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 chemical agents on biological systems."[1] While an age-old science, toxicology is still struggling to 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 harmful—it is only a question of *dose*.[2] Even water, if consumed in large quantities, can be *toxic.* Second, many chemical agents produce a specific pattern of toxic effects that are used to establish disease causation.[3] Third, the responses of laboratory animals are useful predictors of toxic responses in humans. Each of these tenets, and their exceptions, are discussed in greater detail below.

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, if any, 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 an 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 helps rule out other risk factors for the disease. Toxi-

1. Louis J. Casarett & John Doull, Casarett and Doull's Toxicology: The Basic Science of Poisons 3 (Mary O. Amdur et al. eds., 4th ed. 1991).

2. A discussion of more modern formulations of this principle, which was articulated by Paracelsus in the sixteenth century, may 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.

cological evidence also explains how a chemical causes a disease by describing metabolic, cellular, and other physiological effects of exposure.

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 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 proceedings. 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 this situation toxicological evidence addresses the question of how exposure affects populations rather than specific causation, and agency determinations are usually subject to 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. This 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 provides model questions for evaluating the admissibility and strength of an expert's opinion. Following each question is an explanation of the type of information or toxicological data that is offered in response to the question, as well as a discussion of its significance.

C. Toxicological Research Design

Toxicological research usually involves exposing laboratory animals (*in vivo* research) or cells or tissues (*in vitro* research) to chemicals, monitoring their out-

5. *See, e.g.,* Daubert v. Merrell Dow Pharmaceuticals, Inc., 113 S. Ct. 2786 (1993).

6. *See, e.g.*, 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 tort litigation is discussed at length in Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 Nw. U. L. Rev. 643 (1992). *See also* Joan E. Bertin & Mary S. Henifin, *Science, Law, and the Search for Truth in the Courtroom: Lessons from Daubert v. Merrell Dow*, 22 J.L. Med. & Ethics 6 (1994). For a more general discussion of issues that arise in considering expert testimony, see Margaret A. Berger, Evidentiary Framework, in this manual.

comes, such as cellular abnormalities or tumor formation, and comparing them to 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 almost always unethical to experiment on humans by exposing them to known doses of suspected poisons, animal toxicological evidence often provides the best scientific information about the risk of disease from a chemical exposure.[10]

Only rarely are humans exposed to chemicals in a manner that permits a quantitative determination of adverse outcomes. This area of toxicological research, known as *clinical toxicology,* may consist of case series, case reports, or even experimental studies in which individuals or groups of individuals have been exposed under circumstances that permit analysis of *dose-response* relationships, mechanisms of action, or other aspects of toxicology. For example, individuals occupationally and environmentally exposed to 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 due to any one chemical.[11]

Toxicologists use a relatively 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 metals; body system effects, such as *neurotoxicology* and *immunotoxicology*; and effects on physiological process, including inhalation toxicology and molecular biology (the study of how chemicals interact with cell molecules). Each of these areas of research include both in vivo and in vitro research.[12]

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 tech-

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.

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

11. *Id*.

12. *See infra* §§ I.C.1, I.C.2.

niques often prescribed by regulatory agencies, such as the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA).

Basic toxicological laboratory research focuses on the mechanisms of action of exogenous agents. It is based on the standard elements of scientific studies, including appropriate experimental design using controls and statistical evaluation. In general, toxicological research attempts to hold all variables constant except for that of the chemical exposure.[13] 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. Thus, most toxicological studies generally use a range of doses for a chemical.[14]

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.[15]

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 a few days. This easily measured endpoint gradually is being abandoned, in part because recent advances in toxicology have provided more pertinent endpoints, and also 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 a chemical—the *no observable effect level* (NOEL).[16] 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 ob-

13. 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).

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

15. *See infra* §§ I.D, III.A.

16. 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).

served.[17] 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, particularly for central nervous system effects.

d. No threshold model and determination of cancer risk

Certain mutational events, such as those leading to cancer and some inherited disorders, are believed to occur without any threshold. In theory, the cancer-specific alteration in the genetic material of the cell can be produced by any one molecule of the mutational agent. The *no threshold model* led to the development of the *one hit theory* of cancer risk, in which each molecule of a 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 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.[18]

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

Another type of study uses different doses of a chemical agent to establish what is known as the *maximum tolerated dose* (MTD) (the highest dose that does not cause death or 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*

17. The significance of the NOEL was relied on by the court in Graham v. Canadian Nat'l Ry. Co., 749 F. Supp. 1300 (D. Vt. 1990), in granting judgment for defendants. The court found the defendant's expert, a medical toxicologist, persuasive. The expert testified that 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. 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 14, at 391.

