Reference Guide on Toxicology

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I. Introduction

Toxicology classically is known as the science of poisons. A modern definition is "the study of the adverse effects of chemicals on living organisms."[1] Although it is an age-old science, toxicology has only recently become a discipline distinct from pharmacology, biochemistry, cell biology, and related fields.

There are three central tenets of toxicology. First, "the dose makes the poison"; this implies that all chemical agents are intrinsically hazardous—whether they cause harm is only a question of dose.[2] Even water, if consumed in large quantities, can be toxic. Second, each chemical agent tends to produce a specific pattern of biological effects that can be used to establish disease causation.[3] Third, the toxic responses in laboratory animals are useful predictors of toxic responses in humans. Each of these tenets, and their exceptions, are discussed in greater detail in this reference guide.

The science of toxicology attempts to determine at what doses foreign agents produce their effects. The foreign agents of interest to toxicologists are all chemicals (including foods) and physical agents in the form of radiation, but not living organisms that cause infectious diseases.[4]

The discipline of toxicology provides scientific information relevant to the following questions:

1. What hazards does a chemical or physical agent present to human populations or the environment?
2. What degree of risk is associated with chemical exposure at any given dose?

Toxicological studies, by themselves, rarely offer direct evidence that a disease in any one individual was caused by a chemical exposure. However, toxicology can provide scientific information regarding the increased risk of contracting a disease at any given dose and help rule out other risk factors for the disease. Toxicological evidence also explains how a chemical causes a disease by describing metabolic, cellular, and other physiological effects of exposure.

1. Casarett and Doull's Toxicology: The Basic Science of Poisons 13 (Curtis D. Klaassen ed., 5th ed. 1996).

2. A discussion of more modern formulations of this principle, which was articulated by Paracelsus in the sixteenth century, can be found in Ellen K. Silbergeld, *The Role of Toxicology in Causation: A Scientific Perspective,* 1 Cts. Health Sci. & L. 374, 378 (1991).

3. Some substances, such as central nervous system toxicants, can produce complex and nonspecific symptoms, such as headaches, nausea, and fatigue.

4. Forensic toxicology, a subset of toxicology generally concerned with criminal matters, is not addressed in this reference guide, since it is a highly specialized field with its own literature and methodologies which do not relate directly to toxic tort or regulatory issues.

A. Toxicology and the Law

The growing concern about chemical causation of disease is reflected in the public attention devoted to lawsuits alleging toxic torts, as well as in litigation concerning the many federal and state regulations related to the release of potentially toxic compounds into the environment. These lawsuits inevitably involve toxicological evidence.

Toxicological evidence frequently is offered in two types of litigation: tort and regulatory. In tort litigation, toxicologists offer evidence that either supports or refutes plaintiffs' claims that their diseases or injuries were caused by chemical exposures.[5] In regulatory litigation, toxicological evidence is used to either support or challenge government regulations concerning a chemical or a class of chemicals. In regulatory litigation, toxicological evidence addresses the issue of how exposure affects populations rather than addressing specific causation, and agency determinations are usually subject to the court's deference.[6]

B. Purpose of the Reference Guide on Toxicology

This reference guide focuses on scientific issues that arise most frequently in toxic tort cases. Where it is appropriate, the reference guide explores the use of regulatory data and how the courts treat such data. The reference guide provides an overview of the basic principles and methodologies of toxicology and offers a scientific context for proffered expert opinion based on toxicological data.[7] The reference guide describes research methods in toxicology and the relationship between toxicology and epidemiology, and it provides model questions for evaluating the admissibility and strength of an expert's opinion. Following each question is an explanation of the type of toxicological data or information that is offered in response to the question, as well as a discussion of its significance.

5. *See, e.g.,* General Elec. Co. v. Joiner, 522 U.S. 136 (1997); Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993).

6. *See, e.g.,* Troy Corp. v. Browner, 129 F.3d 1290 (D.C. Cir. 1997) (EPA's decision to list chemical under Emergency Planning and Community Right to Know Act supported by substantial evidence in that animal studies demonstrated significant increases in pathology); AFL-CIO v. OSHA, 965 F.2d 962, 969–70 (11th Cir. 1992) (determinations of the Secretary of Labor are conclusive if supported by substantial evidence); Simpson v. Young, 854 F.2d 1429, 1435 (D.C. Cir. 1988) (toxicology research methods approved by the Food and Drug Administration (FDA) given deference by the court).

7. The use of toxicological evidence in regulatory decision making is discussed in more detail in Richard A. Merrill, *Regulatory Toxicology, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 1011. For a more general discussion of issues that arise in considering expert testimony, see Margaret A. Berger, The Supreme Court's Trilogy on the Admissibility of Expert Testimony § IV, in this manual.

C. Toxicological Research Design

Toxicological research usually involves exposing laboratory animals (in vivo research) or cells or tissues (in vitro research) to chemicals, monitoring the outcomes (such as cellular abnormalities, tissue damage, organ toxicity, or tumor formation), and comparing the outcomes with those for unexposed control groups. As explained below,[8] the extent to which animal and cell experiments accurately predict human responses to chemical exposures is subject to debate.[9] However, because it is often unethical to experiment on humans by exposing them to known doses of chemical agents, animal toxicological evidence often provides the best scientific information about the risk of disease from a chemical exposure.[10]

In contrast to their exposure to drugs, only rarely are humans exposed to environmental chemicals in a manner that permits a quantitative determination of adverse outcomes.[11] This area of toxicological research, known as clinical toxicology, may consist of individual or multiple case reports, or even experimental studies in which individuals or groups of individuals have been exposed to a chemical under circumstances that permit analysis of dose–response relationships, mechanisms of action, or other aspects of toxicology. For example, individuals occupationally or environmentally exposed to polychlorinated biphenyls (PCBs) prior to prohibitions on their use have been studied to determine the routes of absorption, distribution, metabolism, and excretion for this chemical. Human exposure occurs most frequently in occupational settings where workers are exposed to industrial chemicals like lead or asbestos; however, even under these circumstances, it is usually difficult, if not impossible, to quantify the amount of exposure. Moreover, human populations are exposed to many other chemicals and risk factors, making it difficult to isolate the increased risk of a disease that is due to any one chemical.[12]

Toxicologists use a wide range of experimental techniques, depending in part on their area of specialization. Some of the more active areas of toxicological research are classes of chemical compounds, such as solvents and metals; body system effects, such as neurotoxicology, reproductive toxicology, and immunotoxicology; and effects on physiological processes, including inhalation toxicology, dermatotoxicology, and molecular toxicology (the study of how chemicals

8. *See infra* §§ I.D, III.A.

9. The controversy over the use of toxicological evidence in tort cases is described in Silbergeld, *supra* note 2, at 378.

10. *See, e.g.,* Office of Tech. Assessment, U.S. Congress, Reproductive Health Hazards in the Workplace 8 (1985).

11. However, it is from drug studies in which multiple animal species are compared directly with humans that many of the principles of toxicology have been developed.

12. *See, e.g.,* Office of Tech. Assessment, U.S. Congress, *supra* note 10, at 8.

interact with cell molecules). Each of these areas of research includes both in vivo and in vitro research.[13]

1. In vivo research

Animal research in toxicology generally falls under two headings: safety assessment and classic laboratory science, with a continuum in between. As explained in section I.E, safety assessment is a relatively formal approach in which a chemical's potential for toxicity is tested in vivo or in vitro using standardized techniques often prescribed by regulatory agencies, such as the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA).

The roots of toxicology in the science of pharmacology are reflected in an emphasis on understanding the absorption, distribution, metabolism, and excretion of chemicals. Basic toxicological laboratory research also focuses on the mechanisms of action of external chemical and physical agents. It is based on the standard elements of scientific studies, including appropriate experimental design using control groups and statistical evaluation. In general, toxicological research attempts to hold all variables constant except for that of the chemical exposure.[14] Any change in the experimental group not found in the control group is assumed to be perturbation caused by the chemical. An important component of toxicological research is dose–response relationships. Thus, most toxicological studies generally test a range of doses of the chemical.[15]

a. Dose–response relationships

Animal experiments are conducted to determine the dose–response relationships of a compound by measuring the extent of any observed effect at various doses and diligently searching for a dose that has no measurable physiological effect. This information is useful in understanding the mechanisms of toxicity and extrapolating data from animals to humans.[16]

b. Acute toxicity testing—lethal dose 50 (LD50)

To determine the dose–response relationship for a compound, a short-term lethal dose 50 (LD50) is derived experimentally. The LD50 is the dose at which a compound kills 50% of laboratory animals within a period of days to weeks.

13. *See infra* §§ I.C.1, I.C.2.

14. *See generally* Alan Poole & George B. Leslie, A Practical Approach to Toxicological Investigations (1989); Principles and Methods of Toxicology (A. Wallace Hayes ed., 2d ed. 1989); *see also* discussion on acute, short-term, and long-term toxicity studies and acquisition of data in Frank C. Lu, Basic Toxicology: Fundamentals, Target Organs, and Risk Assessment 77–92 (2d ed. 1991).

15. Rolf Hartung, *Dose–Response Relationships, in* Toxic Substances and Human Risk: Principles of Data Interpretation 29 (Robert G. Tardiff & Joseph V. Rodricks eds., 1987).

16. *See infra* §§ I.D, III.A.

The use of this easily measured end point for acute toxicity is being abandoned, in part because recent advances in toxicology have provided other pertinent end points, and in part because of pressure from animal rights activists to reduce or replace the use of animals in laboratory research.

c. No observable effect level (NOEL)

A dose–response study also permits determination of another important characteristic of the biological action of a chemical—the no observable effect level (NOEL).[17] The NOEL sometimes is called a threshold, since it is the level above which observable effects in test animals are believed to occur and below which no toxicity is observed.[18] Of course, since the NOEL is dependent on the ability to observe the effect, the level is sometimes lowered once more sophisticated methods of detection are developed.

d. No threshold model and determination of cancer risk

Certain genetic mutations, such as those leading to cancer and some inherited disorders, are believed to occur without any threshold. In theory, the cancer-causing mutation to the genetic material of the cell can be produced by any one molecule of certain chemicals. The no threshold model led to the development of the one hit theory of cancer risk, in which each molecule of a cancer-causing chemical has some finite possibility of producing the mutation that leads to cancer. This risk is very small, since it is unlikely that any one molecule of a potentially cancer-causing agent will reach that one particular spot in a specific cell and result in the change that then eludes the body's defenses and leads to a

17. For example, undiluted acid on the skin can cause a horrible burn. As the acid is diluted to lower and lower concentrations less and less of an effect occurs until there is a concentration sufficiently low (e.g., one drop in a bathtub of water, or a sample with less than the acidity of vinegar) that no effect occurs. This no observable effect concentration differs from person to person. For example, a baby's skin is more sensitive than that of an adult, and skin that is irritated or broken responds to the effects of an acid at a lower concentration. However, the key point is that there is some concentration that is completely harmless to the skin. *See, e.g.,* Paul Kotin, *Dose–Response Relationships and Threshold Concepts,* 271 Annals N.Y. Acad. Sci. 22 (1976).

