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## TOXIC TORTS: THE DEVIL IS IN THE DOSE

*Bernard D. Goldstein, M.D.\**

### SUMMARY

Dose is a central concept in toxicology—"the dose makes the poison" is the oldest maxim in the field.<sup>1</sup> The judicial system nevertheless appears uncomfortable in dealing with dose issues and instead prefers reductionist approaches which overly simplify decision-making about general and specific causation in toxic tort cases to the detriment of both plaintiffs and defendants. Contrasting this approach, scientific enquiry is moving toward a more systems based, holistic approach to incorporating a broad range of scientific evidence. This is particularly true for the examination of chemical causation of disease. Longstanding science-based processes evaluating the weight of evidence have increased the extent to which they incorporate scientific data from multiple disciplines, including toxicological studies exploring dose-related

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<sup>1</sup> See David L. Eaton, *Scientific Judgment and Toxic Torts— A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & POL'Y 5, 15 (2003).

"Dose" is defined as concentration multiplied by frequency or duration. Thus exposure to 10 parts per million ("ppm") in air for one hour to a pollutant is a dose of 10 ppm-hours. Exposure to 1 ppm in air for 10 hours also results in a dose of 10 ppm-hours. In the first example the dose rate is higher than the second example, but the total dose is the same.

mechanisms of disease. This runs counter to recent judicial decisions that more narrowly define the evidence acceptable in a toxic tort case.<sup>2</sup>

## I. INTRODUCTION

The interface of science and law is central to toxic tort litigation. The challenge of eliciting valid and pertinent expert opinions in toxic tort cases has led to changes in the role of the judge and to what is admissible in court.<sup>3</sup> *Daubert v. Merrell Dow Pharmaceuticals, Inc.*<sup>4</sup> and other cases have had a major impact upon toxic tort litigation at a time when the science is also changing rapidly.<sup>5</sup> This article explores the role of the central toxicological concept of dose in toxic tort litigation. Additionally, this article contends that science and law are going in opposite directions—in science towards a more systems-based holistic approach to

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<sup>2</sup> This article focuses upon environmental cases. Litigation concerning pharmaceuticals and medical devices may raise different issues because of the role of the FDA. See *infra* text accompanying notes 27–31.

<sup>3</sup> See sources cited *infra* note 5.

<sup>4</sup> 509 U.S. 579 (1993).

<sup>5</sup> I will not delve into the legal arguments concerning whether the intention of the Supreme Court in *Daubert* was to liberalize the rules of scientific evidence. The proposition that in fact the opposite has occurred has been advanced by legal scholars and by scientists. See Lisa Heinzerling, *Doubling Daubert*, 14 J.L. & POL'Y 65 (2006) (discussing the “mess that has followed in the wake of *Daubert*”); Ronald L. Melnick, *A Daubert Motion: A Legal Strategy to Exclude Essential Scientific Evidence in Toxic Tort Litigation*, 95 AM. J. PUBLIC HEALTH S30 (2005) (discussing difficulties for plaintiffs to prevail in *Daubert* motions); CARL F. CRANOR, *Judge-Jury Responsibilities and the Right to a Jury Trial*, in TOXIC TORTS: SCIENCE, LAW, AND THE POSSIBILITY OF JUSTICE 70–71 (2006) (noting that, under *Daubert*, plaintiffs have to “win twice”). This proposition is consistent with my argument that courts have generally become reductionist in their approach to toxic torts. The potential impact on toxic torts of changes in science arising out of molecular biology and increased understanding of the human genome have been discussed by Gary Marchant and by Jamie Grodsky. Gary E. Marchant, *Toxicogenomics and Toxic Torts*, 20 TRENDS IN BIOTECH. 329 (2002); Jamie A. Grodsky, *Genomics and Toxic Torts: Dismantling the Risk-Injury Divide*, 59 STAN. L. REV. 1671 (2007).

understanding the revealed complexity of human biology and of cause-and-effect relations, while in law towards a more reductionist and overly simplistic approach. I use examples to demonstrate how a reductionist approach inappropriately excludes animal toxicology and mechanistic information of pertinent value in evaluating a toxic tort.

## II. THE SCIENCE OF TOXICOLOGY

Toxicology is the science of poisons. It is an ancient science, reflecting the trial and error approaches of our ancestors in selecting nutritious components of an otherwise highly toxic natural world. The use of known poisons to kill animals or enemies reflects this same experimentation. Toxicologists accept Paracelsus—a 16th century alchemist and a bit of a charlatan—as their ancestor and credit him with the first law of toxicology—that the dose makes the poison. In the present review, I focus primarily on issues related to dose, although I will also discuss aspects of the two other major maxims that are the basis for modern toxicology: 1) that chemicals are specific in their biological effects, which has been credited to Ambrose Pare;<sup>6</sup> and 2) that humans are animals.