18. For further discussion of the no threshold model of carcinogenesis, see Office of Technology Assessment, U.S. Congress, Assessment of Technologies for Determining the Cancer Risks from the Environment (1981); Gary M. Williams & John H. Weisburger, *Chemical Carcinogenesis, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 127.

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 (D.C. Cir. 1987).

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). On the other hand, nonmutational responses to asbestos cause its carcinogenic effect. What the appropriate mathematical model is to depict the dose-response relationship for such an agent is still a matter of debate. *Id.* at 197–201.

effects of exposure.[19] These studies last about two years depending on the species.

Chronic toxicity tests evaluate carcinogenicity or other types of toxic effects. Federal regulatory agencies frequently require lifetime carcinogenicity studies on both sexes of two species, usually rats and mice. A standard 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.

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 significant loss of statistical power, thereby limiting the ability of the test to detect carcinogens or other toxic compounds. Consider the possibility of a chemical in which a realistic dose causes a tumor in 1 in 100 laboratory animals. If the lifetime background incidence without exposure to the chemical is 6 in 100 animals, a toxicological test involving 100 control animals and 100 exposed animals who were fed the realistic dose would reveal 6 control animals and 7 exposed animals with the cancer. A researcher may not detect this difference using conventional statistical tests. However, if the study started with ten times the realistic dose, the researcher would 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.[20] Regulators are responding to public concern about cancer by regulating risks of 1 in 1 million—not 1 in 100 as in the example given above. To test risks of 1 in 1 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 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 review of research studies that extrapolate from animal experiments involving doses significantly higher than that to which humans are exposed.[21] Such extrapolation is accepted in the regulatory

19. 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 number two dye as safe because researchers failed to administer the MTD to research animals, as required by FDA protocols). *See also* 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).

20. *See, e.g.*, Committee on Risk Assessment Methodology, National Research Council, *supra* note 18, at 43–51.

21. *See, e.g.*, Human Risk Assessment: The Role of Animal Selection and Extrapolation (M. Val Roloff ed., 1987).

arena. However, in toxic tort cases, experts use additional background information[22] to offer opinions about disease causation and risk.[23]

2. In vitro research

In vitro research concerns the effects of a chemical on cells, bacteria, body organs, 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 proposed for just about every physiological response and every organ system, such as perfusion tests and DNA studies. Relatively few of the tests described in the research literature have been validated by many different laboratories or compared with outcomes in animal studies to determine if they are predictive of whole animal toxicity.[24]

Criteria of reliability for in vitro tests 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 it 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. If a heavy metal such as mercury causes kidney toxicity in laboratory animals, it will almost certainly 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 of 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.[25]

22. *See infra* §§ IV, V.

23. 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).

24. *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).

25. For example, benzene undergoes a complex metabolic sequence that results in toxicity to the bone marrow in all species, including humans. Robert Snyder et al., *The Toxicology of Benzene*, 100 Envtl. Health Persp. 293 (1990). The exact metabolites responsible for this bone marrow toxicity are the subject of much interest but remain incompletely known. Mice are more susceptible to benzene than rats. If researchers could

Mathematical depiction of the process by which an external dose moves through various compartments in the body until it reaches the target organ is often called physiologically based *pharmacokinetics*. Regulatory agencies are using research into factors causing differences in *target organ doses* for laboratory animals and humans after exposure to the same external doses to improve extrapolation in the risk-assessment process.[26]

Extrapolation from studies in nonmammalian species requires 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, reliance on in vitro data for elucidating mechanisms of toxicity is more persuasive where positive human epidemiological data also exist.

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, the government imposed a code on industrial and contract laboratories involved in safety assessment. Known as *Good Laboratory Practice* (GLP), this code governs many aspects of laboratory standards, including such details as the number of animals per cage and the handling of tissue specimens.[27] Although both the FDA and

determine the differences in metabolism of benzene between mice and rats, they would have a useful clue into which portion of the metabolic scheme is responsible for benzene toxicity to the bone marrow. *See, e.g.*, Curtis D. Klaassen & Karl Rozman, *Absorption, Distribution, and Excretion of Toxicants, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 50; I. Glenn Sipes & A. Jay Gandolfi, *Biotransformation of Toxicants, in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 88.