18. The significance of the NOEL was relied on by the court in *Graham v. Canadian National Railway Co.*, 749 F. Supp. 1300 (D. Vt. 1990), in granting judgment for the defendants. The court found the defendant's expert, a medical toxicologist, persuasive. The expert testified that the plaintiffs' injuries could not have been caused by herbicides, since their exposure was well below the reference dose, which he calculated by taking the NOEL and decreasing it by a safety factor to ensure no human effect. *Id.* at 1311–12 & n.11. *But see* Louderback v. Orkin Exterminating Co., 26 F. Supp. 2d 1298 (D. Kan. 1998) (failure to consider threshold levels of exposure does not necessarily render expert's opinion unreliable where temporal relationship, scientific literature establishing an association between exposure and various symptoms, plaintiffs' medical records and history of disease, and exposure to or the presence of other disease-causing factors were all considered). For additional background on the concept of NOEL, see Robert G. Tardiff & Joseph V. Rodricks, *Comprehensive Risk Assessment, in* Toxic Substances and Human Risk: Principles of Data Interpretation, *supra* note 15, at 391.

clinical case of cancer. However, the risk is not zero. The same model also can be used to predict the risk of inheritable mutational events.[19]

e. Maximum tolerated dose (MTD) and chronic toxicity tests

Another type of study uses different doses of a chemical agent to establish over a 90-day period what is known as the maximum tolerated dose (MTD) (the highest dose that does not cause significant overt toxicity). The MTD is important because it enables researchers to calculate the dose of a chemical that an animal can be exposed to without reducing its life span, thus permitting evaluation of the chronic effects of exposure.[20] These studies are designed to last the lifetime of the species.

Chronic toxicity tests evaluate carcinogenicity or other types of toxic effects. Federal regulatory agencies frequently require carcinogenicity studies on both sexes of two species, usually rats and mice. A pathological evaluation is done on the tissues of animals that died during the study and those that are sacrificed at the conclusion of the study.

19. For further discussion of the no threshold model of carcinogenesis, see Office of Tech. Assessment, U.S. Congress, Assessment of Technologies for Determining the Cancer Risks from the Environment (1981); Henry C. Pitot III & Yvonne P. Dragan, *Chemical Carcinogenesis, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 201, 254–55. *But see* Marvin Goldman, *Cancer Risk of Low-Level Exposure,* 271 Science 1821 (1996); V.P. Bond et al., *Current Misinterpretations of the Linear No-Threshold Hypothesis,* 70 Health Physics 877 (1996).

The no threshold model, as adopted by the Occupational Safety and Health Administration (OSHA) in its regulation of workplace carcinogens, has been upheld. Public Citizen Health Research Group v. Tyson, 796 F.2d 1479, 1498 (D.C. Cir. 1986) (as set forth in 29 C.F.R. § 1990.143(h) (1985), "no determination will be made that a 'threshold' or 'no effect' level of exposure can be established for a human population exposed to carcinogens in general, or to any specific substance"), *clarified sub nom.* Public Citizen Health Research Group v. Brock, 823 F.2d 626, 628 (D.C. Cir. 1987). *But see* Sutera v. Perrier Group of Am., Inc., 986 F. Supp. 655, 666–67 (D. Mass. 1997) (no scientific evidence that linear no-safe threshold analysis is an acceptable scientific technique as used by experts in this case to determine causation).

While the one hit model explains the response to most carcinogens, there is accumulating evidence that for certain cancers there is in fact a multistage process and that some cancer-causing agents act through nonmutational processes, so-called epigenetic or nongenotoxic agents. Committee on Risk Assessment Methodology, National Research Council, Issues in Risk Assessment 34–35, 187, 198–201 (1993). For example, the multistage cancer process may explain the carcinogenicity of benzo(a)pyrene (produced by the combustion of hydrocarbons such as oil) and chlordane (a termite pesticide). However, nonmutational responses to asbestos, dioxin, and estradiol cause their carcinogenic effects. What the appropriate mathematical model is to depict the dose–response relationship for such carcinogens is still a matter of debate. *Id.* at 197–201.

20. Even the determination of the MTD can be fraught with controversy. *See, e.g.,* Simpson v. Young, 854 F.2d 1429, 1431 (D.C. Cir. 1988) (petitioners unsuccessfully argued that the FDA improperly certified color additive Blue No. 2 dye as safe because researchers failed to administer the MTD to research animals, as required by FDA protocols). *See generally* David P. Rall, *Laboratory and Animal Toxicity and Carcinogenesis Testing: Underlying Concepts, Advantages and Constraints,* 534 Annals N.Y. Acad. Sci. 78 (1988); Frank B. Cross, Environmentally Induced Cancer and the Law: Risks, Regulation, and Victim Compensation 54–57 (1989).

The rationale for using the MTD in chronic toxicity tests, such as carcinogenicity bioassays, often is misunderstood. It is preferable to use realistic doses of carcinogens in all animal studies. However, this leads to a loss of statistical power, thereby limiting the ability of the test to detect carcinogens or other toxic compounds. Consider the situation in which a realistic dose of a chemical causes a tumor in 1 in 100 laboratory animals. If the lifetime background incidence of tumors in animals without exposure to the chemical is 6 in 100, a toxicological test involving 100 control animals and 100 exposed animals who were fed the realistic dose would be expected to reveal 6 control animals and 7 exposed animals with the cancer. This difference is too small to be recognized as statistically significant. However, if the study started with ten times the realistic dose, the researcher would expect to get 16 cases in the exposed group and 6 cases in the control group, a significant difference that is unlikely to be overlooked.

Unfortunately, even this example does not demonstrate the difficulties of determining risk.[21] Regulators are responding to public concern about cancer by regulating risks often as low as 1 in a million—not 1 in 100, as in the example given above. To test risks of 1 in a million, a researcher would have to either increase the lifetime dose from 10 times to 100,000 times the realistic dose or expand the numbers of animals under study into the millions. However, increases of this magnitude are beyond the world's animal-testing capabilities and are also prohibitively expensive. Inevitably, then, animal studies must trade statistical power for extrapolation from higher doses to lower doses.

Accordingly, proffered toxicological expert opinion on potentially cancer-causing chemicals almost always is based on a review of research studies that extrapolate from animal experiments involving doses significantly higher than that to which humans are exposed.[22] Such extrapolation is accepted in the regulatory arena. However, in toxic tort cases, experts often use additional background information[23] to offer opinions about disease causation and risk.[24]

21. *See, e.g.,* Committee on Risk Assessment Methodology, National Research Council, *supra* note 19, at 43–51.

22. *See, e.g.,* James Huff, *Chemicals and Cancer in Humans: First Evidence in Experimental Animals,* 100 Envtl. Health Persp. 201, 204 (1993); International Agency for Research on Cancer, World Health Org., *Preamble, in* 63 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 9, 17 (1995).

23. Researchers have developed numerous biomathematical formulas to provide statistical bases for extrapolation from animal data to human exposure. *See generally* Pitot & Dragen, *supra* note 19, at 255–57; Animal Models in Toxicology (Shayne Cox Gad & Christopher P. Chengelis eds., 1992); V.A. Filov et al., Quantitative Toxicology: Selected Topics (1979). *See also infra* §§ IV, V.

24. Policy arguments concerning extrapolation from low doses to high doses are explored in Troyen A. Brennan & Robert F. Carter, *Legal and Scientific Probability of Causation of Cancer and Other Environmental Disease in Individuals,* 10 J. Health Pol. Pol'y & L. 33 (1985).

2. In vitro research

In vitro research concerns the effects of a chemical on human or animal cells, bacteria, yeast, isolated tissues, or embryos. Thousands of in vitro toxicological tests have been described in the scientific literature. Many tests are for mutagenesis in bacterial or mammalian systems. There are short-term in vitro tests for just about every physiological response and every organ system, such as perfusion tests and DNA studies. Relatively few of these tests have been validated by replication in many different laboratories or by comparison with outcomes in animal studies to determine if they are predictive of whole-animal or human toxicity.[25]

Criteria of reliability for an in vitro test include the following: (1) whether the test has come through a published protocol in which many laboratories used the same in vitro method on a series of unknown compounds prepared by a reputable organization (such as the National Institutes of Health (NIH) or the International Agency for Research on Cancer (IARC)) to determine if the test consistently and accurately measures toxicity; (2) whether the test has been adopted by a U.S. or international regulatory body; and (3) whether the test is predictive of in vivo outcomes related to the same cell or target organ system.

D. Extrapolation from Animal and Cell Research to Humans

Two types of extrapolation must be considered: from animal data to humans and from higher doses to lower doses. In qualitative extrapolation, one can usually rely on the fact that a compound causing an effect in one mammalian species will cause it in another species. This is a basic principle of toxicology and pharmacology. If a heavy metal, such as mercury, causes kidney toxicity in laboratory animals, it is highly likely to do so at some dose in humans. However, the dose at which mercury causes this effect in laboratory animals is modified by many internal factors, and the exact dose–response curve may be different from that for humans. Through the study of factors that modify the toxic effects of chemicals, including absorption, distribution, metabolism, and excretion, researchers can improve the ability to extrapolate from laboratory animals to humans and from higher to lower doses.[26] Mathematical depiction of the process by which an external dose moves through various compartments in the body

25. *See generally* In Vitro Toxicity Testing: Applications to Safety Evaluation (John M. Frazier ed., 1992); In Vitro Methods in Toxicology (C.K. Atterwill & C.E. Steele eds., 1987) (discussion of the strengths and weaknesses of specific in vitro tests). Use of in vitro data for evaluating human mutagenicity and teratogenicity is described in John M. Rogers & Robert J. Kavlock, *Developmental Toxicology, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 301, 319–21; George R. Hoffman, *Genetic Toxicology, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 269, 277–93. For a critique of expert testimony using in vitro data, see *Wade-Greaux v. Whitehall Laboratories, Inc.*, 874 F. Supp. 1441, 1480 (D.V.I.), *aff'd,* 46 F.3d 1120 (3d Cir. 1994).

