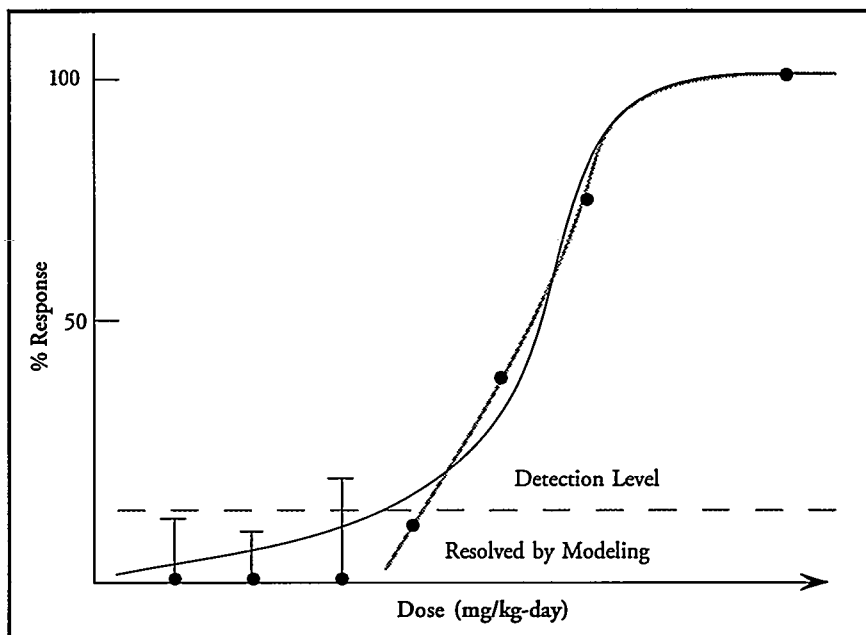
⁴⁸ Ashby & Tennant, *supra* note 27; Williams & Weisburger, *supra* note 28 and Melvin E. Andersen et al., *Physiologically-Based Pharmacokinetics and the Risk Assessment for Methylene Chloride*, 87 *Toxicol. Appl. Pharm.* 185 (1987).

⁴⁹ Krewski, Murdoch & Withey, *supra* note 47 and Gold et al., *supra* note 47.

⁵⁰ Bois, Zeise & Tozer, *supra* note 25; Melvin E. Andersen et al., *Physiologically-Based Pharmacokinetic Modeling with Dichloromethane, Its Metabolite, Carbon Monoxide, and Blood Carboxyhemoglobin in Rats and Humans*, 108 *Toxicol. Appl. Pharm.* 14 (1991) and Dennis J. Paustenbach et al., *A Physiologically-Based Pharmacokinetic Model for Carbon Tetrachloride*, 96 *Toxicol. Appl. Pharm.* 191 (1988).

⁵¹ EPA (1991), *supra* note 41; Krewski, Murdoch & Withey, *supra* note 47; Gold et al., *supra* note 47 and Food Safety Council, *supra* note 47.

Figure 1
Dose-Response Curve from Carcinogenicity Study



Low-dose extrapolation modeling (sometimes called quantitative risk assessment [QRA] outside the U.S.) has become the backbone of dose-response assessments for carcinogens. Because these statistical models play such a dominant role in the regulatory process, it is useful to understand some of their characteristics. First, the six most routinely used models will usually fit the rodent data in the dose region used in the animal tests.⁵² Second, the different models usually yield very different results at the doses to which humans are exposed, as exemplified below by the analysis of DDT (Figure 2) and methylene chloride.⁵³

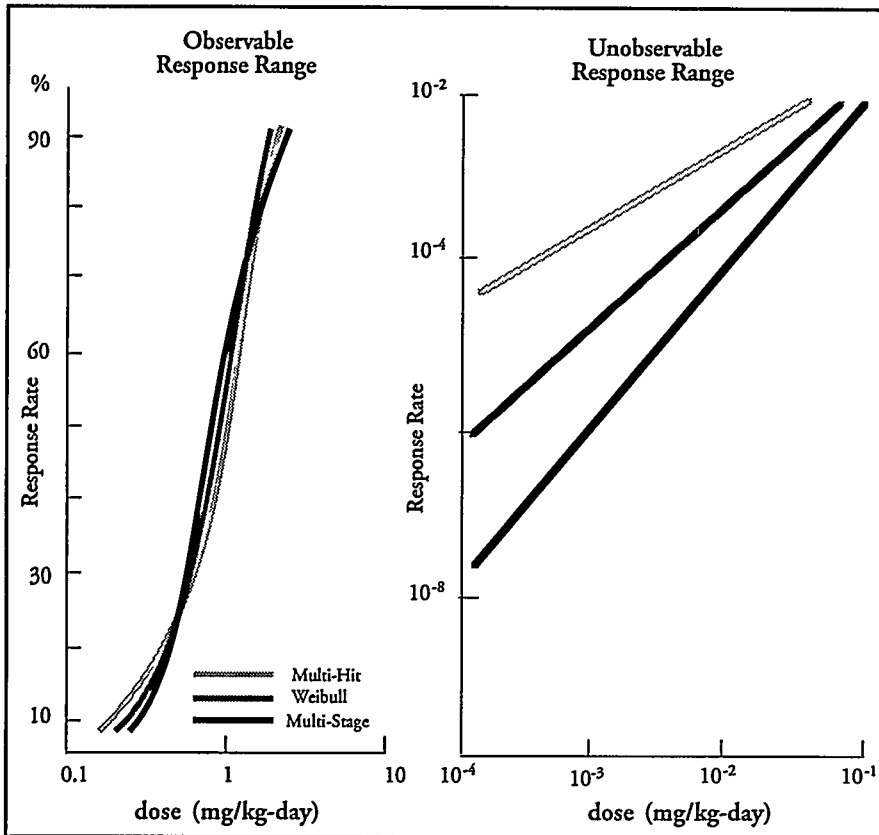
To date, in the U.S. most regulatory approaches for identifying safe or acceptable levels of exposure to air, water and soil contaminants have been based on statistical rather than biologically-based models. As discussed below, the physiologically-based pharmacokinetic (PB-PK) models are the most scientifically rigorous (and likely most valid)

⁵² Krewski, Murdoch & Withey, *supra* note 47 and Food Safety Council, *supra* note 47.

⁵³ Paustenbach, *supra* note 8 and Food Safety Council, *supra* note 47.

models for estimating safe levels of human exposure based on animal data.⁵⁴

Figure 2
Low-Dose Extrapolations for DDT



In the not-so-distant future, it can be expected that much greater weight will be placed on those assessments that attempt to account quantitatively for biological phenomena.⁵⁵ The fit of most dose-

⁵⁴ Anderson and Andersen et al., *supra* note 25; Bois, Zeise & Tozer, *supra* note 25; D'Souza & Boxenbaum, *supra* note 38; Reitz, *supra* note 38; Andersen et al., *supra* note 48; Andersen et al., *supra* note 50 and Paustenbach et al., *supra* note 50.

⁵⁵ Flamm & Lehman-McKeeman, *supra* note 26; Connolly et al., *supra* note 25; Paustenbach et al., *supra* note 50; Orville E. Paynter, G.J. Burin & C.A. Gregorio, *Goitrogens and Thyroid Follicular Cell Neoplasia: Evidence for a Threshold Process*, 8 Regul. Toxicol. Pharm. 102 (1988); Hon-Wing Leung & Dennis J. Paustenbach, The Acceptance of PB-PK Modelling as a Critical Component of Health Risk Assessment (Presented, EPA Workshop on PB-PK models, Savannah, GA 1993; Rory B. Connolly & Melvin E. Andersen, *Biologically-Based Pharmacodynamic Models* (1991); Dennis J., Paustenbach, et al., *Risk Assessment for 2,3,7,8-TCDD Using a Biologically Based Cancer Model: A Reevaluation of the Kociba et al. Bioassay Using*

response models to data in the observable range is generally similar (left plot). Yet, due to the differences in the assumptions and equations upon which the models are based, the risk estimates at low doses (e.g., less than 0.1mg/kg-day) can vary dramatically between them (right plot).

Finally, as shown in Table 2⁵⁶ the results of commonly-used models usually vary in a predictable manner because they use different mathematical equations for predicting the chemical's carcinogenic potency.

Table 2
Estimates of Lifetime Cancer Risk to Humans from Exposures to Methylene Chloride Based on Salivary Gland Region Sarcomas in Male Rats Derived from Four Different Models
(95% Upper Confidence Limit of Additional Risks)

Air Concentration ($\mu\text{g}/\text{m}^3$)	Multistage Model	One-Hit Model	Weibull Model	Log-Probit Model
1	1.8×10^{-7}	2.0×10^{-7}	4.8×10^{-10}	3.5×10^{-31}
10	1.8×10^{-6}	2.0×10^{-6}	1.7×10^{-8}	1.6×10^{-22}
100	1.8×10^{-5}	2.0×10^{-5}	6.1×10^{-6}	2.5×10^{-15}
1,000	1.8×10^{-4}	2.0×10^{-4}	2.0×10^{-5}	1.3×10^{-9}
10,000	1.8×10^{-5}	2.0×10^{-3}	6.1×10^{-4}	2.4×10^{-1}

At most exposures, the one-hit and linearized multi-stage models will predict the highest risk and the probit model will predict the lowest.⁵⁷

It is noteworthy that rodent studies now used to predict the magnitude of human risk were never intended for that purpose.⁵⁸ They were designed to qualitatively identify potential human cancer hazards, not to quantitatively estimate the human risk at low levels of exposure.⁵⁹ As in hazard identification, whenever adherence to strict

1978 and 1990 Histopathology Criteria, 34 J. Toxicol. Environ. Health 11 (1991); James D. Wilson, *Assessment of Low-Exposure from Carcinogens: Implications of the Knudson-Moolgavkar Two-Critical Mutation Theory in Biologically-Based Methods in Cancer Risk Assessment 275* (Curtis C. Travis, ed. 1989) and Corley et al., *supra* note 46.

⁵⁶ EPA, Health Assessment Document for Dichloromethane (Methylene Chloride) (Fin. Rep. 1985).

⁵⁷ Paustenbach, *supra* note 8.