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<sup>6</sup> Bernard D. Goldstein & M.A. Gallo, *Paré's Law: The Second Law of Toxicology*, 60 TOXICOLOGICAL SCI. 194–95 (2001). Paré told the King of France that he had wasted his money in purchasing what was claimed to be an antidote to all poisons. Paré reasoned that each poison had its own specific mechanism of action and that a universal antidote did not exist. The king put Paré's reasoning to the test. The king's apothecary gave a man condemned to be hung a poison followed by a so-called universal antidote. The condemned man died anyhow, thereby proving Paré's point. *Id.*

*A. The Maxims of Toxicology*<sup>7</sup>*1. The Dose Makes the Poison*

Depending upon dose, everything is poisonous, including such essentials as water and salt. Dose is defined as concentration multiplied by frequency or duration—it is not just the exposure level at any one point in time. Understanding how dose affects response is central to the science of toxicology. Dose-response curves are a classic means of illustrating this relationship, and developing a dose-response curve through direct observation or through extrapolation is an essential element of the function of toxicologists. Extrapolation may be from high to lower doses, from one group of humans to another, or between species.

Toxicologists generally posit two main dose response curves: those that have a “threshold” and those that do not.<sup>8</sup> Certain chemicals produce no effects at low doses. The highest dose at which no effect is observed for these chemicals is known as the threshold.<sup>9</sup> The presumption that a chemical has a threshold is of obvious importance to toxic torts in that it permits the argument

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<sup>7</sup> These maxims also underlie the four-part risk assessment paradigm: hazard identification, dose-response analysis, exposure analysis, and risk characterization. Dose-response analysis is clearly based on the dose makes the poison; specificity is the basis for hazard identification; and both depend heavily on extrapolating from animal studies. Bernard D. Goldstein & Russel Lynn Carruth, *Toxicology: Scientific Status*, in MODERN SCIENTIFIC EVIDENCE: THE LAW AND SCIENCE OF EXPERT TESTIMONY 149 (Faigman et al. ed., vol. 3 2007).

<sup>8</sup> Reviews of toxicological science in relation to toxic torts can be found in Joseph V. Rodricks, *Evaluating Disease Causation in Humans Exposed to Toxic Substances*, 14 J.L. & POL’Y 39 (2006); Goldstein & Carruth, *supra* note 7, at 122–50; Bernard D. Goldstein & Mary S. Henifin, *Reference Guide on Toxicology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 401–37 (2d ed. 2000); Ellen K. Silbergeld, *The Role of Toxicology in Causation: A Scientific Perspective*, 1 CTS HEALTH SCI. & L. 374–78 (1991).

<sup>9</sup> The technical and more appropriate term is a “no-observed effect level,” or NOEL. Goldstein & Henifin, *supra* note 8, at 407.

that a dose was too low to cause a particular plaintiff's injury.<sup>10</sup> As dose increases, so does response, until eventually there is a dose which has maximal effect—perhaps the death of the organism.

The second general type of a dose response curve is one that is considered to have no threshold. The most important example for toxic torts is that of cancer. The underlying cause of many cancers is a persistent genetic mutation allowing the unbridled growth of a cell which then results in a clone of cancer cells.<sup>11</sup> As any one molecule can theoretically cause this persistent mutation, no threshold exists below which the risk is zero. The dose response curve relating the level of a cancer causing chemical to the risk of cancer is usually considered to be roughly linear; e.g., if the risk of cancer for a dose of 100 units is X, then the risk of cancer for a dose of 200 units is likely to be about twice the amount of X and the risk of cancer for a dose of 50 units only one-half X.<sup>12</sup>

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<sup>10</sup> This form of a dose-response curve is not only scientifically acceptable but easily understood by a layperson. The smallest residue of a ground up baby aspirin tablet is useless for treating an adult headache, but an overdose of aspirin can be fatal.

<sup>11</sup> Normally, a progenitor cell, such as a cell at the base of our skin, divides into two other cells: another progenitor cell and a cell that will mature and die. Put very simply, cancer is caused by a genetic mutation leading the progenitor cell to form two progenitor cells, which themselves continue to divide to form other progenitor cells. As a mutation can be caused by a chemical or physical agent producing a single small change in the DNA constituents of a gene, it is at least theoretically possible that any one molecule of a chemical, or packet of radiation, capable of changing DNA can lead to a cancer-causing mutation. Note that most mutations are silent, kill the cell, or do something other than cause cancer. Stable mutations of germ cells can similarly lead to inherited disorders. Cancer is usually a more complex process than a single mutation.