26. For example, benzene undergoes a complex metabolic sequence that results in toxicity to the

until it reaches the target organ is often called physiologically based pharmacokinetics.[27]

Extrapolation from studies in nonmammalian species to humans is much more difficult and can only be done if there is sufficient information on similarities in absorption, distribution, metabolism, and excretion; quantitative determinations of human toxicity based on in vitro studies usually are not considered appropriate. As discussed in section I.F, in vitro or animal data for elucidating mechanisms of toxicity are more persuasive when positive human epidemiological data also exist.[28]

E. Safety and Risk Assessment

Toxicological expert opinion also relies on formal safety and risk assessments. Safety assessment is the area of toxicology relating to the testing of chemicals and drugs for toxicity. It is a relatively formal approach in which the potential for toxicity of a chemical is tested in vivo or in vitro using standardized techniques. The protocols for such studies usually are developed through scientific consensus and are subject to oversight by governmental regulators or other watchdog groups.

After a number of bad experiences, including outright fraud, government agencies have imposed codes on laboratories involved in safety assessment, including industrial, contract, and in-house laboratories.[29] Known as Good Laboratory Practice (GLP), these codes govern many aspects of laboratory standards,

bone marrow in all species, including humans. Robert Snyder et al., *The Toxicology of Benzene,* 100 Envtl. Health Persp. 293 (1993). The exact metabolites responsible for this bone-marrow toxicity are the subject of much interest but remain unknown. Mice are more susceptible to benzene than are rats. If researchers could determine the differences between mice and rats in their metabolism of benzene, they would have a useful clue as to which portion of the metabolic scheme is responsible for benzene toxicity to the bone marrow. *See, e.g.,* Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 91; Andrew Parkinson, *Biotransformation of Xenobiotics, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 113.

27. For an analysis of methods used to extrapolate from animal toxicity data to human health effects, see, e.g., Robert E. Menzer, *Selection of Animal Models for Data Interpretation, in* Toxic Substances and Human Risk: Principles of Data Interpretation, *supra* note 15, at 133; Thomas J. Slaga, *Interspecies Comparisons of Tissue DNA Damage, Repair, Fixation and Replication,* 77 Envtl. Health Persp. 73 (1988); Lorenzo Tomatis, *The Predictive Value of Rodent Carcinogenicity Tests in the Evaluation of Human Risks,* 19 Ann. Rev. Pharmacol. & Toxicol. 511 (1979); Willard J. Visek, *Issues and Current Applications of Interspecies Extrapolation of Carcinogenic Potency as a Component of Risk Assessment,* 77 Envtl. Health Persp. 49 (1988); Gary P. Carlson, *Factors Modifying Toxicity, in* Toxic Substances and Human Risk: Principles of Data Interpretation, *supra* note 15, at 47; Michael D. Hogan & David G. Hoel, *Extrapolation to Man, in* Principles and Methods of Toxicology, *supra* note 14, at 879; James P. Leape, *Quantitative Risk Assessment in Regulation of Environmental Carcinogens,* 4 Harv. Envtl. L. Rev. 86 (1980).

28. *See, e.g.,* Goewey v. United States, 886 F. Supp. 1268, 1280–81 (D.S.C. 1995) (extrapolation of neurotoxic effects from chickens to humans unwarranted without human confirmation).

29. A dramatic case of fraud involving a toxicology laboratory that performed tests to assess the

including such details as the number of animals per cage, dose and chemical verification, and the handling of tissue specimens. GLP practices are remarkably similar across agencies, but the tests called for differ depending on mission. For example, there are major differences between the FDA's and the EPA's required procedures for testing drugs and environmental chemicals.[30] The FDA requires and specifies both efficacy and safety testing of drugs in humans and animals. Carefully controlled clinical trials using doses within the expected therapeutic range are required for premarket testing of drugs because exposures to prescription drugs are carefully controlled and should not exceed specified ranges or uses. However, for environmental chemicals and agents, no premarket testing in humans is required by the EPA. Moreover, since exposures are less predictable, a wider range of doses usually is given in the animal tests.[31]

Since exposures to environmental chemicals may continue over the lifetime and affect both young and old, test designs called lifetime bioassays have been developed in which relatively high doses are given to experimental animals. Interpretation of results requires extrapolation from animals to humans, from high to low doses, and from short exposures to multiyear estimates. It must be emphasized that less than 1% of the 60,000–75,000 chemicals in commerce have been subjected to a full safety assessment, and there are significant toxicological data on only 10%–20%.

Risk assessment is an approach increasingly used by regulatory agencies to estimate and compare the risks of hazardous chemicals and to assign priority for avoiding their adverse effects.[32] The National Academy of Sciences defines four components of risk assessment: hazard identification, dose–response estimation, exposure assessment, and risk characterization.[33]

Although risk assessment is not an exact science, it should be viewed as a

safety of consumer products is described in *United States v. Keplinger,* 776 F.2d 678 (7th Cir. 1985), *cert. denied,* 476 U.S. 1183 (1986). Keplinger and the other defendants in this case were toxicologists who were convicted of falsifying data on product safety by underreporting animal morbidity and mortality and omitting negative data and conclusions from their reports.

30. *See, e.g.,* 40 C.F.R. §§ 160, 792 (1993); Lu, *supra* note 14, at 89.

31. It must be appreciated that the development of a new drug inherently requires searching for an agent that at useful doses has a biological effect (e.g., decreasing blood pressure), whereas those developing a new chemical for consumer use (e.g., a house paint) hope that at usual doses no biological effects will occur. There are other compounds, such as pesticides and antibacterial agents, for which a biological effect is desired, but it is intended that at usual doses humans will not be affected. These different expectations are part of the rationale for the differences in testing information available for assessing toxicological effects.

32. Committee on Risk Assessment Methodology, National Research Council, *supra* note 19, at 1.

33. *See generally* National Research Council, Risk Assessment in the Federal Government: Managing the Process (1983); Bernard D. Goldstein, *Risk Assessment/Risk Management Is a Three-Step Process: In Defense of EPA's Risk Assessment Guidelines,* 7 J. Am. C. Toxicol. 543 (1988); Bernard D. Goldstein, *Risk Assessment and the Interface Between Science and Law,* 14 Colum. J. Envtl. L. 343 (1989).

useful estimate on which policy making can be based. In recent years, codification of the methodology used to assess risk has increased confidence that the process can be reasonably free of bias; however, significant controversy remains, particularly when actual data are limited and generally conservative default assumptions are used.[34]

While risk assessment information about a chemical can be somewhat useful in a toxic tort case, at least in terms of setting reasonable boundaries as to the likelihood of causation, the impetus for the development of risk assessment has been the regulatory process, which has different goals.[35] Because of their use of appropriately prudent assumptions in areas of uncertainty and their use of default assumptions when there are limited data, risk assessments intentionally encompass the upper range of possible risks.

F. Toxicology and Epidemiology

Epidemiology is the study of the incidence and distribution of disease in human populations. Clearly, both epidemiology and toxicology have much to offer in elucidating the causal relationship between chemical exposure and disease.[36] These sciences often go hand in hand in assessments of the risks of chemical exposure, without artificial distinctions being drawn between them. However, although courts generally rule epidemiological expert opinion admissible, admissibility of toxicological expert opinion has been more controversial because of uncertain-

34. An example of conservative default assumptions can be found in Superfund risk assessment. The EPA has determined that Superfund sites should be cleaned up to reduce cancer risk from 1 in 10,000 to 1 in 1,000,000. A number of assumptions can go into this calculation, including conservative assumptions about intake, exposure frequency and duration, and cancer-potency factors for the chemicals at the site. *See, e.g.,* Robert H. Harris & David E. Burmaster, *Restoring Science to Superfund Risk Assessment,* 6 Toxics L. Rep. (BNA) 1318 (Mar. 25, 1992).

35. *See, e.g.,* Ellen Relkin, *Use of Governmental and Industrial Standards of Exposure and Toxicological Data in Toxic Tort Litigation, reprinted in* Proving Causation of Disease: Update 1996, at 199 (New Jersey Inst. for Continuing Legal Educ. 1996); Steven Shavell, *Liability for Harm Versus Regulation of Safety,* 13 J. Legal Stud. 357 (1984). Risk assessment has been heavily criticized on a number of grounds. The major argument of industry has been that it is overly conservative and thus greatly overstates the actual risk. The rationale for conservatism is in part the prudent public health approach of "above all, do no harm." The conservative approach is also used, especially in regard to cancer risk, because it is sometimes more feasible to extrapolate to a plausible upper boundary for a risk estimate than it is to estimate a point of maximum likelihood. For a sample of the debate over risk assessment, see Bruce N. Ames & Lois S. Gold, *Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis,* 249 Science 970 (1990); Jean Marx, *Animal Carcinogen Testing Challenged,* 250 Science 743 (1990); Philip H. Abelson, *Incorporation of a New Science into Risk Assessment,* 250 Science 1497 (1990); Frederica P. Perera, *Letter to the Editor: Carcinogens and Human Health, Part 1,* 250 Science 1644 (1990); Bruce N. Ames & Lois S. Gold, *Response,* 250 Science 1645 (1990); David P. Rall, *Letter to the Editor: Carcinogens and Human Health, Part 2,* 251 Science 10 (1991); Bruce N. Ames & Lois S. Gold, *Response,* 251 Science 12 (1991); John C. Bailar III et al., *One-Hit Models of Carcinogenesis: Conservative or Not?,* 8 Risk Analysis 485 (1988).