⁵⁸ Barnard, Moolenaar & Stevenson, *supra* note 27; Abelson, *supra* note 39 and Barr, *supra* note 39.

regulatory guidance requires that dose-response assessments must use a single mathematical model, the assessment can become so constrained that valuable biological information (which could dramatically alter the results) is not fully accounted for.⁶⁰

We have now learned a good deal about the biology of cancer, and this information should be considered in the dose-response assessment whenever possible. For example, we now know that there are at least three broad classes of mechanisms by which chemicals may produce a carcinogenic response in rodents: repeated cytotoxicity, promotion and initiation.⁶¹ Some have suggested as many as eight different classes of mechanisms through which chemicals produce tumors.⁶² 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 different than that for an initiator.⁶³ Because at relatively high doses non-genotoxicants may produce repeated cytotoxicity, the primary reason for excessive cell turnover, many scientists expect them to possess a threshold dose below which no cancer hazard would be present.⁶⁴ This is in contrast to genotoxicants or mutagens that may pose some risk, albeit small, at very low doses.

In general, the scientific underpinnings of the dose-response models used for assessing carcinogens are based on our understanding of ionizing radiation and genotoxic chemicals.⁶⁵ Both types of agents may well have a linear, or a nearly linear, response in the low-dose region. However, promoters and cytotoxicants need not have a linear dose-response curve. Scientific data increasingly suggest that promoters and other non-genotoxic agents will have a very non-linear dose-

⁵⁹ Friess, *supra* note 19.

⁶⁰ Paustenbach, *supra* note 17.

⁶¹ Andersen, *supra* note 25; Butterworth, *supra* note 26; Butterworth & Slaga, *supra* note 26 and Williams & Weisburger, *supra* note 28.

⁶² Butterworth, *supra* note 26.

⁶³ Wilson, *supra* note 55; Daniel Krewski, Charles Brown & Duncan Murdoch, *Determining "Safe" Levels of Exposure: Safety Factors or Mathematical Models*, 4 *Fund. Appl. Toxicol.* 383 (1984) and Kirk Kitchin, Janice Brown & R. Woodrow Setzer, *Dose-Response Relationship in Multistage Carcinogenesis: Promoters*, 102 (Supp. 1) *Environ. Health Perspect.* 255 (1994).

⁶⁴ Williams & Weisburger, *supra* note 28.

⁶⁵ David G. Hoel, *Cancer Risk Models for Ionizing Radiation*, 76. *Environ. Health Perspect.* 121 (1987).

response relationship at low doses and, as importantly, probably have a genuine or practical threshold.⁶⁶ The increased acceptance of this postulate is evidenced by EPA's position that the linearized multi-stage model is inappropriate for dioxin,⁶⁷ thyroid type carcinogens,⁶⁸ nitrilotriacetic acid (NTA),⁶⁹ d-limonene⁷⁰ and, presumably, similar non-genotoxic chemicals.

Over the past twenty years, the scientific community has learned at least six ways to improve the way that regulatory agencies in the U.S. have predicted the possible human risk at low levels of exposure to carcinogens (Table 1).

First, we have learned that it is important to identify the best estimates from the cancer models, as well as the upper and lower bounds of the risk.⁷¹ The objective of the bounding techniques is to attempt to account for the statistical uncertainty in the results of the animal tests, however, we have rarely presented the degree of potential conservatism within the bounding procedure.⁷² The problem of not presenting all of the results is that the risk manager will not be fully aware of the breadth of equally plausible risk estimates.⁷³ For example, the cancer risk associated with exposure to chloroform in most U.S. drinking water has been reported to be as high as one in 10,000 using the upper bound risk estimate of the multi-stage model;⁷⁴ however, using the same model, the best or maximum likelihood estimate (MLE) of the risk is about one in 1M and the lower bound estimate is virtually zero (about one in ten million). Therefore, the plausible range of risk is as high as one in 10,000 and as low as zero.

⁶⁶ Williams & Weisburger, *supra* note 28.

⁶⁷ EPA, Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds Vol. I-III (Draft 1994).

⁶⁸ Paynter, Burin & Gregorio, *supra* note 55.

⁶⁹ Anderson & Alden, *supra* note 44.

⁷⁰ Flamm & Lehman-McKeeman, *supra* note 25.

⁷¹ Paustenbach, *supra* note 8.

⁷² Sielken, *supra* note 25 and Robert L. Sielken, *Useful Tools for Evaluating and Presenting More Science in Quantitative Cancer Risk Assessments*, 9 *Tox. Subs. J.* 353 (1989).

⁷³ Thomas E. McKone & Kenneth T. Bogen, *Uncertainties in Health-Risk Assessment: An Integrated Case Study Based on Tetrachloroethylene in California Groundwater*, 15 *Regul. Toxicol. Pharm.* 86 (1992).

⁷⁴ Corley et al., *supra* note 46.

When biological factors are considered, such as its weak genotoxicity and pharmacokinetics, the carcinogenic risk associated with low concentrations of chloroform in chlorinated drinking water is likely to be quite small or negligible.⁷⁵ Yet, as a matter of policy, the risk of one in 10,000 is most cited by regulators and appears in newspapers.

Second, we have learned not to rely on only one mathematical model. There are at least six different models that may need to be considered when estimating the risks at low doses. Each of them can yield results which are plausible, depending on the mechanism of action and pharmacokinetics of the chemical, as well as the characteristics of the dose-response curve.⁷⁶ With better understanding of carcinogenesis and the shortcomings of statistical models, regulators have recently become more willing to consider models that can quantitatively account for chemical-specific mechanisms of action.⁷⁷ However, support for encouraging flexibility in the risk-estimation process has been criticized on the grounds that our knowledge about carcinogenesis is insufficient to regulate in other than a very conservative manner.⁷⁸ The application of Monte Carlo techniques to dose-response assessment and the polling of experts should help resolve some of these philosophical differences in how to establish regulatory goals.

Third, we need to give greater weight to epidemiology studies. It is usually claimed that these studies are almost never as statistically robust as the animal studies and, therefore, are not very useful.⁷⁹ Yet, total acceptance of this assertion is inappropriate because epidemiological studies can, at least, establish the degree of confidence that should be placed in the results of low-dose extrapolation models.⁸⁰ Often, even

⁷⁵ *Id.*

⁷⁶ Sielken, *supra* note 25; Starr & Buck, *supra* note 25 and Anderson & Alden, *supra* note 44.

⁷⁷ Andersen et al., *supra* note 48; Corley et al., *supra* note 46 and EPA, *supra* note 67.

⁷⁸ Silbergeld, *supra* note 18; Fredrica Perera, *The Genotoxic/Epigenetic Distinction: Relevance to Cancer Policy*, 34 *Environ. Res.* 175 (1984) and Fredrica Perera & Pat Boffetta, *Perspectives on Comparing Risks of Environmental Carcinogens*, 80 *J. Natl. Cancer Inst.* 1282 (1988).

⁷⁹ Ellen K. Silbergeld, *Epidemiology versus Risk Assessment: Resolving Some Old Controversies*, 8 *Risk Anal.* 555 (1988).

⁸⁰ Goodman & Wilson, *supra* note 25; Kenny S. Crump, *Correlation of Carcinogenic Potency in Animals and Humans*, 5 *Cell Biol. Toxicol.* 393 (1989); Maxwell Layard & Abe Silvers, *Epidemiology in Environmental Risk Assessment*, in

less-than-perfect epidemiology, coupled with retrospective exposure assessments, can yield much more defensible estimates of likely human health hazards than statistical models based on animal studies. Recent work evaluating benzene furnishes an example.⁸¹

Fourth, we should quantitatively scale up data from rodents to predict the human response. For example, when evaluating most toxicologic effects, statisticians and biologists 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. This approach is usually reasonably accurate for noncarcinogenic effects. In contrast, for carcinogens, several factors need to be considered when trying to predict how humans will respond compared to rodents. First, the biologic half-life between rodents and humans can be expected to be different for virtually all chemicals. 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 the life span.⁸² This may be valid for those chemical carcinogens which require metabolic activation, but may not be very accurate for those carcinogens that do not. Consequently, for regulatory purposes, surface area corrections have been used in an attempt to adjust for the pharmacokinetic differences between rodents and humans. Recent work suggests that body weight

The Risk Assessment of Environmental and Human Health Hazards: A Text Book of Case Studies 157 (D. J. Paustenbach, ed. 1989) and Dennis J. Paustenbach & William J. Butler, Discussion of John D. Graham, "Epidemiology and Risk Assessment: They Aren't Antonyms!" at Federal Focus Conference: The Role of Epidemiology in Regulatory Risk, Annandale VA, Oct. 13-14, 1994.

⁸¹ Dennis J. Paustenbach et al., *Re-Evaluation of Benzene Exposure for the Pliofilm Workers (1939-1976)*, 36 *J. Toxicol. Environ. Health* 177 (1992); Mary B. Paxton et al., *Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution*, 14 *Risk Anal.* 147 (1994); Mary B. Paxton et al., *Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: II. Risk Estimates*, 14 *Risk Anal.* 155 (1994) and Kenny S. Crump, *Risk of Benzene-Induced Leukemia: A Sensitivity Analysis of the Pliofilm Cohort with Additional Follow-up and New Exposure Estimates*, 42 *J. Toxicol. Environ. Health* 219 (1994).

⁸² EPA, *A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of Mg/Kg^{3/4}/Day* (Draft Report), 57 *Fed. Reg.* 24,152 (1992); Curtis C. Travis & Robin K. White, *Interspecies Scaling of Toxicity Data*, 8 *Risk Anal.* 119 (1988); D. A. Freedman & H. Zeisel, *From Mouse to Man: The Quantitative Assessment of Cancer Risk*, 3 *Statist. Sci.* 3 (1988) and Richard H. Reitz, *Quantitating the Production of Biologically Reactive Intermediates in Target Tissues: Example, Dichloromethane in Advances in Experimental Biology and Medicine*, Vol. 283, *Biological Reactive Intermediates IV*, (C. M. Witmer et al., eds. 1991).

to the 2/3 power is the most valid scale-up factor if no compelling information to the contrary is available.⁸³

Table 3
PB-PK Models Have Been Developed for at Least 40
Different, Widely-Used Industrial Chemicals Often Found in the Environment

Benzene	Benzo(α)pyrene
Butoxyethanol	1,3-Butadiene
Carbon Tetrachloride	Chlorfenvinphos
Chloroalkanes	Chloroform
Chloropentafluorobenzene	Cis-Dichlorodiamine Platinum
Dichloroethane	Dichloroethylene
Dichloromethane	Dieldrin
Diisopropylfluorophosphate	Dimethylloxazolidine dione
Dioxane	Ethylene oxide
Hexane	Isoprene
Kepone	Lead
Methanol	Methoxyethanol
Methylethylketone	Nickel
Nicotine	Parathion
Physostigmine	PPBs
PCBs	Styrene
Toluene	TCDF
TCDD	Tetrachloroethylene
Trichloroethane	Trichloroethylene
Trichlorotrifluoroethane	Vinylidene Fluoride
Xylene	

The most promising method for predicting the human response from rodent data is the physiologically-based pharmacokinetic model (PB-PK).⁸⁴ These quantitatively account for the various differences between the test species and humans by considering body weight, metabolic capacity and products, respiration rate, blood flow, fat content and several other parameters.