26. 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 14, 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 14, at 47; Michael D. Hogan & David G. Hoel, *Extrapolation to Man*, *in* Principles and Methods of Toxicology, *supra* note 13, at 879; James P. Leape, *Quantitative Risk Assessment in Regulation of Environmental Carcinogens*, 4 Harv. Envtl. L. Rev. 86 (1980).

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

the EPA also have published good laboratory practice standards,[28] major differences exist in the required procedures for testing drugs and environmental chemicals. Federal law 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. This is because exposures to prescription drugs are carefully controlled and do not exceed specified ranges. However, in the case of environmental chemicals and agents, no premarket testing in humans is required. Moreover, since exposures are less predictable, a wider range of doses usually is given in the animal tests. Finally, 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 only 10%–20% have any toxicological data at all.

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.[29] The National Academy of Sciences defines four components of risk assessment: *hazard identification,* dose-response estimation, exposure assessment, and *risk characterization.*[30]

Although risk assessment is not an exact measurement, it should be viewed as a useful estimate on which policy decision 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 generally conservative default assumptions are used where limited actual data are available.[31]

While risk assessment information about a chemical can be somewhat useful in a toxic tort situation, 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.[32] Because of the

28. *See, e.g.*, 40 C.F.R. § 160 (1989); Lu, *supra* note 13, at 89.

29. Committee on Risk Assessment Methodology, National Research Council, *supra* note 18, at 1.

30. National Research Council, Risk Assessment in the Federal Government: Managing the Process (1983). *See also* 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).

31. 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 between 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 (March 25, 1992).

32. *See, e.g.*, 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

necessarily conservative assumptions in areas of uncertainty and the use of default assumptions where 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.[33] These sciences often go hand in hand in assessing the risks of chemical exposure without artificial distinctions being drawn between the two fields. However, while courts generally rule epidemiological expert opinion admissible, admissibility of toxicological expert opinion has been more controversial because of uncertainties regarding extrapolation from animal and in vitro data to humans. This particularly has been the case where relevant epidemiological research data exist. However, 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.[34]

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.[35] It is much easier, and more economical, to expose an animal to a chemical or to perform in vitro studies than it

that it is overly conservative, and thus greatly overstates the actual risk. The rationale for conservatism in part is the prudent public health approach of "above all, do no harm." In other cases, including cancer risk, the conservative approach is used 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, *e.g.,* 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).

33. *See* Linda A. Bailey et al., Reference Guide on Epidemiology § IV, in this manual.

34. Both commonalities and differences between animal and human responses to chemical exposures were recognized by the court in International Union, United Auto., Aerospace & Agric. Implement Workers of Am. v. Pendergrass, 878 F.2d 389, 394 (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. In light of the epidemiological evidence [of carcinogenicity] that was not the main problem. Rather it was the absence of data at low levels." 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 1,000,000 or less.

35. National Research Council, *supra* note 30. *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).

is to perform epidemiological studies.[36] 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, in addition to a handful of others for which the epidemiological database is equivocal (e.g., butadiene).[37] To clarify 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 leading to relatively high levels of exposure to a limited number of individuals that, fortunately, in most cases no longer occur. 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.

36. *See* Linda A. Bailey et al., Reference Guide on Epidemiology § II, in this manual.
37. Rall, *supra* note 32.

II. Expert Qualifications

The basis of the toxicologist's expert opinion is a thorough review of the research literature and treatises concerning effects of exposure to the chemical at issue, applied to the specific case. 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, however, can be explored, relevant to both 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.

However, given the relatively recent establishment of 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 to develop an 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. Most practicing physicians have little knowledge of environmental and occupational medicine. Generally, physicians

are quite knowledgeable as to identification of effects, and 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). However, most physicians have little training in chemical toxicology and lack an understanding of exposure assessment and dose-response relationships. An exception is physicians who are certified in medical toxicology by the American Board of Medical Toxicology based on their substantial training in toxicology and successful completion of rigorous examinations.

Some physicians who are occupational health specialists also have training in toxicology. Of the occupational physicians practicing today, only a small group, perhaps 1,000, has successfully completed the board examination in occupational medicine, which contains some questions about chemical toxicology. [38]

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 December 1989, 991 individuals from nine countries have received board certification from the American Board of Toxicology, Inc. To sit for the examination, which has a pass rate of 67%, 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. Diplomats 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. They do not administer examinations for certification.