36. *See* Michael D. Green et al., Reference Guide on Epidemiology § V, in this manual.

ties regarding extrapolation from animal and in vitro data to humans. This particularly has been true in cases in which relevant epidemiological research data exist. However, the methodological weaknesses of some epidemiological studies, including their inability to accurately measure exposure and their small numbers of subjects, render these studies difficult to interpret.[37] In contrast, since animal and cell studies permit researchers to isolate the effects of exposure to a single chemical or to known mixtures, toxicological evidence offers unique information concerning dose–response relationships, mechanisms of action, specificity of response, and other information relevant to the assessment of causation.[38]

Even though there is little toxicological data on many of the 75,000 compounds in general commerce, there is far more information from toxicological studies than from epidemiological studies.[39] It is much easier, and more economical, to expose an animal to a chemical or to perform in vitro studies than it is to perform epidemiological studies. This difference in data availability is evident even for cancer causation, for which toxicological study is particularly expensive and time-consuming. Of the perhaps two dozen chemicals that reputable international authorities agree are known human carcinogens based on positive epidemiological studies, arsenic is the only one not known to be an animal carcinogen. Yet, there are more than 100 known animal carcinogens for which there is no valid epidemiological database, and a handful of others for which the epidemiological database is equivocal (e.g., butadiene).[40] To clarify

37. *Id.*

38. Both commonalities and differences between animal responses and human responses to chemical exposures were recognized by the court in *International Union, United Automobile, Aerospace and Agricultural Implement Workers of America v. Pendergrass,* 878 F.2d 389 (D.C. Cir. 1989). In reviewing the results of both epidemiological and animal studies on formaldehyde, the court stated: "Humans are not rats, and it is far from clear how readily one may generalize from one mammalian species to another. But in light of the epidemiological evidence [of carcinogenicity] that was not the main problem. Rather it was the absence of data at low levels." *Id.* at 394. The court remanded the matter to OSHA to reconsider its findings that formaldehyde presented no specific carcinogenic risk to workers at exposure levels of 1 part per million or less. *See also* Hopkins v. Dow Corning Corp., 33 F.3d 1116 (9th Cir. 1994); Ambrosini v. Labarraque, 101 F.3d 129, 141 (D.C. Cir. 1996).

39. *See generally* National Research Council, *supra* note 33. *See also* Lorenzo Tomatis et al., *Evaluation of the Carcinogenicity of Chemicals: A Review of the Monograph Program of the International Agency for Research on Cancer,* 38 Cancer Res. 877, 881 (1978); National Research Council, Toxicity Testing: Strategies to Determine Needs and Priorities (1984); Myra Karstadt & Renee Bobal, *Availability of Epidemiologic Data on Humans Exposed to Animal Carcinogens,* 2 Teratogenesis, Carcinogenesis & Mutagenesis 151 (1982).

40. The absence of epidemiological data is due, in part, to the difficulties in conducting cancer epidemiology studies, including the lack of suitably large groups of individuals exposed for a sufficient period of time, long latency periods between exposure and manifestation of disease, the high variability in the background incidence of many cancers in the general population, and the inability to measure actual exposure levels. These same concerns have led some researchers to conclude that "many negative epidemiological studies must be considered inconclusive" for exposures to low doses or weak carcinogens. Pitot & Dragan, *supra* note 19, at 240–41.

any findings, regulators can require a repeat of an equivocal two-year animal toxicological study or the performance of additional laboratory studies in which animals deliberately are exposed to the chemical. Such deliberate exposure is not possible in humans. As a general rule, equivocally positive epidemiological studies reflect prior workplace practices that led to relatively high levels of chemical exposure for a limited number of individuals and that, fortunately, in most cases no longer occur now. Thus, an additional prospective epidemiological study often is not possible, and even the ability to do retrospective studies is constrained by the passage of time.

II. Expert Qualifications

The basis of the toxicologist's expert opinion in a specific case is a thorough review of the research literature and treatises concerning effects of exposure to the chemical at issue. To arrive at an opinion, the expert assesses the strengths and weaknesses of the research studies. The expert also bases an opinion on fundamental concepts of toxicology relevant to understanding the actions of chemicals in biological systems.

As the following series of questions indicates, no single academic degree, research specialty, or career path qualifies an individual as an expert in toxicology. Toxicology is a heterogeneous field. A number of indicia of expertise can be explored, however, which are relevant to both the admissibility and weight of the proffered expert opinion.

A. Does the Proposed Expert Have an Advanced Degree in Toxicology, Pharmacology, or a Related Field? If the Expert Is a Physician, Is He or She Board Certified in a Field Such As Occupational Medicine?

A graduate degree in toxicology demonstrates that the proposed expert has a substantial background in the basic issues and tenets of toxicology. Many universities have established graduate programs in toxicology only recently. These programs are administered by the faculties of medicine, pharmacology, pharmacy, or public health.

Given the relatively recent establishment of academic toxicology programs, a number of highly qualified toxicologists are physicians or hold doctoral degrees in related disciplines (e.g., pharmacology, biochemistry, environmental health, or industrial hygiene). For a person with this type of background, a single course in toxicology is unlikely to provide sufficient background for developing expertise in the field.

A proposed expert should be able to demonstrate an understanding of the discipline of toxicology, including statistics, toxicological research methods, and disease processes. A physician without particular training or experience in toxicology is unlikely to have sufficient background to evaluate the strengths and weaknesses of toxicological research.[41] Most practicing physicians have little knowledge of environmental and occupational medicine. Generally, physicians are quite knowledgeable about identification of effects and their treatment. The cause of these effects, particularly if they are unrelated to the treatment of the disease, is generally of little concern to the practicing physician. Subspecialty physicians may have particular knowledge of a cause-and-effect relationship (e.g., pulmonary physicians have knowledge of the relationship between asbestos exposure and asbestosis),[42] but most physicians have little training in chemical toxicology and lack an understanding of exposure assessment and dose–response relationships. An exception is a physician who is certified in medical toxicology by the American Board of Medical Toxicology, based on substantial training in toxicology and successful completion of rigorous examinations.

Some physicians who are occupational health specialists also have training in toxicology. Knowledge of toxicology is particularly strong among those who work in the chemical, petrochemical, and pharmaceutical industries, in which surveillance of workers exposed to chemicals is a major responsibility. Of the occupational physicians practicing today, only about 1,000 have successfully completed the board examination in occupational medicine, which contains some questions about chemical toxicology.[43]

41. *See* Mary Sue Henifin et al., Reference Guide on Medical Testimony, § II, in this manual.

42. *See, e.g.,* Moore v. Ashland Chem., Inc., 126 F.3d 679, 701 (5th Cir. 1997) (treating physician's opinion admissible as to causation of reactive airway disease); McCullock v. H.B. Fuller Co., 61 F.3d 1038, 1044 (2d Cir. 1995) (treating physician's opinion admissible as to effect of fumes from hot-melt glue on throat, where physician was board certified in otolaryngology and based his opinion on medical history and treatment, pathological studies, differential etiology, and scientific literature); Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378, 1384 (4th Cir. 1995) (treating physician's opinion admissible as to causation of liver failure by mixture of alcohol and acetaminophen, based on medical history, physical examination, lab and pathology data, and scientific literature—the same methodologies used daily in the diagnosis of patients).

Treating physicians also become involved in considering cause-and-effect relationships when they are asked whether a patient can return to a situation in which an exposure has occurred. The answer is obvious if the cause-and-effect relationship is clearly known. However, this relationship is often uncertain, and the physician must consider the appropriate advice. In such situations, the physician will tend to give advice as if the causality was established, both because it is appropriate caution and because of fears concerning medicolegal issues.

43. Clinical ecologists, another group of physicians, have offered opinions regarding multiple-chemical hypersensitivity and immune-system responses to chemical exposures. These physicians generally have a background in the field of allergy, not toxicology, and their theoretical approach is derived in part from classic concepts of allergic responses and immunology. This theoretical approach has often led clinical ecologists to find cause-and-effect relationships or low-dose effects that are not generally accepted by toxicologists. Clinical ecologists often belong to the American Academy of Environmental Medicine.

B. Has the Proposed Expert Been Certified by the American Board of Toxicology, Inc., or Does He or She Belong to a Professional Organization, Such As the Academy of Toxicological Sciences or the Society of Toxicology?

As of January 1999, 1,631 individuals from twenty-one countries had received board certification from the American Board of Toxicology, Inc. To sit for the examination, which has a pass rate of less than 75%, the candidate must be involved full-time in the practice of toxicology, including designing and managing toxicological experiments or interpreting results and translating them to identify and solve human and animal health problems. To become certified, the candidate must pass all three parts of the examination within two years. Diplomates must be recertified through examination every five years.

The Academy of Toxicological Sciences (ATS) was formed to provide credentials in toxicology through peer review only. It does not administer examinations for certification.

The Society of Toxicology (SOT), the major professional organization for the field of toxicology, was founded in 1961 and has grown dramatically in recent years; it currently has 4,672 members.[44] It has reasonably strict criteria for membership. Qualified people must have conducted and published original research in some phase of toxicology (excluding graduate work) or be generally recognized as expert in some phase of toxicology and be approved by a majority vote of the board of directors. Many environmental toxicologists who meet these qualifications belong to SOT.

Physician toxicologists can join the American College of Medical Toxicology and the American Academy of Clinical Toxicologists. Other organizations in the field are the American College of Toxicology, which has less stringent criteria for membership; the International Society of Regulatory Toxicology and Pharmacology; and the Society of Occupational and Environmental Health. The last two organizations require only the payment of dues for membership.

In 1991, the Council on Scientific Affairs of the American Medical Association concluded that until "accurate, reproducible, and well-controlled studies are available, . . . multiple chemical sensitivity should not be considered a recognized clinical syndrome." Council on Scientific Affairs, American Med. Ass'n, Council Report on Clinical Ecology 6 (1991). In *Bradley v. Brown,* 42 F.3d 434, 438 (7th Cir. 1994), the court considered the admissibility of an expert opinion based on clinical ecology theories. The court ruled the opinion inadmissible, finding that it was "hypothetical" and based on anecdotal evidence as opposed to scientific research. *See also* Coffin v. Orkin Exterminating Co., 20 F. Supp. 2d 107, 110 (D. Me. 1998); Frank v. New York, 972 F. Supp. 130, 132 n.2 (N.D.N.Y 1997). *But see* Elam v. Alcolac, Inc., 765 S.W.2d 42, 86 (Mo. Ct. App. 1988) (expert opinion based on clinical ecology theories admissible), *cert. denied,* 493 U.S. 817 (1989).

44. There are currently fifteen specialty sections of SOT that represent the different types of research needed to understand the wide range of toxic effects associated with chemical exposures. These sections include mechanisms, molecular biology, inhalation toxicology, metals, neurotoxicology, carcinogenesis, risk assessment, and immunotoxicology.