Figure 3⁸⁵ depicts a physiologically-based pharmacokinetic (PB-PK) model for inhalation exposure to ¹⁴C-carbon tetrachloride.⁸⁶ Such models allow scientists to predict how humans will respond to a

⁸³ EPA, *supra*; Travis & White, *supra* and Allen, Crump & Shipp, *supra* note 27.

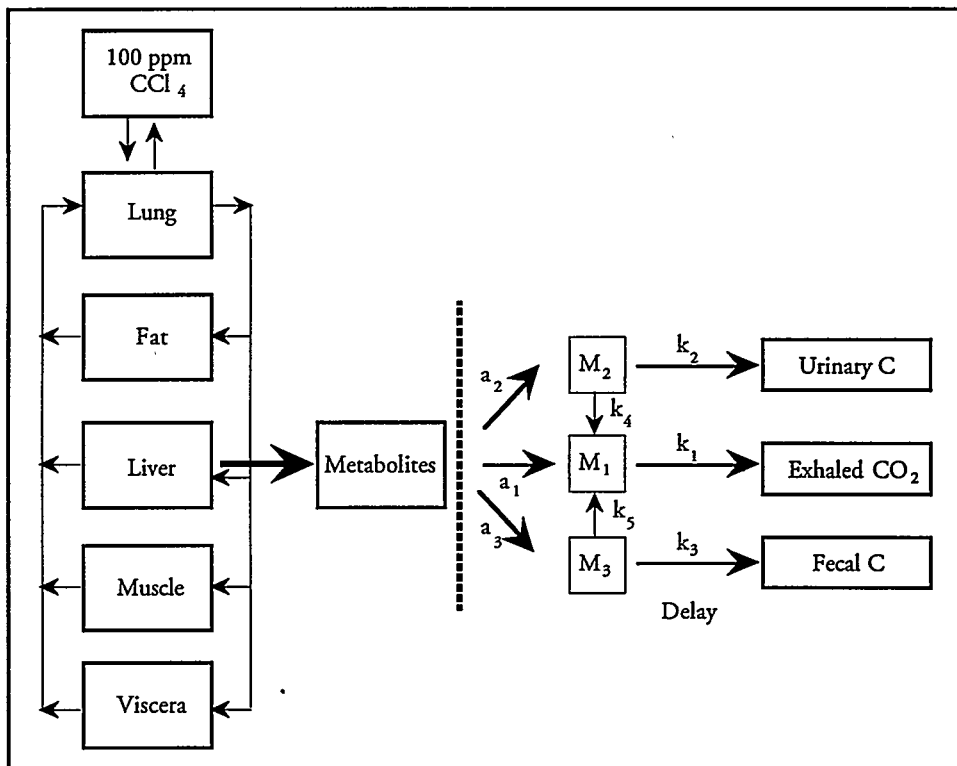
⁸⁴ Andersen, *supra* note 25; Andersen et al., *supra* notes 25, 48 and 50; Paustenbach & Butler, *supra* note 81 and Hon-Wing Leung, *Development and Utilization of Physiologically Based Pharmacokinetic Models for Toxicological Applications*, 32 J. Toxicol. Environ. Health 247 (1991).

⁸⁵ Leung, *supra*.

⁸⁶ Dennis J. Paustenbach, *A Physiologically-Based Description of the Inhalation Pharmacokinetics of Carbon Tetrachloride*, 96 Toxicol. Appl. Pharm. 191 (1986).

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. If the rodent data tracks a chemical's behavior in humans, one can be confident that the model can quantitatively predict the human response at several different doses.

Figure 3
A PB-PK Model for Inhalation Exposure to $^{14}\text{C}\text{-Cl}_4$



This methodology has only been used by toxicologists since about 1984 but became widely accepted by 1991. Although the results of PB-PK models often rely on some frequently untestable assumptions such as the delivered dose of an unstable metabolite to a target organ, it represents one of the most important advances in toxicology and health risk assessment of the past 50 years. The variability in predicting the results in humans based exclusively on the animal data can be significant and some of these have been evaluated.⁸⁷ To date, PB-PK

⁸⁷ Christopher J. Portier & M. L. Kaplan, *The Variability of Safe Dose Estimates*

models have been developed and validated for carbon tetrachloride, styrene, methylene chloride, chloroform, trichloroethane, dioxane, tetrachlorodibenzo-p-furan, tetrachlorodibenzo-p-dioxin (TCDD), benzene, trichloroethylene, vinyl chloride, and others (Table 2). The benefits of this approach have been so impressive that two major symposia have been held to encourage its use; one by the National Academy of Science (NAS)⁸⁸ and the other by the EPA in 1993.⁸⁹

The fifth, and possibly most important, lesson we have learned is that low-dose models are useful for ranking classes of carcinogens objectively, but they should not be expected to precisely predict the cancer risk because they cannot account for biological information such as the mechanism of action, types of tumor, differences among species, metabolism and genotoxicity. Perhaps the most promising approach to incorporating biologic factors into cancer risk estimates is the use of biologically-based models such as the one by Moolgavkar-Knudson-Venzon (MKV).⁹⁰ This model accounts for the number of mutations required for malignancy and the role of target cell birth and death processes associated with these mutations. A key element is a quantitative description of how the carcinogen affects the cellular birth, death and mutation rates. Unfortunately, because most of the information needed to perform these analyses is not yet available, and may not be measurable, it holds limited promise in the near future.

Sixth, experience has shown that EPA-recommended cancer models often do not respond to the characteristics of the dose-response curve. As discussed by Sielken,⁹¹ it does not seem appropriate to base important regulatory decisions on the results of models which are minimally "responsive" to the very costly information collected in

When Using Complicated Models of the Carcinogenic Process: A Case Study — Methylene Chloride, 13 *Fund. Appl. Tox.* 533 (1989); Harvey J. Clewell, Tze-San Lee & R.L. Carpenter, *Sensitivity of Physiologically-Based Pharmacokinetics Models to Variation in Model Parameters: Methylene Chloride*, 14 *Risk Anal.* 533 (1994) and Daniel Krewski, Duncan J. Murdock & James R. Withey, *The Application of Pharmacokinetic Data in Carcinogenic Risk Assessment, Pharmacokinetics in Risk Assessment* (1987), Vol. VIII in the series *Drinking Water and Health*.

⁸⁸ Krewski, *supra*.

⁸⁹ Leung & Paustenbach, *supra* note 55.

⁹⁰ Moolgavkar, Dewanji & Venzon, *supra* note 26 and Suresh H. Moolgavkar & Alfred G. Knudson, *Mutation and Cancer: A Model for Human Carcinogenesis*, 66 *J. Natl. Cancer Inst.* 1037 (1981).

⁹¹ Sielken, *supra* note 25 and Sielken, *supra* note 72.

standard lifetime rodent studies. Another way to look at this is to understand the fragility or sturdiness of these models not only when interpreting bioassay data, but also when selecting the dosing regimen to be used in future bioassays. If one conducts only one statistical test to select the form of the model, this limits the ability to learn as much as possible from rodent data. A way to avoid this problem is to conduct simulations of the model's responsiveness to alternative, but similar, data sets to ensure that the extrapolation is reasonable.⁹² As shown by Reith and Starr,⁹³ the potential range of tumor incidences that may be analyzed with the multistage model are restricted by the experimental design (specifically, by numbers of doses and animals) of the bioassay; this in turn limits the possible values of carcinogenic potency that can arise. This needs to be considered when selecting the doses to be used in bioassays.

Exposure Assessment

Of the four portions of a risk assessment, exposure assessment has made the biggest improvement in quality over the history of health risk assessment.⁹⁴ In general, exposure assessment should contain less uncertainty than other steps in risk assessment. Admittedly, a large number of factors need to be considered when estimating exposure, and it is a complicated procedure to understand the transport and distribution of a chemical after release into the environment.⁹⁵ Nonetheless, available data indicate that scientists can do an adequate job of quantifying the concentration of chemicals in various media and resulting uptake by exposed persons if they account for all factors that

⁹² Sielken, *supra* note 25.

⁹³ James P. Reith & Thomas B. Starr, *Experimental Design Constraints on Carcinogenic Potency Estimates*, 27 *J. Toxicol. Environ. Health* 287 (1989) and James P. Reith & Thomas B. Starr, *Chronic Bioassays: Relevance to Quantitative Risk Assessment of Carcinogens*, 10 *Regul. Toxicol. Pharm.* 160 (1989).

⁹⁴ Paustenbach *supra* note 1, Finley & Paustenbach, *supra* note 17; Finley et al., *supra* note 17 and Brent L. Finley, Paul Scott & Dennis J. Paustenbach, *Evaluating the Adequacy of Maximum Contaminant Levels as Health Prospective Cleanup Goals: An Analysis Based on Monte Carlo Techniques*, 18 *Regul. Toxicol. Pharm.* 438 (1993).

⁹⁵ George F. Fries & Dennis J. Paustenbach, *Evaluation of Potential Transmission of 2,3,7,8-Tetrachlorodibenzo-p-dioxin-Contaminated Incinerator Emissions to Humans via Foods*, 29 *Toxicol. Environ. Health* 1 (1990) and Thomas E. McKone, *Human Exposure to Chemicals from Multiple Media and Through Multiple Pathways: Research Overview and Comments*, 11 *Risk Anal.* 5 (1991).

should be considered.⁹⁶ For some chemicals, the actual uptake by exposed persons need not be estimated; they can often be measured directly in body fluids, excrement or hair.⁹⁷

The primary routes of exposure to chemicals in the environment are inhalation of dusts and vapors, dermal contact with contaminated soils or dusts, and ingestion of contaminated foods, water or soil.⁹⁸ Initial efforts to quantitatively estimate the uptake of environmental contaminants by humans were first conducted by scientists in the field of radiological health⁹⁹ and their work can be a source of valuable information when conducting assessments of chemical contaminants. Numerous methodologies for estimating the human uptake of contaminants have been proposed and refined in recent years.¹⁰⁰

We have learned at least eleven rather significant lessons about conducting exposure assessments that can immediately be adopted elsewhere. These could potentially save other nations hundreds of millions of dollars and thousands of person-years of work (Table 1).