The Society of Toxicology (SOT), the major professional organization for the field of toxicology, was formed in 1960 and has grown dramatically in recent

38. Another group of physicians, known as *clinical ecologists,* has 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. Clinical ecologists often belong to the American Academy of Environmental Medicine.

In Sterling v. Velsicol Chem. Corp., 855 F.2d 1188, 1208–09 (6th Cir. 1988), the court considered the admissibility of expert opinions based on clinical ecology theories. The court ruled the opinions inadmissible, finding that the experts "never personally examined or interviewed plaintiffs, nor performed the requisite medical tests." *But see* Elam v. Alcolac, Inc., 765 S.W.2d 42, 86 (Mo. Ct. App. 1988), *cert. denied*, 493 U.S. 817 (1989) (expert opinion based on clinical ecology theories admissible). *See also* Gregg L. Spyridon, *Scientific Evidence vs. "Junk Science"—Proof of Medical Causation in Toxic Tort Litigation: The Fifth Circuit "Fryes" a New Test (Christophersen v. Allied Signal Corp.),* 61 Miss. L.J. 287, 295–96 (1991); California Medical Ass'n Scientific Bd. Task Force on Clinical Ecology, *Clinical Ecology—A Critical Appraisal*, 144 W.J. Med. 239 (1986).

years; it currently has 2,944 members.[39] 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 include 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.

C. What Other Indicia of Expertise Does the Proposed Expert Possess?

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 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.[40]

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

Selection for local, national, and international regulatory advisory panels usually implies a degree of recognition in the field. Examples include panels convened by the EPA, the FDA, the World Health Organization (WHO), and the International Agency for Research on Cancer (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

39. There are currently six 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 are mecha nisms, molecular biology, inhalation toxicology, metals, neurotoxicology, and immunotoxicology.

40. Examples of reputable, peer-reviewed journals are Journal of Toxicology and Environmental Health; 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.

the supply of available toxicologists. It is thus common for reputable toxicologists to serve on advisory panels.

Finally, a faculty appointment in toxicology, risk assessment, or a related field signifies an expertise in that area.

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 toxicologist 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. Finally, 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 permits the extrapolation from one species to another in most cases. Through the study of factors that modify the toxic effects of chemicals, including absorption, distribution, metabolism, and excretion, the ability to extrapolate from laboratory animals to humans can improve.[41]

41. *See, e.g.*, *supra* notes 25–26 and accompanying text; Edward J. Calabrese, Principles of Animal Extrapolation (1983); Human Risk Assessment: The Role of Animal Selection and Extrapolation, *supra* note 21.

The expert should review similarities and differences in absorption, distribution, metabolism, and excretion in the animal species in which the compound has been tested and in humans. This should form the basis of the opinion as to whether extrapolation between animals and humans is warranted.

In general, there is an overwhelming similarity in the biology of all living things and a particularly good relationship 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.[42]

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

Some chemical and physical agents demonstrate specific effects at a particular dose. The organ specificity of a toxic chemical may be due to absorption, distribution, metabolism, excretion, or organ dysfunction.[43] For example, specificity may reflect the relatively high level in an organ of an enzyme system capable of metabolizing a parent compound to a toxic metabolite, or it may reflect the relatively low level of an enzyme system capable of detoxifying a compound. An example of the former is liver toxicity caused by inhaled carbon tetrachloride, for which there is extensive metabolism to a toxic intermediate within the liver but relatively little such metabolism in the lung.[44]

Some chemicals, on the other hand, may cause nonspecific effects or even multiple effects. Liver toxins may interfere with the role of red blood cells in the metabolism of certain drugs and release cellular enzymes into blood, leading to a number of nonspecific effects. Lead is an example of a *toxic agent* that affects many organ systems, including red blood cells, the central and peripheral nervous systems, reproductive systems, and the kidneys, leading to cardiovascular effects.