C. What Other Criteria Does the Proposed Expert Meet?

The success of academic scientists in toxicology, as in other biomedical sciences, usually is measured by the following types of criteria: the quality and number of peer-reviewed publications, the ability to compete for research grants, service on scientific advisory panels, and university appointments.

Publication of articles in peer-reviewed journals indicates an expertise in toxicology. The number of articles, their topics, and whether the individual is the principal author are important factors in determining the expertise of a toxicologist.[45]

Most research grants from government agencies and private foundations are highly competitive. Successful competition for funding and publication of the research findings indicate competence in an area.

Selection for local, national, and international regulatory advisory panels usually implies recognition in the field. Examples of such panels are the National Institutes of Health Toxicology Study Section and panels convened by the EPA, the FDA, the World Health Organization (WHO), and the IARC. Recognized industrial organizations, including the American Petroleum Institute, Electric Power Research Institute, and Chemical Industry Institute of Toxicology, and public interest groups, such as the Environmental Defense Fund and the Natural Resources Defense Council, employ toxicologists directly and as consultants and enlist academic toxicologists to serve on advisory panels. Because of a growing interest in environmental issues, the demand for scientific advice has outgrown the supply of available toxicologists. It is thus common for reputable toxicologists to serve on advisory panels.

Finally, a university appointment in toxicology, risk assessment, or a related field signifies an expertise in that area, particularly if the university has a graduate education program in that area.

45. Examples of reputable, peer-reviewed journals are the *Journal of Toxicology and Environmental Health*; *Toxicological Sciences*; *Toxicology and Applied Pharmacology*; *Science*; *British Journal of Industrial Medicine*; *Clinical Toxicology*; *Archives of Environmental Health*; *Journal of Occupational Medicine*; *Annual Review of Pharmacology and Toxicology*; *Teratogenesis, Carcinogenesis and Mutagenesis*; *Fundamental and Applied Toxicology*; *Inhalation Toxicology*; *Biochemical Pharmacology*; *Toxicology Letters*; *Environmental Research*; *Environmental Health Perspectives*; and *American Journal of Industrial Medicine*.

III. Demonstrating an Association Between Exposure and Risk of Disease

Once the expert has been qualified, he or she is expected to offer an opinion on whether the plaintiff's disease was caused by exposure to a chemical. To do so, the expert relies on the principles of toxicology to provide a scientifically valid methodology for establishing causation and then applies the methodology to the facts of the case.

An opinion on causation should be premised on three preliminary assessments. First, the expert should analyze whether the disease can be related to chemical exposure by a biologically plausible theory. Second, the expert should examine if the plaintiff was exposed to the chemical in a manner that can lead to absorption into the body. Third, the expert should offer an opinion as to whether the dose to which the plaintiff was exposed is sufficient to cause the disease.

The following questions help evaluate the strengths and weaknesses of toxicological evidence.

A. On What Species of Animals Was the Compound Tested? What Is Known About the Biological Similarities and Differences Between the Test Animals and Humans? How Do These Similarities and Differences Affect the Extrapolation from Animal Data in Assessing the Risk to Humans?

All living organisms share a common biology that leads to marked similarities in the responsiveness of subcellular structures to toxic agents. Among mammals, more than sufficient common organ structure and function readily permit the extrapolation from one species to another in most instances. Comparative information concerning factors that modify the toxic effects of chemicals, including absorption, distribution, metabolism, and excretion, in the laboratory test animals and humans enhances the expert's ability to extrapolate from laboratory animals to humans.[46]

The expert should review similarities and differences in the animal species in which the compound has been tested and in humans. This analysis should form the basis of the expert's opinion as to whether extrapolation from animals to humans is warranted.[47]

46. *See generally supra* notes 26–27 and accompanying text; Animal Models in Toxicology, *supra* note 23; Edward J. Calabrese, Principles of Animal Extrapolation (1983); Human Risk Assessment: The Role of Animal Selection and Extrapolation (M. Val Roloff ed., 1987); Filov et al., *supra* note 23.

47. The failure to review similarities and differences in metabolism in performing cross-species extrapolation has led to the exclusion of opinions based on animal data. *See* Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1410 (D. Or. 1996); Nelson v. American Sterilizer Co., 566 N.W.2d 671 (Mich. Ct. App. 1997). *But see In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 779–80 (3d Cir. 1994)

In general, there is an overwhelming similarity in the biology of all living things and a particularly strong similarity among mammals. Of course, laboratory animals differ from humans in many ways. For example, rats do not have gall bladders. Thus, rat data would not be pertinent to the possibility that a compound produces human gall bladder toxicity.[48] Note that many subjective symptoms are poorly modeled in animal studies. Thus, complaints that a chemical has caused nonspecific symptoms, such as nausea, headache, and weakness, for which there are no objective manifestations in humans are difficult to test in laboratory animals.

B. Does Research Show That the Compound Affects a Specific Target Organ? Will Humans Be Affected Similarly?

Some toxic agents affect only specific organs and not others. This organ specificity may be due to particular patterns of absorption, distribution, metabolism, and excretion; the presence of specific receptors; or organ function. For example, organ specificity may reflect the presence in the organ of relatively high levels of an enzyme capable of metabolizing or changing a compound to a toxic form of the compound known as a metabolite, or it may reflect the relatively low level of an enzyme capable of detoxifying a compound. An example of the former is liver toxicity caused by inhaled carbon tetrachloride, which affects the liver but not the lungs because of extensive metabolism to a toxic metabolite within the liver but relatively little such metabolism in the lung.[49]

Some chemicals, however, may cause nonspecific effects or even multiple effects. Lead is an example of a toxic agent that affects many organ systems, including red blood cells, the central and peripheral nervous systems, the reproductive system, and the kidneys.

The basis of specificity often reflects the function of individual organs. For

(noting that humans and monkeys are likely to show similar sensitivity to PCBs), *cert. denied sub nom.* General Elec. Co. v. Ingram, 513 U.S. 1190 (1995).

As the Supreme Court noted in *General Electric Co. v. Joiner,* 522 U.S. 136, 144 (1997), the issue as to admissibility is not whether animal studies are ever admissible to establish causation, but whether the particular studies relied upon by plaintiff's experts were sufficiently supported. *See* Carl F. Cranor et al., *Judicial Boundary Drawing and the Need for Context-Sensitive Science in Toxic Torts After* Daubert v. Merrell Dow Pharmaceuticals, Inc., 16 Va. Envtl. L.J. 1, 38 (1996).

48. *See, e.g.,* Calabrese, *supra* note 46, at 583–89 tbl.14-1. Species differences that produce a qualitative difference in response to xenobiotics are well known. Sometimes understanding the mechanism underlying the species difference can allow one to predict whether the effect will occur in humans. Thus, carbaryl, an insecticide commonly used for gypsy moth control, among other things, produces fetal abnormalities in dogs but not in hamsters, mice, rats, and monkeys. Dogs lack the specific enzyme involved in metabolizing carbaryl; the other species tested all have this enzyme, as do humans. Therefore, it has been assumed that humans are not at risk for fetal malformations produced by carbaryl.

49. Brian Jay Day et al., *Potentiation of Carbon Tetrachloride-Induced Hepatotoxicity and Pneumotoxicity by Pyridine,* 8 J. Biochemical Toxicol. 11 (1993).

example, the thyroid is particularly susceptible to radioactive iodine in atomic fallout because thyroid hormone is unique within the body in that it requires iodine. Through evolution a very efficient and specific mechanism has developed which concentrates any absorbed iodine preferentially within the thyroid, thus rendering the thyroid particularly at risk from radioactive iodine. In a test tube the radiation from radioactive iodine can affect the genetic material obtained from any cell in the body, but in the intact laboratory animal or human, only the thyroid is at risk.

The unfolding of the human genome is already beginning to provide information pertinent to understanding the wide variation in human risk to environmental chemicals. The impact of this understanding on toxic tort causation issues remains to be explored.[50]

C. What Is Known About the Chemical Structure of the Compound and Its Relationship to Toxicity?

Understanding of the structural aspects of chemical toxicology has led to the use of structure activity relationships (SAR) as a formal method of predicting the potential toxicity of new chemicals. This technique compares the chemical structure of compounds with known toxicity and the chemical structure of compounds with unknown toxicity. Toxicity then is estimated based on molecular similarities between the two compounds. Although SAR is used extensively by the EPA in evaluating many new chemicals required to be tested under the registration requirements of the Toxic Substances Control Act (TSCA), its reliability has a number of limitations.[51]

50. The wide range in the rate of metabolism of chemicals is at least partly under genetic control. A recent study in China found approximately a doubling of risk in people with high levels of either an enzyme that increased the rate of formation of a toxic metabolite or an enzyme that decreased the rate of detoxification of this metabolite. There was a sevenfold increase in risk for those who had both genetically determined variants. *See* Frederica P. Perera, *Molecular Epidemiology: Insights into Cancer Susceptibility, Risk Assessment, and Prevention,* 88 J. Nat'l Cancer Inst. 496 (1996).

51. For example, benzene and the alkyl benzenes (which include toluene, xylene, and ethyl benzene) share a similar chemical structure. SAR works exceptionally well in predicting the acute central nervous system anesthetic-like effects of both benzene and the alkyl benzenes. Although there are slight differences in dose–response relationships, they are readily explained by the interrelated factors of chemical structure, vapor pressure, and lipid solubility (the brain is highly lipid). National Research Council, The Alkyl Benzenes (1981). However, only benzene produces damage to the bone marrow and leukemia; the alkyl benzenes do not have this effect. This difference is the result of specific toxic metabolic products of benzene in comparison with the alkyl benzenes. Thus, SAR is predictive of neurotoxic effects but not bone-marrow effects. *See* Hoffman, *supra* note 25, at 277.

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579 (1993), the Court rejected a per se exclusion of SAR, animal data, and reanalyses of previously published epidemiological data where there were negative epidemiological data. However, as the court recognized in *Sorensen v. Shaklee Corp.,* 31 F.3d 638, 646 n.12 (8th Cir. 1994), the problem with SAR is that "'[m]olecules with minor structural differences can produce very different biological effects.'" (quoting Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases,* 46 Stan. L. Rev. 1, 19 (1993)).

D. Has the Compound Been the Subject of In Vitro Research, and If So, Can the Findings Be Related to What Occurs In Vivo?