First, U.S. experience has shown that in attempts to be prudent, we have overemphasized the "maximally exposed individual" (MEI).¹⁰¹

⁹⁶ T. Lavy, J. Shepard & D. Bouchard, *Field Worker Exposure and Helicopter Spray Pattern of 2,4,5-T*, 24 *Bull. Environ. Contam. Toxicol.* 90 (1980) and T. Lavy et al., *(2,4-Dichlorophenoxy)Acetic Acid Exposure Received By Aerial Application Crews During Forest Spray Operations*, 30 *J. Agric. Food Chem.* 375 (1982).

⁹⁷ Adrian Lynch, *Methods in Biological Monitoring* (1987).

⁹⁸ Fries & Paustenbach, *supra* note 95; McKone, *supra* note 95; Renate D. Kimbrough et al., *Health Implications of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Contamination of Residential Soil*, 14 *J. Toxicol. Environ. Health* 47 (1984); Alan E. Eschenroeder et al., *Health Risk Analysis of Human Exposures to Soil Amended With Sewage Sludge Contaminated With Polychlorinated Dibenzodioxins and Dibenzofurans*, 28 *Vet. Hum. Toxicol.* 435 (1986) and Dennis J. Paustenbach et al., *An Assessment and Quantitative Uncertainty Analysis of the Health Risks to Workers Exposed to Chromium Contaminated Soils*, 7 *Toxicol. Ind. Health* 159 (1991).

⁹⁹ E. M. Romney et al., *Contamination of Plant Foliage with Radioactive Nuclides*, 14 *Ann. Rev. Plant Physiol.* 271 (1963); W. E. Martin, *Loss of Sr-90, Sr-89 and I-131 from Fallout of Contaminated Plants*, 4 *Radiat. Bot.* 275 (1964); R. S. Russell, *Entry of Radioactive Materials into Plants*, in *Radioactivity and Human Diet*, Ch. 5 (R.S. Russell, ed. 1966); C. F. Baes III et al., *A Review and Analysis of Parameters for Assessing Transport of Environmental Released Radionuclides Through Agriculture* (1984) and EPA, *Assessing Exposure to Dioxin-like Compounds* (1993).

¹⁰⁰ Finley et al., *supra* note 17; Paustenbach et al., *supra* note 98; Thomas E. McKone & Jeffrey I. Daniels, *Estimating Human Exposure Through Multiple Pathways from Air, Water, and Soil*, 13 *Reg. Toxicol. Pharm.* 36 (1991) and California Environmental Protection Agency, *The Caltox Program* (1994).

¹⁰¹ Nichols & Zeckhauser, *supra* note 17; Daniel Maxim, *Problems Associated*

Often, the results of these analyses were misinterpreted by the public and/or misrepresented by some scientists or lawyers. For example, some assessments addressed only risks to the MEI. Yet, that the risk may affect only the 99.5th or 99.9th percentile of all exposed populations was rarely stated. Current EPA exposure guidelines and NAS guidance acknowledge this deficiency and note that a worst-case or MEI analysis should be used only to decide if an exposure is insignificant and should not be used to characterize the actual or plausible human risks. In short, most MEI analyses should only be used in screening assessments, although some have noted that so-called "reasonable" person assessments often don't present the full picture.¹⁰²

Second, as we have learned to characterize accurately the risks of exposure for about 95% of the population, more emphasis has been placed on evaluating various special groups (e.g., Eskimos, subsistence fisherman, dairy farmers), who can be exposed to particularly high doses (the 95%-99.9% group). Although the risk for these populations needs to be understood, the typical levels of exposure for the majority of exposed individuals should be the initial focus of most risk assessments. For example, if a regulatory agency bases its decision on the results of an assessment of persons who eat about 100g of freshwater fish every day (99th percentile), yet the average American eats only 18g of fish per day (lifetime average), the analysis should reflect the fact that 99 of 100 persons are not represented by the corresponding risk estimate. To help minimize the potential for misunderstanding, it is important to describe the number of exposed persons at each anticipated dose level, along with the most likely and upper estimates of exposure and the associated plausible risk.¹⁰³ With this information, risk managers can decide whether large or small sums of money are warranted to reduce the health hazard.¹⁰⁴

with the Use of Conservative Assumptions in Exposure & Risk Analysis, in *The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies* 525 (D. J. Paustenbach, ed. 1989); Finley & Paustenbach, *supra* note 17; Hawkins, *supra* note 17; Copeland et al., *supra* note 17 and Barnard Goldstein, *The Problem with the Margin of Safety: Toward the Concept of Protection*, 10 *Risk Anal.* 7 (1990).

¹⁰² Adam M. Finkel, *Is Risk Assessment Really Too Conservative? Revising the Revisionists*, 14 *Colum. J. Environ. L.* 427 (1989).

¹⁰³ Paustenbach, *supra* note 17 and Betsy Ruffle et al., *Lognormal Distributions for Fish Consumption by the General U.S. Population*, 14 *Risk Anal.* 395 (1994).

Third, don't allow the repeated use of conservative assumptions to dictate assessment results. In recent years, several investigators have discussed this issue and have demonstrated its importance.¹⁰⁵ The problem can be illustrated by one assessment of the dioxin hazard posed by municipal waste incinerators. Before deciding to issue a permit, the EPA conducted a screening level assessment, evaluating the theoretical cancer risk for a child who lived within a short distance (0.8 KM) from the hypothetical incinerator. They assumed that a child could eat as much as about one small spoonful of dirt each day, that his house was down-wind of the stack, that he ate fish from a pond near the incinerator, that his fish consumption was at the 95th percentile level, that he drank contaminated water from the pond, that he ate food grown primarily from the family garden, and that he drank milk from a cow which grazed on forage at the farm. Not surprisingly, it was predicted that siting the incinerator could plausibly increase the child's lifetime cancer risk (if he lived there for 70 years) by one in 100; but he could hardly be portrayed as a typical person living near a municipal incinerator. Regrettably, the associated upper-estimate of the risk was the only one reported by the press. Certainly, it would have been more appropriate to have studied and presented the number of persons likely to be exposed to this amount of contaminant, 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 most incinerators since operators try to minimize transportation costs from urban areas.

Fourth, in exposure assessment the problems associated with the repeated use of overly conservative assumptions and the need to properly account for small (but highly exposed) populations can now be overcome with Monte Carlo techniques.¹⁰⁶ The probabilistic or Monte

¹⁰⁴ Breyer, *supra* note 19; Graham, *supra* note 22 and Richard Wilson & W. Clark, *Risk Assessment and Risk Management: Their Separation Should not Mean Divorce in Risk Analysis* 187 (C. Zervos, ed. 1991).

¹⁰⁵ Nichols & Zeckhauser, *supra* note 17; Maxim, *supra* note 101; Finley & Paustenbach, *supra* note 17; Hawkins, *supra* note 17, Copeland et al., *supra* note 17; Burmaster & von Stackelberg, *supra* note 25 and McKone & Bogen, *supra* note 73.

¹⁰⁶ Finley et al., *supra* note 17; Copeland et al. (1993 and 1994), *supra* note 17; Moolgavkar, Dewanji & Venzon, *supra* note 25 and Kimberly M. Thompson, David E. Burmaster & Edmund A.C. Crouch, *Monte Carlo Techniques for Quantitative*

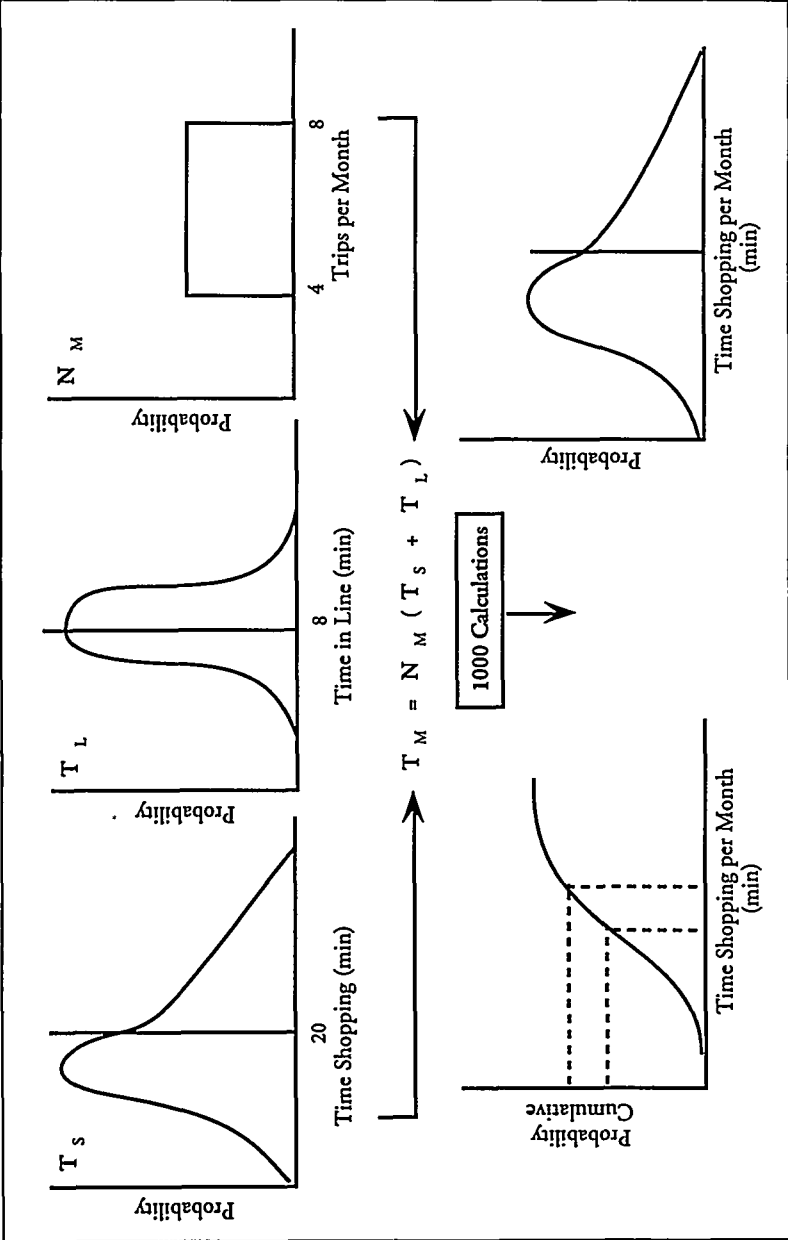
Carlo technique addresses the main deficiencies of the point estimate approach because it imparts a great deal more information to the risk manager.