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

42. *See, e.g.*, *Table 14-1: Some Biochemical/Physiological/Morphological Differences of Potential Toxicological Significance Between Rats and Humans*, *in* Human Risk Assessment: The Role of Animal Selection and Extrapolation, *supra* note 21, at 583–89. Species differences producing a qualitative difference in response to xenobiotics are well known. Sometimes understanding the mechanism underlying the species difference can allow prediction of whether the effect will occur in humans. Thus, carbaryl, an insecticide commonly used, among other things, for gypsy moth control, produces fetal abnormalities in dogs but not in hamsters, mice, rats, and monkeys. Dogs lack the specific enzyme involved to metabolize carbaryl; the other species tested all have this enzyme, as do humans. On this basis, it has been reasoned that humans are not at risk for fetal malformations produced by carbaryl.

43. *See infra* § IV.

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

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.

C. 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 dosages that cause cellular toxicity to whole animal toxicity. In many critical areas, knowledge that permits such extrapolation is lacking.[45] Nevertheless, the ability to quickly test new products through in vitro tests, using human cells, makes these tests invaluable "early warning systems" for toxicity.

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

Understanding the structural aspects of chemical toxicology has led to the use of *structure activity relationships* (SAR) as a formal method of predicting toxicity of new chemicals. This technique compares the chemical structure of compounds with known toxicity to the chemical structure of compounds with unknown toxicity. Toxicity then is estimated based on molecular similarities between the two compounds. While SAR is used extensively by the EPA in testing 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.[46]

45. In Vitro Toxicity Testing: Applications to Safety Evaluation, *supra* note 24, at 8.

46. For example, benzene and alkyl benzenes, which include toluene, xylene, and ethyl benzene, share a similar chemical structure and are common bulk chemicals and constituents of gasoline. SAR works exceptionally well in predicting the acute central nervous system anesthetic-like effects of these compounds; the slight difference in dose-response is readily explainable 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, among these closely related compounds it is only benzene that produces damage to the bone marrow and leukemia. This is because of the specific metabolic products of benzene, a specificity so great that when the closely related compound toluene is administered with benzene to laboratory animals it actually protects against bone marrow toxicity.

Expert opinion based on SAR has been proffered in a number of cases alleging that fetal exposure to the pregnancy antinausea drug Bendectin resulted in birth defects. Lower courts, applying varying standards, have accepted and rejected expert opinion based on SAR. These cases are analyzed in Joseph Sanders, *The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts*, 43 Hastings L.J. 301 (1992); Ernest J. Getto et al., *The Artification of Science: The Problem of Unscientific "Scientific" Evidence*, 23 Envtl. L. Rep. 10435 (1993); Green, *supra* note 7. *See also* Daubert v. Merrell Dow Pharmaceuticals, Inc., 113 S. Ct. 2786 (1993), which rejected a per se exclusion of SAR, animal data, and reanalyses of previously published epidemiological data where there was negative epidemiological data, and remanded the issue of admissibility to the trial court for reconsideration.

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 where no mechanism can be ascribed by which the chemical exposure leads to the putative effect.

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.[47] In most instances, cancers and other diseases do not wear labels documenting their causation.[48] The opinion is based on an assessment of the individual's exposure, including the amount, the temporal relationship between the exposure and disease, and exposure to other disease-causing factors. This information is then compared to research 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*).[49]

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.[50] The extent of certainty required for regulation 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, while regulatory activity under TSCA clearly asks

47. 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).

48. Research, which is still in the preliminary stages, shows that certain cancers do "wear labels" in the form of DNA adducts and mutational spectra. National Research Council, Biologic Markers in Reproductive Toxicology (1989).

49. Causation issues are discussed in Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases,* 46 Stan. L. Rev. 1 (1993); Troyen A. Brennan, *Causal Chains and Statistical Links: The Role of Scientific Uncertainty in Hazardous-Substance Litigation*, 73 Cornell L. Rev. 469 (1988); Daniel A. Farber, *Toxic Causation,* 71 Minn. L. Rev. 1219 (1987); Steve Gold, *Note, Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence*, 96 Yale L.J. 376 (1986); 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); and William V. Dunlap & E. Michael Thomas, *Tort Actions for Cancer: Deterrence, Carcinogenesis*, 90 Yale L.J. 840 (1981). *See also In re* Joint E. & S. Dists. Asbestos Litig., 827 F. Supp. 1014, 1026 (S.D.N.Y. 1993) (under *Daubert* standards worker's causation evidence insufficient to support jury finding that asbestos exposure caused colorectal cancer).