Cellular and tissue-culture research can be particularly helpful in identifying mechanisms of toxic action and potential target-organ toxicity. The major barrier to use of in vitro results is the frequent inability to relate doses that cause cellular toxicity to doses that cause whole-animal toxicity. In many critical areas, knowledge that permits such quantitative extrapolation is lacking.[52] Nevertheless, the ability to quickly test new products through in vitro tests, using human cells, provides invaluable "early warning systems" for toxicity.[53]

E. Is the Association Between Exposure and Disease Biologically Plausible?

No matter how strong the temporal relationship between exposure and development of disease, or the supporting epidemiological evidence, it is difficult to accept an association between a compound and a health effect when no mechanism can be identified by which the chemical exposure leads to the putative effect.[54]

IV. Specific Causal Association Between an Individual's Exposure and the Onset of Disease

An expert who opines that exposure to a compound caused a person's disease engages in deductive clinical reasoning.[55] In most instances, cancers and other diseases do not wear labels documenting their causation.[56] The opinion is based on an assessment of the individual's exposure, including the amount, the temporal relationship between the exposure and disease, and other disease-causing

52. In Vitro Toxicity Testing: Applications to Safety Evaluation, *supra* note 25, at 8. Despite its limitations, in vitro research can strengthen inferences drawn from whole-animal bioassays and can support opinions regarding whether the association between exposure and disease is biologically plausible. *See* Hoffman, *supra* note 25, at 278–93; Rogers & Kavlock, *supra* note 25, at 319–23.

53. Graham v. Playtex Prods., Inc., 993 F. Supp. 127, 131–32 (N.D.N.Y. 1998) (opinion based on in vitro experiments showing that rayon tampons were associated with higher risk of toxic shock syndrome was admissible in the absence of epidemiological evidence).

54. However, theories of bioplausibility, without additional data, have been found to be insufficient to support a finding of causation. *See, e.g.,* Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1414 (D. Or. 1996); Golod v. Hoffman La Roche, 964 F. Supp. 841, 860–61 (S.D.N.Y. 1997).

55. For an example of deductive clinical reasoning based on known facts about the toxic effects of a chemical and the individual's pattern of exposure, see Bernard D. Goldstein, *Is Exposure to Benzene a Cause of Human Multiple Myeloma?,* 609 Annals N.Y. Acad. Sci. 225 (1990).

56. Research still in the preliminary stages shows that certain cancers do wear labels in the form of DNA adducts and mutational spectra. *See generally* National Research Council, Biologic Markers in Reproductive Toxicology (1989).

factors. This information is then compared with scientific data on the relationship between exposure and disease. The certainty of the expert's opinion depends on the strength of the research data demonstrating a relationship between exposure and the disease at the dose in question and the absence of other disease-causing factors (also known as confounding factors).[57]

Particularly problematic are generalizations made in personal injury litigation from regulatory positions. For example, if regulatory standards are discussed in toxic tort cases to provide a reference point for assessing exposure levels, it must be recognized that there is a great deal of variability in the extent of evidence required to support different regulations.[58] The extent of evidence required to support regulations depends on

1. the law (e.g., the Clean Air Act has language focusing regulatory activity for primary pollutants on adverse health consequences to sensitive populations with an adequate margin of safety and with no consideration of economic consequences, whereas regulatory activity under TSCA clearly asks for some balance between the societal benefits and risks of new chemicals[59]);
2. the specific end point of concern (e.g., consider the concern caused by cancer and adverse reproductive outcomes versus almost anything else); and
3. the societal impact (e.g., the public's support for control of an industry that causes air pollution versus the public's desire to alter personal automobile use patterns).

These three concerns, as well as others, including costs, politics, and the virtual certainty of litigation challenging the regulation, have an impact on the level of scientific proof required by the regulatory decision maker.[60]

57. Causation issues are discussed in Michael D. Green et al., Reference Guide on Epidemiology, § V, and Mary Sue Henifin et al., Reference Guide on Medical Testimony, § IV, in this manual. *See also* Joseph Sanders, *Scientific Validity, Admissibility and Mass Torts After* Daubert, 78 Minn. L. Rev. 1387 (1994); Susan R. Poulter, *Science and Toxic Torts: Is There a Rational Solution to the Problem of Causation?,* 7 High Tech. L.J. 189 (1992); Troyen A. Brennan, *Causal Chains and Statistical Links: The Role of Scientific Uncertainty in Hazardous-Substance Litigation,* 73 Cornell L. Rev. 469 (1988); Orrin E. Tilevitz, *Judicial Attitudes Towards Legal and Scientific Proof of Cancer Causation,* 3 Colum. J. Envtl. L. 344, 381 (1977); David L. Bazelon, *Science and Uncertainty: A Jurist's View*, 5 Harv. Envtl. L. Rev. 209 (1981).

58. The relevance of regulatory standards to toxic tort litigation is explored in Silbergeld, *supra* note 2; Relkin, *supra* note 35; *In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 781 (3d Cir. 1994) (district court abused its discretion in excluding animal studies relied upon by the EPA), *cert. denied sub nom.* General Elec. Co. v. Ingram, 513 U.S. 1190 (1995); John Endicott, *Interaction Between Regulatory Law and Tort Law in Controlling Toxic Chemical Exposure,* 47 SMU L. Rev. 501 (1994).

59. *See, e.g.,* Clean Air Act Amendments of 1990, 42 U.S.C. § 7412(f) (1994); Toxic Substances Control Act, 15 U.S.C. § 2605 (1994).

60. These concerns are discussed in Stephen Breyer, Breaking the Vicious Circle: Toward Effective Risk Regulation (1993).

In addition, regulatory standards traditionally include protective factors to reasonably ensure that susceptible individuals are not put at risk. Furthermore, standards are often based on the risk that is due to lifetime exposure. Accordingly, the mere fact that an individual has been exposed to a level above a standard does not necessarily mean that an adverse effect has occurred.

A. Was the Plaintiff Exposed to the Substance, and If So, Did the Exposure Occur in a Manner That Can Result in Absorption into the Body?

Evidence of exposure is essential in determining the effects of harmful substances. Basically, potential human exposure is measured in one of three ways. First, when direct measurements cannot be made, exposure can be measured by mathematical modeling, in which one uses a variety of physical factors to estimate the transport of the pollutant from the source to the receptor. For example, mathematical models take into account such factors as wind variations to allow calculation of the transport of radioactive iodine from a federal atomic research facility to nearby residential areas. Second, exposure can be directly measured in the medium in question—air, water, food, or soil. When the medium of exposure is water, soil, or air, hydrologists or meteorologists may be called upon to contribute their expertise to measuring exposure. The third approach directly measures human receptors through some form of biological monitoring, such as blood tests to determine blood lead levels or urinalyses to check for a urinary metabolite, which shows pollutant exposure. Ideally, both environmental testing and biological monitoring are performed; however, this is not always possible, particularly in instances of past exposure.[61]

The toxicologist must go beyond understanding exposure to determine if the individual was exposed to the compound in a manner that can result in absorption into the body. The absorption of the compound is a function of its physiochemical properties, its concentration, and the presence of other agents or conditions that assist or interfere with its uptake. For example, inhaled lead is absorbed almost totally, whereas ingested lead is taken up only partially into the body. Iron deficiency and low nutritional calcium intake, both common conditions of inner-city children, increase the amount of ingested lead that is absorbed in the gastrointestinal tract and passes into the bloodstream.

61. *See, e.g., In re* Three Mile Island Litig. Consol. Proceedings, 927 F. Supp. 834, 870 (M.D. Pa. 1996) (plaintiffs failed to present direct or indirect evidence of exposure to cancer-inducing levels of radiation); Mitchell v. Gencorp Inc., 165 F.3d 778, 781 (10th Cir. 1999) ("[g]uesses, even if educated, are insufficient to prove the level of exposure in a toxic tort case"). *See also* Wright v. Willamette Indus., Inc., 91 F.3d 1105, 1107 (8th Cir. 1996); Valentine v. Pioneer Chlor Alkali Co., 921 F. Supp. 666, 678 (D. Nev. 1996).

B. Were Other Factors Present That Can Affect the Distribution of the Compound Within the Body?

Once a compound is absorbed into the body through the skin, lungs, or gastrointestinal tract, it is distributed throughout the body through the bloodstream. Thus, the rate of distribution depends on the rate of blood flow to various organs and tissues. Distribution and resulting toxicity are also influenced by other factors, including the dose, the route of entry, tissue solubility, lymphatic supplies to the organ, metabolism, and the presence of specific receptors or uptake mechanisms within body tissues.

C. What Is Known About How Metabolism in the Human Body Alters the Toxic Effects of the Compound?

Metabolism is the alteration of a chemical by bodily processes. It does not necessarily result in less toxic compounds being formed. In fact, many of the organic chemicals that are known human cancer-causing agents require metabolic transformation before they can cause cancer. A distinction often is made between direct-acting agents, which cause toxicity without any metabolic conversion, and indirect-acting agents, which require metabolic activation before they can produce adverse effects. Metabolism is complex, since a variety of pathways compete for the same agent; some produce harmless metabolites, and others produce toxic agents.[62]

D. What Excretory Route Does the Compound Take, and How Does This Affect Its Toxicity?

Excretory routes are urine, feces, sweat, saliva, expired air, and lactation. Many inhaled volatile agents are eliminated primarily by exhalation. Small water-soluble compounds are usually excreted through urine. Higher-molecular-weight compounds are often excreted through the biliary tract into the feces. Certain fat-soluble, poorly metabolized compounds, such as PCBs, may persist in the body for decades, although they can be excreted in the milk fat of lactating women.

E. Does the Temporal Relationship Between Exposure and the Onset of Disease Support or Contradict Causation?

In acute toxicity, there is usually a short time period between cause and effect. However, in some situations, the length of basic biological processes necessitates a longer period of time between initial exposure and the onset of observable

62. Courts have explored the relationship between metabolic transformation and carcinogenesis. *See, e.g.,* Stites v. Sundstrand Heat Transfer, Inc., 660 F. Supp. 1516, 1519 (W.D. Mich. 1987).

disease. For example, in acute myelogenous leukemia, the adult form of acute leukemia, at least one to two years must elapse from initial exposure to radiation, benzene, or cancer chemotherapy before the manifestation of a clinically recognizable case of leukemia. A toxic tort claim alleging a shorter time period between cause and effect is scientifically untenable. Much longer time periods are necessary for the manifestation of solid tumors caused by asbestos.[63]

F. If Exposure to the Substance Is Associated with the Disease, Is There a No Observable Effect, or Threshold, Level, and If So, Was the Individual Exposed Above the No Observable Effect Level?