Figure 4 illustrates how a Monte Carlo analysis is applied to understand the distribution of time needed to go shopping based on the three activities involved in shopping. Time spent shopping each month (minutes) is estimated by the product of two parameters: the number of trips per month and the total time spent in the store (minutes). Total time spent in the store is the sum of time spent shopping and time spent in line. Using Monte Carlo techniques, a distribution of likely values is associated with each of these parameters. These distributions are dependent upon the detail of information available to characterize each parameter. For example, the distribution compares all of the information such as those days when the line at the check-out counter is short, as well as those when it's long. It is noteworthy that each parameter has a different distribution: log-normal, gaussian, and square. Total time spent shopping is then calculated repeatedly by combining parameter values that are randomly selected from these distributions. The result is a distribution of likely time spent shopping each month. Using this technique, information concerning each parameter is carried along to the final estimate.

Instead of presenting a single point estimate of risk, probabilistic analyses characterize a range of potential risks and their likelihood of occurrence. In addition, those factors which most affect the results can be easily identified. For example, in a probabilistic analysis, one can present the risk manager with the following type of statement:

The plausible increased cancer risks for the 50th, 95th, and 99th percentiles of the exposed population are 1×10^{-8} , 5×10^{-7} and 1×10^{-6} , respectively. However, if there was to be a fishing ban on catfish and other bottom feeders, the risks for the 50th, 95th, and 99th percentile groups would drop by 100-fold.

Figure 4
Time per Month Spent Grocery Shopping



Fifth, risk managers and the public want to know the statistical confidence in risk estimates. Sensitivity analyses can yield important information about critical exposure variables;¹⁰⁷ e.g., we can now state:

Our understanding of the concentration of DDT in the edible portion of smallmouth bass, is based on high quality, reliable data; therefore, our confidence in the risk estimates is high. Our analysis indicates a 95% level of confidence that 90% of the increased cancer risk could be eliminated by a ban on catching carp or catfish in the river and that little additional risk reduction would be achieved if bass and trout fishing were also banned.

This type of characterization provides the kind of information risk managers need to make informed decisions regarding the necessary magnitude of response, the cost/benefit of particular decisions, and whether a range of risk-reduction alternatives should be considered.

We have also refined our approach to conducting statistical analyses of environmental data (lesson six). For example, we now see the importance of accounting for the log-normal and truncated distributions. As has been shown repeatedly, most environmental and occupational data are log-normally distributed rather than conform to a gaussian distribution,¹⁰⁸ but few environmental scientists were aware of the significance until recently. As noted in the recently proposed EPA guidelines for exposure assessment, inappropriate statistical analysis of environmental data is one of the most easily corrected of the common errors in exposure analysis.¹⁰⁹

Seventh, we have improved techniques for statistically handling samples having no detectable amount of contaminants.¹¹⁰ Frequently, agencies have used the limit of detection (LOD) in exposure

¹⁰⁷ Steve M. Rappaport & James Selvin, *A Method for Evaluating the Mean Exposure from a Log-Normal Distribution*, 48 *Am. Ind. Hyg. Assoc. J.* 374 (1987); Richard O. Gilbert, *Statistical Methods for Environmental Pollution Monitoring* (1987); Curtis C. Travis, Miriam L. Land & Holly Hattemer-Frey, *Estimating the Mean of Data Sets with Nondetectable Values*, 24 *Environ. Sci. Technol.* 961 (1990) and Charles N. Haas & Peter A. Scheff, *Estimation of Averages in Truncated Samples*, 24 *Environ. Sci. Technol.* 912 (1990).

¹⁰⁸ See references, *supra* and T. B. Parkin et al., *Evaluation of Statistical Estimation Methods for Lognormally Distributed Variables*, 52 *Soil Sci. J.* 323 (1988).

¹⁰⁹ EPA, *Guidelines for Exposure Assessment*, 57 *Fed. Reg.* 22888 (1992).

¹¹⁰ Travis, Land & Hattemer-Frey, *supra* note 107.

calculations on the premise that the contaminant might be present at that level. Many agencies have suggested that 50% of the LOD should be used to calculate the plausible degree of human exposure when no detectable amount is identified; others have suggested that the LOD divided by the square root of two, and other much more complex approaches have been recommended. In short, when such approaches are used on a site that may only be 2–10% contaminated (based on surface area) the impact of a few samples on the calculated average level of contamination will be much higher than what is likely to be present across the site unless proper statistical methods are applied. Several approaches have been suggested to help avoid this problem.¹¹¹

Eighth, we need to account for the environmental fate of chemicals. Many factors such as degradation by sunlight, soil and water microbes, and evaporation can dramatically influence the degree of human exposure. Yet, many assessments have frequently assumed concentrations measured today will exist and remain constant for 30–50 years.¹¹² For instance, the public health hazard posed by the potential release of dioxin vapors from incinerators was recently evaluated. After it was alleged that the vapors posed a serious health hazard to surrounding residents, a risk assessment was conducted. Yet, the environmental half-life of dioxin (as a vapor) proved to be critical because it has a half-life of only 90 minutes. In contrast, TCDD in deep soil, fly-ash or sediment may have an environmental half-life of 50–500 years. What had been portrayed as a potentially serious health hazard was shown to be insignificant, given its photolytic half-life.¹¹³

Ninth, we have recognized the need to validate exposure assumptions or model estimates by using field measurements. Although past sampling and analytical procedures were inadequate to measure the low concentrations of toxicants found in the environment, better ones are now available. As field measurement techniques are further refined,

¹¹¹ N. Cressie, *Statistics for Spatial Data* (Revised 1993) and J. D. Istok, J. D. Smyth, & A. L. Flint, *Multivariate Geostatistical Analysis of Groundwater Contamination: A Case History*, 31 *Groundwater* 63 (1993).

¹¹² Maxim, *supra* note 101; Dennis J. Paustenbach et al., *The Potential Inhalation Hazard Posed by Dioxin-Contaminated Soil*, 41 *J. Air. Waste Mgt. Assn.* 1334 (1991) and Edward J. Calabrese & Paul T. Kostecki, *Risk Assessment and Environmental Fate Methodologies* (1992).

¹¹³ Paustenbach et al., *supra*.

less reliance should be placed on mathematical models for predicting chemical distributions in the environment, and more confidence should be placed on environmental samples.¹¹⁴

Tenth, and perhaps the most significant advance in exposure assessment of airborne contaminants, is recognition of the need to account for indirect exposure pathways. For example, the uptake of a contaminant in water by direct ingestion is obvious, but uptake of the same contaminant from watering garden vegetables or inhaling volatiles while showering have not always been evaluated.¹¹⁵ When regulating airborne nonvolatiles, the most important indirect route of exposure, not considered before 1986, may be ingestion of particulates deposited on plants subsequently eaten by grazing animals.¹¹⁶ The ingestion of the meat and milk from these animals can produce, depending on the chemical and conditions, risks 50–200 fold greater than that from inhalation.¹¹⁷ Methods for estimating uptake through virtually all indirect routes have been developed and continue to be refined.¹¹⁸

Finally, whenever possible one should use biological monitoring to confirm predicted human exposures. Over the past five to ten years, analytical chemists can increasingly detect very small quantities of dozens of chemicals in the blood, urine, hair, feces, breath and fat of exposed persons. Measuring parts per trillion and part per quadrillion is now possible. For many chemicals, this represents a direct indicator of recent exposure, and in some cases like PCBs and dioxins, chronic exposure. For example, the uptake of dioxin by Vietnam veterans exposed to 2,4,5-T 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

¹¹⁴ Calabrese & Kostecki, *supra* note 112.

¹¹⁵ James Byard, *Hazard Assessment of 1,1,1-Trichloroethane in Groundwater*, in *The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies* 331 (D. J. Paustenbach, ed. 1989) and Wan C. Jo, Clifford P. Weisel & Paul J. Lioy, *Routes of Chloroform Exposure and Body Burden from Showering with Chlorinated Water*, 10 *Risk Anal.* 575 (1990).

¹¹⁶ Fries & Paustenbach, *supra* note 95.

¹¹⁷ *Id.* and James B. Stevens & Elizabeth N. Gerbec, *Dioxin in the Agricultural Food Chain*, 8 *Risk Anal.* 329 (1988).

¹¹⁸ McKone & Daniels, *supra* note 100; Copeland et al (1994), *supra* note 17; Fries & Paustenbach, *supra* note 95; and California Air Pollution Control Offices Association, *Handbook* (1990).

to conclude that the vast majority of veterans had only a modest degree of exposure to a chemical alleged to produce numerous adverse health effects in field soldiers.¹¹⁹

Risk Characterization

Characterizing risk has consistently been the weakest part of risk assessments because it requires assessors to draw on many aspects of science and regulatory policy to describe specific human health hazards.¹²⁰ Thorough characterization of chemicals should discuss background environmental and human tissue concentrations, pharmacokinetic differences between test animals and humans, the impact of using a PB-PK or biologically-based model, the effect of selecting specific exposure parameters, uncertainty and statistical sensitivity analyses and other factors

A first-rate risk characterization now offers numerous opportunities to describe the "big picture." It has become generally accepted in the U.S. that theoretical increases in cancer risk of one in 1M or even one in 10,000 from exposure to an environmental contaminant should not be depicted as a serious health risk.¹²¹ Risks predicted in most assessments are usually the upper, not the best, estimate of risk. It has been recommended that every assessment should state that risk estimates represent an upper bound of plausible risk (when appropriate), are unlikely to underestimate risk, and that actual risk may be much lower, even zero.¹²² In short, it is important to communicate that conservative procedures and models are likely to overestimate human risk.¹²³ Yet, if risks may be underestimated, this, too, needs to be stated.¹²⁴

¹¹⁹ Larry Needham, *Serum 2,3,7,8-Tetrachlorodibenzo-p-dioxin Levels in U.S. Army Vietnam-Era Veterans: CDC Veterans Health Studies*, 260 J. AMA 1249 (1988) and William H. Wolfe et al., *Determinants of TCDD Half-Life in Veterans of Operation "Ranch Hand"*, 41 J. Toxicol. Env. Health 481 (1994).