50. The relevance of regulatory standards to toxic tort litigation is explored in Silbergeld, *supra* note 2.

for some balance between the societal benefits and risk of new chemicals); (2) the specific endpoint of concern (e.g., consider the concern caused by cancer and adverse reproductive outcomes versus almost anything else); and (3) the societal impact, as evidenced by the different degree of public support for control of an industry versus altering personal automobile use patterns. These three concerns, as well as others, including costs, politics, and the virtual certainty of litigation challenging the regulation, impact on the level of scientific proof required by the regulatory decision maker.

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, where 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 pollutants (e.g., radioactive iodine from a federal atomic research facility to nearby residential areas). Second, exposure can be measured using direct measurements of the medium in question—air, water, food, or soil. Where the medium of exposure is water, soil, or air, exposure calculations frequently draw on the expertise of *hydrogeologists* or meteorologists. The third approach directly measures human receptors through some form of *biological monitoring,* such as blood lead levels or 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 historical exposure.

The toxicologist, on the other hand, must 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, while ingested lead is taken up only partially into the body. An iron deficiency or low nutritional calcium intake, both common conditions among inner-city children, increases the amount of ingested lead that is absorbed in the gastrointestinal tract and passes into the bloodstream.

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, 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.[51]

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. The excretion of small water soluble compounds is usually 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 most *acute* injuries, there is 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 disease. For example, acute myelogenous leukemia, the adult form of acute leukemia, requires one to two years from initial exposure to radiation, benzene, or cancer chemotherapy until the manifestation of a clinically recognizable case of leukemia. A toxic tort claim alleging a shorter time period between cause and

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

effect is scientifically untenable. Much longer time periods are necessary for the manifestation of solid tumors caused by asbestos.

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?

Even if an individual was exposed to a chemical, if the level of exposure was below the no observable effect or threshold level, a relationship between the exposure and disease cannot be established. The NOEL is extrapolated from animals to humans by calculating the animal NOEL based on experimental data and decreasing it by a safety factor to ensure no human effect.[52] 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.[53]

52. *See, e.g., supra* notes 17–18 and accompanying text. Joseph V. Rodricks & Robert G. Tardiff, *Comprehensive Risk Assessment*, *in* Toxic Substances and Human Risk: Principles of Data Interpretation, *supra* note 14, at 391. Joseph V. Rodricks, Calculated Risks 165–70, 193–96 (1992); Lu, *supra* note 13, at 84.

53. *See* sources cited *supra* note 18.

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. While a thorough, standardized patient information questionnaire would be particularly useful for recognizing the *etiology* or causation of illnesses related to toxic exposures, there is currently no validated or widely used questionnaire that gathers all pertinent information.[54] 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 (e.g., medical conditions, diseases of relatives); and personal medical history (e.g., 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 where evaluating acute effects. For example, individuals acutely exposed to organophosphate pesticides report headaches, nausea, and dizziness accompanied by anxiety and restlessness. Other reported symptoms include muscle twitching, weakness, and hypersecretion with sweating, salivation, and tearing.[55]

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

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

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

document beyond the patient's report. Thus, these symptoms can be attributed mistakenly to an exposure to a toxic agent or discounted as unimportant when in fact they reflect a significant exposure.

A careful medical history focuses on the time pattern of symptoms 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.

C. Do Laboratory Tests Indicate Exposure to the Compound?

There are two types of tests: routine tests, which are used in medicine to detect changes in normal body status, and relatively specialized tests, which are used to detect the presence of the chemical or physical agent. 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, just because a laboratory is certified for testing of blood lead in workers, for which the OSHA action level is 40 micrograms per deciliter (μg/dl), does not necessarily mean that it will give reliable data on blood lead levels at the much lower Centers for Disease Control (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, are either caused by a toxic agent or other agents or conditions. A careful medical history examines the possibility of competing causes or confounding factors for any disease, leading to a *differential diagnosis*. The failure of a physician to elicit such history, or of a toxicologist to pay attention to such a history, leaves open the possibility of competing causes of the injury.[56]

56. *See, e.g.,* Bell v. Swift Adhesives, Inc., 804 F. Supp. 157 (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).

E. Is There Evidence of Interaction with Other Chemicals?

Simultaneous exposure to different compounds may change the response from that which would be expected from exposure to only one of the compounds.[57] 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*.[58]

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 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; and the third 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.[59]

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.[60]

Moreover, for any given level of a toxic agent that reaches a target organ, damage may be greater because of differing responses to allergens. 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 preexist-

57. *See, e.g.*, Edward J. Calabrese, Multiple Chemical Interactions (1991).