For agents that produce effects other than through mutations, it is assumed that there is some level that is incapable of causing harm. If the level of exposure was below this no observable effect, or threshold, level, a relationship between the exposure and disease cannot be established.[64] When only laboratory animal data are available, the expert extrapolates the NOEL from animals to humans by calculating the animal NOEL based on experimental data and decreasing this level by one or more safety factors to ensure no human effect.[65] The NOEL can also be calculated from human toxicity data if they exist. This analysis, however, is not applied to substances that exert toxicity by causing mutations leading to cancer. Theoretically, any exposure at all to mutagens may increase the risk of cancer, although the risk may be very slight and not achieve medical probability.[66]

63. The temporal relationship between exposure and causation is discussed in *Cavallo v. Star Enterprise,* 892 F. Supp. 756, 769–74 (E.D. Va. 1995) (expert testimony based primarily on temporal connection between exposure to jet fuel and onset of symptoms, without other evidence of causation, ruled inadmissible). *But see* National Bank of Commerce v. Dow Chem. Co., 965 F. Supp. 1490, 1525 (E.D. Ark. 1996) ("[T]here may be instances where the temporal connection between exposure to a given chemical and subsequent injury is so compelling as to dispense with the need for reliance on standard methods of toxicology.").

64. *See, e.g.,* Allen v. Pennsylvania Eng'g Corp., 102 F.3d 194, 199 (5th Cir. 1996) ("Scientific knowledge of the harmful level of exposure to a chemical, plus knowledge that the plaintiff was exposed to such quantities, are minimal facts necessary to sustain the plaintiff's burden in a toxic tort case."); Redland Soccer Club, Inc. v. Department of Army, 55 F.3d 827, 847 (3d Cir. 1995) (summary judgment for defendant precluded where exposure above cancer threshold level could be calculated from soil samples).

65. *See, e.g., supra* notes 18–19 and accompanying text; Tardiff & Rodricks, *supra* note 18, at 391; Joseph V. Rodricks, Calculated Risks 165–70, 193–96 (1992); Lu, *supra* note 14, at 84.

66. *See* sources cited *supra* note 19.

V. Medical History

A. Is the Medical History of the Individual Consistent with the Toxicologist's Expert Opinion Concerning the Injury?

One of the basic and most useful tools in diagnosis and treatment of disease is the patient's medical history.[67] A thorough, standardized patient information questionnaire would be particularly useful for identifying the etiology, or causation, of illnesses related to toxic exposures; however, there is currently no validated or widely used questionnaire that gathers all pertinent information.[68] Nevertheless, it is widely recognized that a thorough medical history involves the questioning and examination of the patient as well as appropriate medical testing. The patient's written medical records should also be examined.

The following information is relevant to a patient's medical history: past and present occupational and environmental history and exposure to toxic agents; lifestyle characteristics (e.g., use of nicotine and alcohol); family medical history (i.e., medical conditions and diseases of relatives); and personal medical history (i.e., present symptoms and results of medical tests as well as past injuries, medical conditions, diseases, surgical procedures, and medical test results).

In some instances, the reporting of symptoms can be in itself diagnostic of exposure to a specific substance, particularly in evaluating acute effects.[69] For example, individuals acutely exposed to organophosphate pesticides report headaches, nausea, and dizziness accompanied by anxiety and restlessness. Other reported symptoms are muscle twitching, weakness, and hypersecretion with sweating, salivation, and tearing.[70]

B. Are the Complaints Specific or Nonspecific?

Acute exposure to many toxic agents produces a constellation of nonspecific symptoms, such as headaches, nausea, lightheadedness, and fatigue. These types of symptoms are part of human experience and can be triggered by a host of medical and psychological conditions. They are almost impossible to quantify or document beyond the patient's report. Thus, these symptoms can be attributed

67. For a thorough discussion of the methods of clinical diagnosis, see Mary Sue Henifin et al., Reference Guide on Medical Testimony, § IV.B–C, in this manual. *See also* Jerome P. Kassirer & Richard I. Kopelman, Learning Clinical Reasoning (1991). A number of cases have considered the admissibility of the treating physician's opinion based, in part, on medical history, symptomatology, and laboratory and pathology studies. *See* cases cited *supra* note 42.

68. Office of Tech. Assessment, U.S. Congress, *supra* note 10, at 365–89.

69. *But see* Moore v. Ashland Chem., Inc., 126 F.3d 679, 693 (5th Cir. 1997) (discussion of relevance of symptoms within forty-five minutes of exposure).

70. Environmental Protection Agency, Recognition and Management of Pesticide Poisonings (4th ed. 1989).

mistakenly to an exposure to a toxic agent or discounted as unimportant when in fact they reflect a significant exposure.[71]

In taking a careful medical history, the expert focuses on the time pattern of symptoms and disease manifestations in relation to any exposure and on the constellation of symptoms to determine causation. It is easier to establish causation when a symptom is unusual and rarely is caused by anything other than the suspect chemical (e.g., such rare cancers as hemangiosarcoma, associated with vinyl chloride exposure, and mesothelioma, associated with asbestos exposure). However, many cancers and other conditions are associated with several causative factors, thus complicating proof of causation.[72]

C. Do Laboratory Tests Indicate Exposure to the Compound?

Two types of laboratory tests can be considered: tests that are routinely used in medicine to detect changes in normal body status, and specialized tests, which are used to detect the presence of the chemical or physical agent.[73] For the most part, tests used to demonstrate the presence of a toxic agent are frequently unavailable from clinical laboratories. Even when available from a hospital or a clinical laboratory, a test such as that for carbon monoxide combined to hemoglobin is done so rarely that it may raise concerns as to its accuracy. Other tests, such as the test for blood lead levels, are required for routine surveillance of potentially exposed workers. However, if a laboratory is certified for the testing of blood lead in workers, for which the OSHA action level is 40 micrograms per deciliter (μg/dl), it does not necessarily mean that it will give reliable data on blood lead levels at the much lower Centers for Disease Control and Prevention (CDC) action level of 10 μg/dl.

D. What Other Causes Could Lead to the Given Complaint?

With few exceptions, acute and chronic diseases, including cancer, can be caused by either a single toxic agent or a combination of agents or conditions. In taking a careful medical history, the expert examines the possibility of competing causes, or confounding factors, for any disease, which leads to a differential diagnosis. In

71. The issue of whether development of nonspecific symptoms may be related to pesticide exposure was considered in *Kannankeril v. Terminix International, Inc.,* 128 F.3d 802 (3d Cir. 1997). The court ruled that the trial court abused its discretion in excluding expert opinion that considered, and rejected, a negative laboratory test. *Id.* at 808–09.

72. Failure to rule out other potential causes of symptoms may lead to a ruling that the expert's report is inadmissible. *See, e.g.,* Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1413 (D. Or. 1996); Rutigliano v. Valley Bus. Forms, 929 F. Supp. 779, 786 (D.N.J. 1996).

73. *See, e.g.,* Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 807 (3d Cir. 1997).

addition, ascribing causality to a specific source of a chemical requires that a history be taken concerning other sources of the same chemical. The failure of a physician to elicit such a history or of a toxicologist to pay attention to such a history raises questions about competence and leaves open the possibility of competing causes of the disease.[74]

E. Is There Evidence of Interaction with Other Chemicals?

An individual's simultaneous exposure to more than one chemical may result in a response that differs from that which would be expected from exposure to only one of the chemicals.[75] When the effect of multiple agents is that which would be predicted by the sum of the effects of individual agents, it is called an additive effect; when it is greater than this sum, it is known as a synergistic effect; when one agent causes a decrease in the effect produced by another, the result is termed antagonism; and when an agent that by itself produces no effect leads to an enhancement of the effect of another agent, the response is termed potentiation.[76]

Three types of toxicological approaches are pertinent to understanding the effects of mixtures of agents. One is based on the standard toxicological evaluation of common commercial mixtures, such as gasoline. The second approach is from studies in which the known toxicological effect of one agent is used to explore the mechanism of action of another agent, such as using a known specific inhibitor of a metabolic pathway to determine whether the toxicity of a second agent depends on this pathway. The third approach is based on an understanding of the basic mechanism of action of the individual components of the mixture, thereby allowing prediction of the combined effect, which can then be tested in an animal model.[77]

74. *See, e.g.,* Bell v. Swift Adhesives, Inc., 804 F. Supp. 1577, 1580 (S.D. Ga. 1992) (expert's opinion that workplace exposure to methylene chloride caused plaintiff's liver cancer, without ruling out plaintiff's infection with hepatitis B virus, a known liver carcinogen, was insufficient to withstand motion for summary judgment for defendant).

75. *See generally* Edward J. Calabrese, Multiple Chemical Interactions (1991).

76. Courts have been called on to consider the issue of synergy. In *International Union, United Automobile, Aerospace & Agricultural Implement Workers of America v. Pendergrass,* 878 F.2d 389, 391 (D.C. Cir. 1989), the court found that OSHA failed to sufficiently explain its findings that formaldehyde presented no significant carcinogenic risk to workers at exposure levels of 1 part per million or less. The court particularly criticized OSHA's use of a linear low-dose risk curve rather than a risk-adverse model after the agency had described evidence of synergy between formaldehyde and other substances that workers would be exposed to, especially wood dust. *Id.* at 395.

77. *See generally* Calabrese, *supra* note 75.

F. Do Humans Differ in the Extent of Susceptibility to the Particular Compound in Question? Are These Differences Relevant in This Case?

Individuals who exercise inhale more than sedentary individuals and therefore are exposed to higher doses of airborne environmental toxins. Similarly, differences in metabolism, which are inherited or caused by external factors, such as the levels of carbohydrates in a person's diet, may result in differences in the delivery of a toxic product to the target organ.[78]

Moreover, for any given level of a toxic agent that reaches a target organ, damage may be greater because of a greater response of that organ. In addition, for any given level of target-organ damage, there may be a greater impact on particular individuals. For example, an elderly individual or someone with preexisting lung disease is less likely to tolerate a small decline in lung function caused by an air pollutant than is a healthy individual with normal lung function.