¹²⁰ Paustenbach, *supra* note 17.

¹²¹ Curtis C. Travis et al., *Cancer Risk Management: A Review of 132 Federal Regulatory Decisions to Files*, 21 Environ. Sci. Technol. 415 (1987) and Curtis C. Travis & Holly A. Hattemer-Frey, *Determining Acceptable Levels of Risk*, 22 Environ. Sci. Technol. 873 (1988).

¹²² EPA, Cincinnati Office of Environmental Assessment, *Health Assessment Document for Trichloroethylene* (1982).

¹²³ Thomas E. McKone & Kenneth T. Bogen, *Predicting the Uncertainties in Risk Assessment*, 25 Environ. Sci. Technol. 16 (1991) and Copeland et al. (1994), *supra* note 17.

¹²⁴ Finkel, *supra* note 102; Wilson & Clark, *supra* note 104; David Farrar et al.,

Second, we have learned to account for background contaminant levels.¹²⁵ In assessments of the 1970's and 1980's, risks from natural and/or background levels likely to have influenced risk managers were often overlooked. For example, in a preliminary decision regarding the necessary level of clean-up at a Superfund site in a rural community, the state agency suggested that soil levels of a cyclodiene be reduced to 10 ppm — to keep the theoretical cancer risk below one in 1M. However, the administrator decided not to require remediation when it was recognized that the background levels of some cyclodienes in many areas in the U.S. exceed 50 ppm and that no adverse health effects had been observed or suspected.¹²⁶

Third, and perhaps most interesting, we learned during early years of the environmental movement that the hazard may not always be as it appears. For example, at several sites where large sums of money were used to remove lead- or PCB-contaminated soil, there was no decrease in the blood levels of these contaminants in local children or adults.¹²⁷ How could this be? As we have since learned, a primary route of uptake is through the dust in the home which has been transferred from the soil via tracking or deposition of airborne particulate. Thus, cleaning homes is often more effective in reducing the health risks than removing the contaminated soil from the community; and certainly one must accompany the other. In many locations, this type of rather simple but practical solution may be the only financially plausible one for dealing with soil contaminated by persistent chemicals. Thus only paving over contaminated soil (like mine waste that covers hundreds of acres) and then conducting a thorough cleaning of the homes may be a reasonable, although temporary, approach to bringing about a rapid decrease in the health risk.

Evaluation of Uncertainty in Input Parameters to Pharmacokinetic Models and the Resulting Uncertainty in Output, 49 *Toxicol. Lett.* 371 (1989); Adam M. Finkel, *A Quantitative Estimate of the Extent of Human Susceptibility to Cancer and Its Implications for Risk Management* (1994) and Barry Commoner, *The Hazards of Risk Assessment*, 14 *Colum. J. Environ. L.* 365 (1990).

¹²⁵ Brent L. Finley & Dennis J. Paustenbach, *Using Risk Assessment to Design Cost-Effective Remedial Investigation: A Case Study*, 5 *Econ.* 57 (1990) and R. L. Bornschein et al., *Lead in Soil: Issues and Guidelines* (B.E. Davies and B.G. Wixson, eds. 1988).

¹²⁶ Finley & Paustenbach, *supra*.

¹²⁷ Bornschein et al., *supra* note 125.

Fourth, we have learned that the significance of model-estimated cancer risks needs to be communicated thoroughly and understandably. For example, the goal of some standards, such as the maximum contaminant levels (MCLs) for drinking water, is to keep the maximum plausible cancer risk between one in 100,000 and one in 1M. However, it might be useful to note that about 30% of all Americans will develop cancer and about 25% will eventually die from it. Accordingly, a 1×10^{-6} risk is equivalent to ensuring that the lifetime cancer risk for persons exposed to this level of contamination will be no greater than 250,001 in 1M (25.0001%), rather than the background rate of 250,000 in 1M (25%). If society demands this standard of care, that is its choice. However, both society and its risk managers should understand the relative magnitude of various risks before deciding to spend money on one hazard over another. As recently noted by Gough,¹²⁸ even if the EPA were to regulate all carcinogens in air, soil and water at levels generally considered insignificant, the decrease in cancer incidence in the U.S. would probably be only about 0.25% to 1.3% of the annual cancer mortality.

Fifth, since the late 1980's, risk characterizations have been found much more useful if they contain cost/benefit analyses. In general, the public and its elected officials want to know, for each dollar spent, how much risks are apt to be reduced for various portions of the population. Most risk scholars and managers believe that such analyses are the primary justification for performing risk assessments.¹²⁹ For these applications the use of Monte Carlo techniques has been invaluable.

Sixth, we now recognize that the hallmark of a good risk characterization is a discussion of the uncertainties in the risk estimates. Since 1990, many improvements have been made concerning how to conduct quantitative, rather than qualitative, uncertainty analyses and how to present them.¹³⁰ The key element of these analyses is a statistical evaluation of each of the various parameters and the

¹²⁸ Gough, *supra* note 22.

¹²⁹ Wildavsky, *supra* note 19; Dwight D. Briggs & Lester B. Lave, *Regulating Coke Oven Emissions, in Quantitative Risk Assessment in Regulation* ch. 5 (Lester B. Lave, ed. 1982).

¹³⁰ Finley et al., *supra* note 17; McKone & Bogen, *supra* note 73 and M. Granger Morgan & Max Henrion, *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis* (1990).

implication with respect to the risk estimate for various segments of the population. Although at first blush this may sound like a scientific nuance, the public and the courts now insist on understanding the level of confidence in risk predictions.

A key trait of a high-quality risk characterization is the accurate and unbiased discussion of our confidence in the risk estimates. Often, regulatory agencies and the press have erroneously stated or implied that the results of low-dose models actually predict the increased cancer risk for exposed individuals. As noted previously, because statistical models cannot account for all biological mechanisms (including repair), they cannot accurately predict the actual cancer risk. As discussed by Dr. Frank Young, a former FDA Commissioner, risk estimates should not be portrayed as anything more than relative indicators of risk.¹³¹ He noted, for example, that when the FDA uses the risk level of one in 1M, it is confident that the risk to humans is virtually nonexistent, rather than one in 1M exposed persons is likely to develop cancer.¹³² As noted by Finkel, risk scholars and policy makers have rarely used model-derived estimates to predict the incidence of cancer but rather only as a risk-ranking tool.

Although the U.S. may well have spent a large fraction of its environmental monies over the past twenty years attacking problems which were of modest importance, and many of the decisions were influenced by the poor quality of risk characterizations, this level of regulatory activity clearly raised public awareness. Much of their concern however, focussed on the possibility that exposure to industrial chemicals might increase the cancer risk and the public had been convinced by many scientists that there was "no safe level of exposure" to a carcinogen. To most toxicologists, the public's anxiety about exposure to very low concentrations (e.g., doses) of carcinogens was generally greater than it needed to be, nonetheless these concerns fueled the fire to pass more regulations. Fortunately, a significant amount of work has been invested by researchers in an attempt to improve the way we characterize risk so that decision making is likely to be more reasoned in the future. One issue over which we have argued was how to define the word "safe" when talking about exposure to carcinogens.

¹³¹ Young, *supra* note 9.

¹³² *Id.*

A very recent paper appears to do a good job at describing what most people would agree was a "safe" level of exposure or what would constitute "acceptable risk." The authors suggest that if dose is portrayed in units of molecules of exposure, then it would be easier to identify at what dose a cancer risk can be considered "safe." The authors discuss the potent animal carcinogen dioxin (TCDD) in their paper:¹³³

The probability of developing cancer with exposure to one molecule of 2,3,7,8-TCDD a day over a lifetime is calculated by the upper bound EPA approach to be less than 2×10^{-15} . Given the astronomical numbers of cells and molecules that exist in the human body and the myriad of factors that could prevent a single interaction of a carcinogen molecule with a strand of DNA from ultimately creating a tumor, it is not surprising that we should calculate an extremely small risk for such an infinitesimally small level of exposure.

To empower individuals to decide if a "safe" level exists it is instructive to explore the dimensions of this calculated risk for the smallest possible indivisible daily dose. Using the calculated risk value and assuming similar lifetime exposure to 2,3,7,8-TCDD for the entire current population of the world indicates that there would be less than 1 in a 100,000 chance of even a single case of cancer arising from that infinitesimal level of exposure. From another perspective, the calculated risk value indicates that all humans who have ever lived on the planet could have been exposed at this infinitesimal level without ever producing a single case of cancer in the history of the human race.

This analysis does not attempt to consider the current levels of exposure to 2,3,7,8-TCDD nor to evaluate what risk levels may be associated with those particular human exposure levels because different mechanisms likely apply. Furthermore, this calculation for a hypothetical infinitesimal exposure neither supports nor refutes arguments on the contentious issues surrounding the human health significance of 2,3,7,8-TCDD as an environmental contaminant. However, it does illustrate that there is a

¹³³ Steve E. Hrudey and Daniel Krewski, *Is There a Safe Level of Exposure to a Carcinogen?* *Envir. Sci & Technol.* (in press 1995).

quantifiable low level of exposure, which most reasonable individuals would likely find to be below their own worry threshold.[Note omitted.]

Hopefully, this kind of common sense analysis will be instrumental in demystifying the science issues surrounding risk assessment which should, in turn, help us improve our environmental decision making.

Alternative Approaches to Health Risk Assessment

Some environmentalists and politicians have questioned the acceptability of risk assessment as a policy tool. The reason is that the mere use of risk assessment is considered an admission that a certain amount of risk is acceptable, while the imposition of any risk is unlawful under certain statutes and unethical in many circumstances.¹³⁴ This issue has been difficult for policy makers to refute, but it assumes enough discretionary monies are available to eliminate most risks, including those from unwanted man-made chemicals. Perhaps the key point raised by the environmental community is that alternatives to risk assessment are worthy of continued discussion.