58. Courts have been called on to consider the issue of synergy. In International Union, United Auto., Aerospace & Agric. Implement Workers of Am. v. Pendergrass, 878 F.2d 389 (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 1,000,000 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.

59. *See, e.g.,* Calabrese, *supra* note 57.

60. *Id.*

ing 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.[61]

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, it is also one of the most difficult aspects of causation to describe quantitatively. For example, 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.[62]

The more difficult problem is how to evaluate conflicting research results. Where 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.

61. The problem of differences in chemical sensitivity was addressed by the court in Gulf S. Insulation v. United States Consumer Prods. Safety Comm'n, 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 response was slight or severe: "[P]redicting 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.

62. 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 cause oral cancer, moved to exclude epidemiological studies conducted among the populations of Asia that demonstrate a link between smokeless tobacco and oral cancer. 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.

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); Louis J. Casarett & John Doull, Casarett and Doull's Toxicology: The Basic Science of Poisons (Mary O. Amdur et al. eds., 4th ed. 199l); 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 Inst., Glossary of Environment Health Terms (1989).

Acute. Extremely severe or sharp, as in acute pain. Or, with an acute disease, the symptoms develop suddenly and quickly. An acute disease lasts only a short time (a few days).

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

Antagonism. When exposure to one 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 substance 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 toxic agents or the detection of physiological changes due to exposure.

Biologically Plausible. 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 a chemical.

Chronic. A condition that lasts a long time and frequently recurs. Unlike acute conditions, the symptoms develop slowly but continue for a long time and often can go away, only to repeatedly return.

Clinical Ecologists. Physicians who believe that exposure to certain chemical agents can result in damage to the immune system, causing multiple chemical hypersensitivity. Clinical ecologists 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.

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 substances in definite proportions that, when combined, acquire differing properties than the original substances.

Confounding Factors. A variable that is related to both the exposure and the outcome. A confounding factor can obscure the relationship between the toxic agent and the adverse health outcome associated with that agent.

Differential Diagnosis. The method by which a physician determines what disease process has caused a patient's symptoms. The physician considers all relevant potential causes of the symptoms and then eliminates alternative causes based on a physical examination, clinical tests, and a thorough case history.

Direct-Acting Agents. Agents that cause toxic effects without metabolic activation or conversion.

Distribution. Movement of the 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 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. The way a living organism responds to 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.

Dose-Response Curve. A graphic representation of the relationship between the dose administered and the effect produced.

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 the kidney and urinary excretion, the liver and biliary system and fecal excretor, and processes involving 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). A code developed by the federal government in consultation with the laboratory-testing industry that governs 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 that specialize in the movement of ground and surface waters and the distribution and movement of contaminants in 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 exhibit toxic effects on living organisms.

In Vitro. A research or testing methodology that employs an artificial or test tube system, or is otherwise outside of a living organism.

In Vivo. A research or testing methodology that employs living organisms.

Lethal Dose 50 (LD50). The dose at which 50% of laboratory animals die within a few days.

Lifetime Bioassay. See Bioassay.

Maximum Tolerated Dose (MTD). The highest dose 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 undergoes in an organism.

Multiple Chemical Hypersensitivity. A physical condition whereby individuals react to many different chemicals at extremely low exposure levels.

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 level above which observable effects are believed to occur and below which no toxicity is observed.

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 may mutate or change 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 to the target organ.

Potentiation. The process by which the addition of one substance, which by itself has no toxic effect, increases the toxicity of another chemical when exposure to both substances occurs simultaneously.

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 the agent and evaluates it in order to estimate risk.

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.

Structure Activity Relationships (SAR). A method used by toxicologists to predict the toxicity of new chemicals by comparing their molecular similarities and differences to compounds with known toxic effects.

Synergistic Effect. The effect that occurs when one agent enhances the effect of another agent.

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

Target Organ Dose. The dose at which a specific organ is affected.

Teratogen. A substance or agent that changes eggs, sperm, or embryos, thereby increasing the risk of birth defects.

Teratogenic. Pertaining to the ability to produce birth defects. (Teratogenic effects do not pass on to future generations.) See Teratogen.

Threshold. The level above which observable effects occur and below which no observable effects occur. See No Observable Effect Level.

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

Toxic Agent. An agent or substance that is toxic.

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

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