A person's level of physical activity, age, sex, and genetic makeup, as well as exposure to therapeutic agents (such as prescription or over-the-counter drugs), affect the metabolism of the compound and hence its toxicity.[79] Advances in human genetics research are providing information about susceptibility to environmental agents that may be relevant to determining the likelihood that a given exposure has a specific effect on an individual.[80]

G. Has the Expert Considered Data That Contradict His or Her Opinion?

Multiple avenues of deductive reasoning based on research data lead to scientific acceptance of causation in any field, particularly in toxicology. However, the basis for this deductive reasoning is also one of the most difficult aspects of causation to describe quantitatively. If animal studies, pharmacological research on mechanisms of toxicity, in vitro tissue studies, and epidemiological research all document toxic effects of exposure to a compound, an expert's opinion about causation in a particular case is much more likely to be true.[81]

78. *Id.*

79. The problem of differences in chemical sensitivity was addressed by the court in *Gulf South Insulation v. United States Consumer Product Safety Commission*, 701 F.2d 1137 (5th Cir. 1983). The court overturned the commission's ban on urea-formaldehyde foam insulation because the commission failed to document in sufficient detail the level at which segments of the population were affected and whether their responses were slight or severe: "Predicting how likely an injury is to occur, at least in general terms, is essential to a determination of whether the risk of that injury is unreasonable." *Id.* at 1148.

80. *See supra* note 50.

81. Consistency of research results was considered by the court in *Marsee v. United States Tobacco Co.*, 639 F. Supp. 466, 469–70 (W.D. Okla. 1986). The defendant, the manufacturer of snuff alleged to

The more difficult problem is how to evaluate conflicting research results. When different research studies reach different conclusions regarding toxicity, the expert must be asked to explain how those results have been taken into account in the formulation of the expert's opinion.

cause oral cancer, moved to exclude epidemiological studies conducted in Asia that demonstrate a link between smokeless tobacco and oral cancer. The defendant also moved to exclude evidence demonstrating that the nitrosamines and polonium 210 contained in the snuff are cancer-causing agents in some forty different species of laboratory animals. The court denied both motions, finding:

> There was no dispute that both nitrosamines and polonium 210 are present in defendant's snuff products. Further, defendant conceded that animal studies have accurately and consistently demonstrated that these substances cause cancer in test animals. Finally, the Court found evidence based on experiments with animals particularly valuable and important in this litigation since such experiments with humans are impossible. Under all these circumstances, the Court found this evidence probative on the issue of causation.

Id. *See also* sources cited *supra* note 7.

Glossary of Terms

The following terms and definitions were adapted from a variety of sources, including Office of Technology Assessment, U.S. Congress, Reproductive Health Hazards in the Workplace (1985); Casarett and Doull's Toxicology: The Basic Science of Poisons (Curtis D. Klaassen ed., 5th ed. 1996); National Research Council, Biologic Markers in Reproductive Toxicology (1989); Committee on Risk Assessment Methodology, National Research Council, Issues in Risk Assessment (1993); M. Alice Ottoboni, The Dose Makes the Poison: A Plain-Language Guide to Toxicology (2d ed. 1991); Environmental and Occupational Health Sciences Institute, Glossary of Environment Health Terms (1989).

absorption. The taking up of a chemical into the body either orally, through inhalation, or through skin exposure.

acute toxicity. An immediate toxic response following a single or short-term exposure to an agent or dosing.

additive effect. When exposure to more than one toxic agent results in the same effect as would be predicted by the sum of the effects of exposure to the individual agents.

antagonism. When exposure to one toxic agent causes a decrease in the effect produced by another toxic agent.

bioassay. A test for measuring the toxicity of an agent by exposing laboratory animals to the agent and observing the effects.

biological monitoring. Measurement of toxic agents or the results of their metabolism in biological materials, such as blood, urine, expired air, or biopsied tissue, to test for exposure to the toxic agents, or the detection of physiological changes that are due to exposure to toxic agents.

biologically plausible theory. A biological explanation for the relationship between exposure to an agent and adverse health outcomes.

carcinogen. A chemical substance or other agent that causes cancer.

carcinogenicity bioassay. Limited or long-term tests using laboratory animals to evaluate the potential carcinogenicity of an agent.

chronic toxicity. A toxic response to long-term exposure or dosing with an agent.

clinical ecologists. Physicians who believe that exposure to certain chemical agents can result in damage to the immune system, causing multiple-chemical hypersensitivity and a variety of other disorders. Clinical ecologists often have a background in the field of allergy, not toxicology, and their theoretical approach is derived in part from classic concepts of allergic responses and

immunology. There has been much resistance in the medical community to accepting their claims.

clinical toxicology. The study and treatment of humans exposed to chemicals and the quantification of resulting adverse health effects. Clinical toxicology includes the application of pharmacological principles to the treatment of chemically exposed individuals and research on measures to enhance elimination of toxic agents.

compound. In chemistry, the combination of two or more different elements in definite proportions, which when combined, acquire different properties than the original elements.

confounding factors. Variables that are related to both exposure to a toxic agent and the outcome of the exposure. A confounding factor can obscure the relationship between the toxic agent and the adverse health outcome associated with that agent.

differential diagnosis. A physician's consideration of alternative diagnoses that may explain a patient's condition.

direct-acting agents. Agents that cause toxic effects without metabolic activation or conversion.

distribution. Movement of a toxic agent throughout the organ systems of the body (e.g., the liver, kidney, bone, fat, and central nervous system). The rate of distribution is usually determined by the blood flow through the organ and the ability of the chemical to pass through the cell membranes of the various tissues.

dose, dosage. The measured amount of a chemical that is administered at one time, or that an organism is exposed to in a defined period of time.

dose–response curve. A graphic representation of the relationship between the dose of a chemical administered and the effect produced.

dose–response relationships. The extent to which a living organism responds to specific doses of a toxic substance. The more time spent in contact with a toxic substance, or the higher the dose, the greater the organism's response. For example, a small dose of carbon monoxide will cause drowsiness; a large dose can be fatal.

epidemiology. The study of the occurrence and distribution of disease among people. Epidemiologists study groups of people to discover the cause of a disease, or where, when, and why disease occurs.

epigenetic. Pertaining to nongenetic mechanisms by which certain agents cause diseases, such as cancer.

etiology. A branch of medical science concerned with the causation of diseases.

excretion. The process by which toxicants are eliminated from the body, including through the kidney and urinary tract, the liver and biliary system, the fecal excretor, the lungs, sweat, saliva, and lactation.

exposure. The intake into the body of a hazardous material. The main routes of exposure to substances are through the skin, mouth, and lungs.

extrapolation. The process of estimating unknown values from known values.

Good Laboratory Practice (GLP). Codes developed by the federal government in consultation with the laboratory-testing industry that govern many aspects of laboratory standards.

hazard identification. In risk assessment, the qualitative analysis of all available experimental animal and human data to determine whether and at what dose an agent is likely to cause toxic effects.

hydrogeologists, hydrologists. Scientists who specialize in the movement of ground and surface waters and the distribution and movement of contaminants in those waters.

immunotoxicology. A branch of toxicology concerned with the effects of toxic agents on the immune system.

indirect-acting agents. Agents that require metabolic activation or conversion before they produce toxic effects in living organisms.

inhalation toxicology. The study of the effect of toxic agents that are absorbed into the body through inhalation, including their effects on the respiratory system.

in vitro. A research or testing methodology that uses living cells in an artificial or test tube system, or is otherwise performed outside of a living organism.

in vivo. A research or testing methodology that uses living organisms.

lethal dose 50 (LD50). The dose at which 50% of laboratory animals die within days to weeks.

lifetime bioassay. A bioassay in which doses of an agent are given to experimental animals throughout their lifetime. See bioassay.

maximum tolerated dose (MTD). The highest dose of an agent that an organism can be exposed to without causing death or significant overt toxicity.

metabolism. The sum total of the biochemical reactions that a chemical produces in an organism.

molecular toxicology. The study of how toxic agents interact with cellular molecules, including DNA.

multiple-chemical hypersensitivity. A physical condition whereby individuals react to many different chemicals at extremely low exposure levels.

multistage events. A model for understanding certain diseases, including some cancers, based on the postulate that more than one event is necessary for the onset of disease.

mutagen. A substance that causes physical changes in chromosomes or biochemical changes in genes.

mutagenesis. The process by which agents cause changes in chromosomes and genes.

neurotoxicology. A branch of toxicology concerned with the effects of exposure to toxic agents on the central nervous system.

no observable effect level (NOEL). The highest level of exposure to an agent at which no effect is observed. It is the experimental equivalent of a threshold.

no threshold model. A model for understanding disease causation which postulates that any exposure to a harmful chemical (such as a mutagen) may increase the risk of disease.

one hit theory. A theory of cancer risk in which each molecule of a chemical mutagen has a possibility, no matter how tiny, of mutating a gene in a manner that may lead to tumor formation or cancer.

pharmacokinetics. A mathematical model that expresses the movement of a toxic agent through the organ systems of the body, including to the target organ and to its ultimate fate.

potentiation. The process by which the addition of one agent, which by itself has no toxic effect, increases the toxicity of another agent when exposure to both agents occurs simultaneously.

reproductive toxicology. The study of the effect of toxic agents on male and female reproductive systems, including sperm, ova, and offspring.

risk assessment. The use of scientific evidence to estimate the likelihood of adverse effects on the health of individuals or populations from exposure to hazardous materials and conditions.

risk characterization. The final step of risk assessment, which summarizes information about an agent and evaluates it in order to estimate the risks it poses.

safety assessment. Toxicological research that tests the toxic potential of a chemical in vivo or in vitro using standardized techniques required by governmental regulatory agencies or other organizations.

structure activity relationships (SAR). A method used by toxicologists to predict the toxicity of new chemicals by comparing their chemical structures with those of compounds with known toxic effects.

synergistic effect. When two toxic agents acting together have an effect greater than that predicted by adding together their individual effects.

target organ. The organ system that is affected by a particular toxic agent.

target-organ dose. The dose to the organ that is affected by a particular toxic agent.

teratogen. An agent that changes eggs, sperm, or embryos, thereby increasing the risk of birth defects.

teratogenic. The ability to produce birth defects. (Teratogenic effects do not pass on to future generations.) See teratogen.

threshold. The level above which effects will occur and below which no effects occur. See no observable effect level.

toxic. Of, relating to, or caused by a poison—or a poison itself.

toxic agent or toxicant. An agent or substance that causes disease or injury.

toxicology. The science of the nature and effects of poisons, their detection, and the treatment of their effects.

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