One alternative is technology-based approaches. This has, in fact, been adopted in the 1992 Amendments to the U.S. Clean Air Act. Another is to ban substances or legislate prohibitions on industrial chemical emissions. Both approaches rely exclusively on hazard identification and are very dependent on the skills of analytical chemists since any measurable quantity could initiate action. In support of this approach, some have argued that bans are the only successful means to significantly reduce environmental risks.¹³⁵ Bans on the chemicals DDT, PCB and lead in gasoline are often identified as major success stories.

A third alternative to risk assessment, that appeals to some environmentalist groups, is to adopt simpler rules for conducting health assessments. For example, the European approach involves applying a safety or uncertainty factor to the no-observed-effect level from the best animal study and assume that this will prevent the adverse effect.¹³⁶ This scheme places an equal weight on both carcinogenic and

¹³⁴ Silbergeld, *supra* note 18.

¹³⁵ Commoner, *supra* note 124.

¹³⁶ U.S. Congress, Office of Technology Assessment (OTA), *Researching Health*

non-carcinogenic chemicals. The advantage is that it is fast and inexpensive, but a perceived disadvantage is that it concedes that some level of exposure is probably safe for virtually all persons. In California and a few other states in the U.S., risk assessment methods have been standardized so that they can be conducted rapidly and inexpensively. This, too, can promote or introduce many other scientific problems because all the data are often unaccounted for.

A fourth alternative some have advocated relies upon public pressure to minimize hazards. This approach has been used in several states in the 1980's and has been argued to be highly effective. The best documented approaches are California's Proposition 65 and California's Assembly Bill AB-2588, wherein acceptable levels of exposure were established using a single method, and any entity that appears to expose persons above these levels must report both to the agency and to exposed persons.¹³⁷ Sending letters of notification to potentially affected persons is widely considered effective for encouraging chemical users to minimize or eliminate emissions. This sidesteps the many scientific problems with risk assessments by using public pressure to prioritize hazards. Many within the environmental community believe that this approach is quite workable.

Conclusions

In 1994, the U.S. spent nearly \$190B to improve the environment.¹³⁸ This is expected to increase about 7% annually until the turn of the century. In all other countries, approximately \$400B more was spent in 1994 to tackle similar environmental problems. Yet, even this is generally considered inadequate to address the concerns of citizens virtually everywhere. Due to competing pressures for limited funds, most nations are giving serious consideration to adopting risk-assessment techniques to prioritize environmental agendas. For example, nearly twenty proposals regarding the use of risk assessment as a tool for conducting risk/benefit analyses were debated in the U.S. Congress in 1993-95.¹³⁹

Risks (1993).

¹³⁷ Copeland et al. (1994), *supra* note 17.

¹³⁸ Center for Risk Analysis, *supra* note 7 and Carnegie Commission, *supra* note 8.

¹³⁹ See, e.g., Linda-Jo Schierow, *Comparison of Environmental Risk Provisions in the 103d Congress*, 5 Risk 283 (1994).

The scientific underpinnings of about twenty years of health risk assessment practice and the implications for environmental policy have been discussed in more than 600 peer-reviewed and published papers, providing a wealth of information to other countries now in the process of evaluating whether to use risk assessment to resolve difficult environmental issues. Without question, other countries can learn from the U.S. experiences, saving themselves billions of dollars spent as a result of well-intended, but misguided, decisions made during the early years of the environmental revolution.¹⁴⁰

In spite of numerous scientific or methodological uncertainties, properly conducted risk assessments can provide reasonably accurate predictions of the exposure of various populations and relatively accurate estimates of the magnitude of health risk (except, perhaps, for carcinogens).¹⁴¹ Risk-assessment procedures have matured a great deal over the past ten years. Use of less rigid approaches to interpreting the significance of animal bioassay data should produce much more defensible hazard identifications in the coming years. Biologically-based disposition and cancer models should provide better estimates of the actual human cancer risk at low levels of exposure, thus improving the dose-response segment. Reliance on worst-case exposure scenarios is no longer necessary in light of better information on specific exposure parameters and more sensitive techniques for measuring concentrations of contaminants in the environment. The use of Monte Carlo techniques has revolutionized the practice of exposure assessment and soon will change the practice of dose-response analysis. New and highly sensitive analytical procedures will permit us to assay hair, blood, urine, adipose and other biologic media to validate the reasonableness of the exposure estimates. Statistical procedures to account for the distribution of various factors within exposed populations will almost certainly be integral to future risk assessments.

Our awareness of numerous scientific uncertainties, as well as knowledge of how to best characterize them, will almost certainly lead to more credible health risk assessments that will be more useful to risk managers worldwide. If refinements are incorporated into future risk

¹⁴⁰ Barnes, *supra* note 10; Viscusi, *supra* note 1 and EPA, *supra* note 12.

¹⁴¹ Paustenbach, *supra* note 17 and Lavy et al., *supra* note 36.

assessments and are used to establish acceptable levels of chemical exposure, scarce financial resources can be devoted to problems that, when resolved, will yield the largest improvement in public health.

For these reasons, the EPA's Science Advisory Board (SAB)¹⁴² and the NAS¹⁴³ have promoted the routine use of quantitative risk assessment in regulatory decision making. It appears that Australia, New Zealand, Canada, the European community, countries in the Pacific Rim and others will derive significant benefit from studying the costly learning curve through which the U.S. has passed.

Appendix: Health Risk Assessment in Other Countries

The application of health risk assessment is growing rapidly in many countries. It is not possible to discuss each, but a brief review of directions that some are following will illustrate the range of approaches being considered or implemented.

One major difference between the U.S. and other countries is how carcinogens are evaluated and regulated. In countries such as the United Kingdom and Germany, that rely primarily on expert judgments, chemical carcinogens are regulated using a case-by-case approach. Known or suspected chemical carcinogens are subjected to an individual review that considers both the mechanism of action and the epidemiology data. Risk assessment usually involves the formation of expert advisory committees that make the decisions regarding exposure standards or regulations, rather than an agency. The advisory body commonly uses a "weight-of-the-evidence" approach, in which all of the available information and test data are used to formulate a scientific position for consideration as the basis for regulatory decision. This approach has historically been poorly received in the U.S. due to pressure to establish public policy that errs considerably on the side of safety. In the wake of unrelenting financial pressure from competing social needs, and the European experience, the weight-of-evidence approach has gained momentum within EPA in recent years.

¹⁴² EPA, *supra* note 8.

¹⁴³ NAS, *supra* note 3.

Australia and New Zealand

Australia and New Zealand are in the fortunate position of being able to learn from experience elsewhere.¹⁴⁴ Although incomplete, a comparison of the U.S. and Australian practices has recently been published.¹⁴⁵ With regard to contaminated lands, five characteristics seem to differentiate Australian soil clean-up guidelines from most of those adopted in the U.S., the Netherlands, and elsewhere. These seem to have resulted from a careful attempt to avoid the deficiencies in earlier efforts. First, there is a premise that a balance always exists between cost and benefit. For example, recent risk-assessment guidelines suggest that a complete clean-up of contaminated sites may not always be technically achievable and that the benefits of full or partial clean-up may be outweighed by the costs to society.¹⁴⁶

Second, there is a commitment to use risk assessment to help identify the most appropriate level of clean-up. According to recent guidelines, a contaminated site should be cleaned as necessary to minimize short- and long-term, on- and off-site, risks.¹⁴⁷ To accomplish this, there is an emphasis on flexibility to allow the most logical solution to be selected and implemented. For example, regulators are encouraged to consider that it may be appropriate in cases where there is no threat to human health and the environment to accept a strategy of containing contaminants or using planning controls to limit site use. As a consequence, a fourth characteristic, unlike policies adopted elsewhere, is recognition that it may be much less expensive, and therefore wiser, to wait for new technologies to be developed to address particularly difficult environmental problems.

Finally, health risk assessment guidelines in Australia and New Zealand clearly attempt to combine both the human and environmental risks when addressing chemical contamination. The emergence of ecological risk assessment worldwide appears to be gaining greater

¹⁴⁴ National Health and Medical Research of Australia and New Environmental Council, *Australian Guidelines for the Assessment and Management of Contaminated Sites* (1990).

¹⁴⁵ Kenneth M. Murchison, *Environmental Law in Australia and the U.S.: A Comparative Overview* (two parts), 6 *Environ. Plan. L. J.* 179 and 8 *Environ. Plan. L. J.* 254 (1994).

¹⁴⁶ Ossama El Saadi & Andrew Langley, *The Health Assessment and Management of Contaminated Sites*. (South Australian Health Commission 1991).

¹⁴⁷ *Australian Guidelines*, *supra* note 144.

recognition than in the U.S. due, in part, to increased concern about preserving our natural resources and the rapidly growing eco-tourism industry which may well become a central part of some economies.

Canada

In 1988, enactment of the Canada Environmental Protection Act (CEPA) created a mandate for carrying out risk assessments.¹⁴⁸ CEPA and other recent developments have led to a number of nationally or provincially developed exposure standards in Canada. Historically, Canadian regulatory bodies have relied on exposure standards and occupational exposure limits generated by other countries (e.g., Sweden, The Netherlands, Denmark and the U.S.) and organizations (e.g., World Health Organization and the American Conference of Governmental and Industrial Hygienists). In most instances, the Canadian government has not considered using cancer potency factors and reference doses developed by the EPA because they see these figures as overly conservative. In general, risk-assessment decisions in Canada are performed on a case-by-case basis. In each case, scientists use a weight-of-evidence approach (rather than strict regulatory policy) to select the most appropriate dose-extrapolation model.

In regulating chemical substances, the responsible Canadian authorities consider the probable carcinogenic mechanism of action when making decisions about acceptable levels of exposure. For example, for nongenotoxic chemicals, uncertainty factors are added to the no-observed-adverse-effect level (NOAEL) to calculate a tolerable daily intake similar to the U.S. acceptable daily intake (ADI). Conversely, for genotoxic carcinogens, regulators select one of several methods under a policy aimed to reduce health risks by as much as possible. At this time, the approach used to assess genotoxic carcinogens involves estimating an exposure-potency index (EPI). This index compares the expected exposure of a population with an estimate of the carcinogenic potency of the chemical. The potency estimate is derived from epidemiologic or animal data with the objective of identifying the dose that would cause a carcinogenic response in 5% of the test subjects.

¹⁴⁸ OTA, *supra* note 136.

The European Community

For several years, the European Community (E.C.) has worked toward the harmonization of health, safety and environmental regulations, to reduce competitive imbalances among member countries and to prevent regulations from acting as trade barriers. The central goal remains the protection of public health and environmental quality.¹⁴⁹ In an attempt to identify the optimal cost/benefit relationship, the E.C. has adopted risk assessment to determine acceptable standards of chemical exposure and levels of risk, and to identify appropriate chemical-testing procedures. The E.C. procedure for chemical testing was an important advance in harmonizing chemical-assessment guidelines of various member nations. The 1967 E.C. directive has served as a model for environmental regulation in other countries and international organizations, e.g., OECD.¹⁵⁰

European legislation pertaining to risk assessment has been mainly directed at chemical safety, pesticide residues, food additives and occupational exposures. Most countries mandate both qualitative and quantitative risk assessments, depending on the type of chemical and usage. A common characteristic of most directives passed or proposed in those fields is that the member states or individual employers are responsible for performing risk assessments, not the regulatory agencies. Scientific experts are used throughout, both by those performing risk assessments and by various agencies during the review process. Although as recently as 1993 there was significant optimism that roughly similar risk-assessment procedures would be used throughout Europe, this appears unlikely in the near future.

Germany

In Germany, the use of quantitative risk assessment is relatively new to regulation. Previously, regulatory authorities did not quantify the risk from exposure to carcinogens or other toxic substances because the inherent acceptance of a quantitative risk estimate did not comply with principles established within German environmental laws.¹⁵¹ The

¹⁴⁹ Commission of the European Communities, *Chemical Risk Control in the European Community* (1987).

¹⁵⁰ Organisation for Economic Cooperation and Development, *Environmental Directorate, OECD Cooperative Risk Reduction Activities* (1992).

¹⁵¹ R. Turck, *Nature, Conservation and Nuclear Safety* (Fed. Ministry Environment) (1993).

notion of allowing any degree of risk to humans diverges from the German emphasis on eliminating any danger to public health, a basic objective of their environmental regulations. To date, risk assessments have infrequently been used in Germany to resolve important environmental issues. As the need for a quantitative form of risk assessment has become increasingly necessary, regulators have conducted several surveys of the methodologies used by other countries and have selectively adopted some of them. The methodologies of the EPA have had a strong impact on German regulatory committees exploring the process, but they have not mandated its use. Believing that a case-by-case approach to assessing chemicals leads toward more accurate estimations of risk, the German regulators have advocated using flexible, rather than policy-driven, approaches.

Although German authorities do not widely practice risk assessment, known human carcinogens are strictly regulated. To date, known human carcinogens have been subjected to stringent regulations focusing partially on the best available technology (BAT) or, in the case of drinking water regulations, on international E.C. directives. It is also commonplace for decisions concerning the regulation of chemical carcinogens and other hazardous chemicals in Germany to be made by multipartite expert committees on a case-by-case basis. Typically, an expert committee relies upon a NOAEL/ADI approach to identify acceptable levels of exposure to noncarcinogenic chemicals.

The Netherlands

In the Netherlands, and in most other European nations, regulators use the term quantitative risk assessment (QRA) as synonymous with low-dose modeling conducted by risk assessors in the U.S. The QRA approach to low-dose modeling is used to estimate the probability of risks to human health from carcinogens that have been definitively categorized as genotoxic. The method is currently used by all Dutch agencies, but the model varies somewhat based on knowledge about the mechanism of action of the chemical.¹⁵²

In the Dutch risk-assessment process, scientists initially evaluate a chemical to determine its genotoxicity. Subsequently, they use information about functional effects and chemical structure, the results

¹⁵² OTA, *supra* note 136.

of bioassays, and other relevant data to reduce the uncertainties relating to the genotoxic potential in humans. When it is impossible to eliminate completely the risk of exposure to a genotoxic carcinogen, the Dutch approach relies upon a very simple linear extrapolation model to determine a dose-response value for human exposure.¹⁵³ A simple linear extrapolation of animal data to humans is considered a very conservative approach, as the metabolic rate of humans is lower than that of animals and is also inversely proportional to age and weight. DNA repair processes appear to be proportional to body weight, and the sensitivity of man to known human carcinogens is about equal to that of experimental animals.¹⁵⁴

Like most other European countries, virtually all of the safe levels of exposure for a nongenotoxic carcinogen identified in regulations are based on a NOAEL divided by a safety factor of ten to 1,000, depending on the amount of uncertainty in the data. The resulting value represents an acceptable daily intake for the substance.

Dutch regulators have distinguished themselves by having developed a number of innovative methods for assessing the hazards posed by contaminated soils.¹⁵⁵ The Dutch standards are probably the most widely cited soil standards in the world.¹⁵⁶ They recently added guidelines for air, groundwater, surface water and sediment. In support of these efforts, they have also conducted a number of research efforts to evaluate the uptake of soil by humans and the environmental fate of the contaminants.

Scandinavia

In controlling toxic substances, authorities in Denmark recognize different carcinogenic mechanisms and use the safety-factor approach for nongenotoxic carcinogens and noncarcinogens. The basic toxicological data used to generate exposure standards are generally the

¹⁵³ Richard Kroes, *Animal Data: Interpretation and Consequences in Environmental Carcinogenesis* (P. Emmelot & E. Kriek, eds. 1979).

¹⁵⁴ Richard Kroes, *Contribution of Toxicology Toward Risk Assessment of Carcinogens*, 60 *Arch. Toxicol.* 224 (1987).

¹⁵⁵ Joop H. van Wijnen, P. Clausing & B. B. Brunekreef, *Estimated Soil Ingestion by Children*, 51 *Environ. Res.* 147 (1990) and Joop H. van Wijnen, *Health Risk Assessment of Soil Contamination* (1990).

¹⁵⁶ M. E. J. Van der Weiden, *Environmental Quality Objectives in the Netherlands* (1994).

same across the various regulatory agencies, but the manner in which the data are used differs according to the problem being addressed. Danish regulators also use a case-by-case approach when evaluating data for a toxic substance, although reliance on expert advisory committees is not as extensive in Denmark as in other countries,¹⁵⁷ such as the U.K.¹⁵⁸ Currently, Denmark's National Food Agency of the Ministry of Health administers regulations for food additives. ADIs are determined using principles outlined by the Joint FAO/WHO Committee on Food Additives as the basis for permitted use levels.¹⁵⁹ Using such an approach, Denmark has banned all food additives that are classified as genotoxic carcinogens.

Regulators in Denmark employ risk-assessment techniques only to a limited extent when determining exposure standards for carcinogens. In cases where new chemicals may be substituted for a suspected carcinogen, an assessment is required to examine whether exposure can be eliminated effectively. Low-dose extrapolation models are used to estimate risk when a nonthreshold genotoxic carcinogen cannot be replaced by another chemical.¹⁶⁰

In Sweden, the EPA sets exposure standards for a variety of carcinogenic and noncarcinogenic chemicals and uses classic risk-assessment methods to assess health risks for industrial emissions.¹⁶¹ Like other European countries that use risk assessment, regulators consider carcinogens with a pronounced genotoxic mechanism as prime candidates for careful analysis. As part of that process, the Swedish EPA uses mathematical models to extrapolate from animals exposed to high doses of carcinogens to predict the effects on humans exposed to lower doses. The agency also evaluates the carcinogens using a case-by-case approach in which each chemical is assessed individually, as opposed to the more generic approach common in U.S. regulatory agencies that follow fairly strict guidelines.

¹⁵⁷ L. Dragsted, *Low Dose Extrapolation of Data from Animal Bioassays*, in *Risk Managements and Risk Assessment in Different Sectors of Denmark* 77 (1992).

¹⁵⁸ Department of Health (U.K.), *Comm. on Carcinogenicity of Chemicals in Food, Guidelines for Evaluation of Chemicals for Carcinogenicity* (1991)

¹⁵⁹ Dragsted, *supra* note 155.

¹⁶⁰ *Id.*

¹⁶¹ OTA, *supra* note 136.

Swedish regulators use a weight-of-the evidence approach to evaluate a chemical's carcinogenic potential. Like most other European countries, genotoxic carcinogens are typically regulated to ensure the lowest possible levels of exposure; for nongenotoxic chemicals, safe levels of exposure are identified from a NOAEL or lowest-observed-adverse-effect level (LOAEL) and a safety factor applied based on the level of uncertainty in the available information. These ADIs are then used to calculate maximum residue levels of pesticides in food and occupational exposure limits.

United Kingdom

In the U.K., risk-assessment methods have not been used to establish an environmental agenda or to regulate specific chemicals. Regulatory agencies do not use risk-assessment models to generate a probability for the risk of cancer from exposure to certain chemicals. U.K. regulators place little reliance on the quantitative assessment of carcinogens because they believe that the statistical models used to extrapolate dose-response effects from animals to humans are not valid.¹⁶²

Papers list several reasons for U.K. skepticism of commonly-used U.S. dose-extrapolation models. First, a linear low-dose model has yet to be validated. Second, the bioassay data used to derive a low-dose model of chemical carcinogenicity are incomplete. Third, the low-dose models are based more on mathematical assumptions than established biochemical mechanisms; consequently, risk estimates vary widely depending on the model used. Last, models give an unjustified impression of precision, given the approximations and assumptions upon which they are based.¹⁶³

The regulation of chemical carcinogens in the U.K. is based on mechanistic considerations. For example, if a chemical acts by a genotoxic mechanism, regulators assume, as a matter of prudence, that the compound does not have a threshold. If a nongenotoxic mechanism is known to be involved, regulators consider it possible to identify a safe level of exposure.¹⁶⁴

¹⁶² van Wijnen, *supra* note 155.

¹⁶³ U.K., *supra* note 158.

¹⁶⁴ OTA, *supra* note 136.

Chemicals displaying genotoxicity are evaluated using expert judgment and a weight-of-the-evidence approach. In evaluating such compounds, experts consider all available evidence (including human data, animal data, mutagenicity data and structure/activity relationships). If they conclude that the compound should be considered a potential human carcinogen that acts by a genotoxic mechanism, they recommend action to reduce levels to as low as is reasonably practical or to eliminate it entirely. For suspected carcinogenic compounds operating through a well-understood nongenotoxic mechanism, researchers evaluate animal studies to determine the NOAEL, which is then divided by a safety factor to derive an ADI. The safety factor reflects the uncertainties of extrapolating from animals to humans and of variation among individuals.¹⁶⁵ ADIs are also used to calculate maximum residue levels for pesticides on food.



¹⁶⁵ U.K., *supra* note 158.