<sup>12</sup> Dose-response estimation for carcinogens is somewhat more complex in its use than this reasonable approximation, particularly in the usual situation in which extrapolation is needed from high to low dose or from animals to humans. There are also carcinogens that clearly have thresholds. *See, e.g., infra* notes 64 and 65 concerning saccharin. However, in essence, the "burden of proof" is on industry to prove that a carcinogen has a threshold. The question of whether a different dose-response approach should be used for non-genotoxic carcinogens remains under debate.

## 2. *Specificity of Effects*

Chemical and physical agents have specific effects related to both the inherent physiochemical properties of the agent and the biological niche in which it functions. For example, benzene can cause leukemia and asbestos can cause lung cancer, but not vice versa. The concept of specificity—that an agent affects certain biological systems but not others—is a clearly established principle of toxicology.<sup>13</sup> It is also intuitively understood by lay persons. For example, anyone may take aspirin for a headache and a laxative for constipation, but the medicines are not interchangeable. Pharmaceutical drug development to a large extent depends upon working out the relation between chemical structure and both the specificity of a desired effect and the avoidance of undesired effects. Small changes in chemical structure can have a major impact on toxicity in terms of both specificity (general causation) and the extent of human susceptibility to the agent.<sup>14</sup>

## 3. *Humans are Animals*

Much of modern toxicology is based on the study of laboratory animals. There is a commonality of biological function across species. All biological systems must obtain energy, build structure and release waste. The similarity in cellular and organ function is particularly strong among mammals such that extrapolation of effects from one species to another is accepted by the scientific community as a means of evaluating the toxicity of external agents. In terms of general causation, the specificity of toxic effects on organs is relatively similar across mammals, e.g., a kidney poison in

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<sup>13</sup> Somewhat confusing is that the legal equivalent to toxicological specificity is general causation; while specific causation in a toxic tort suit is related to dose rather than toxicological specificity.

<sup>14</sup> For example, n-hexane, the six carbon straight chain hydrocarbon component of gasoline, is toxic to nerves, while the closely related 5 and 7 straight chain hydrocarbons, n-pentane and n-heptane, have no such toxicity. This is because of a specific biological niche within the neuron that spatially allows chemical interaction by a metabolite of n-hexane but not the slightly smaller metabolite of n-pentane or the slightly larger metabolite of n-heptane.

one species is likely to be a kidney poison in another, although there are certainly exceptions. There is more variability among species in dose-response due to differences in absorption, distribution, metabolism, excretion, function and target organ susceptibility. As extrapolation of dose-response from animals to humans is central to deciding appropriate regulatory protection, there is a wealth of research data focusing upon these pathways.<sup>15</sup> Although extrapolation can be complex, there is sufficient information to permit reliable extrapolation in many situations.

A lay person reading the scientific literature might conclude, erroneously but understandably, that human responses most often differ from other mammals. This misconception is a by-product of a publication bias. In fact, there is a commonality of response among mammals, including humans. A difference between humans and animals is worth pursuing scientifically as such a difference can be exploited to understand human physiology and response and it is also readily publishable in a good scientific journal.<sup>16</sup> This means that review of the overall literature comparing animals and humans will be biased toward differences rather than similarities.

Standard safety assessment for chemicals is based totally on

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<sup>15</sup> Physiologically based pharmacokinetic models (“PBPK”) are increasingly used in risk assessment. These models provide linkages between initial exposure to eventual disposition of a chemical and its metabolites, including levels at target organs within the body. For a recent review and for an example assessing the cancer risk of chloroform, see Kai H. Liao et al., *Bayesian Estimation of Pharmacokinetic and Pharmacodynamic Parameters in a Mode-of-Action-Based Cancer Risk Assessment for Chloroform*, 27(6) RISK ANALYSIS 1535 (2007).

<sup>16</sup> Another major reason for the attention paid to differences between animals and humans is that details affecting the extrapolation of animal data to humans can affect regulatory agency conclusions about the risk potency of the agent. Small differences in the estimated potency can mean major differences in the extent of regulatory burden borne by the affected industry. In contrast to a continuous variable, i.e., which of a wide range of numbers should be used to set a regulatory standard, a toxic tort case in essence leads to a binary decision based upon the underlying need of the plaintiff to meet the “more likely than not” standard of tort law. Thus the details of animal/human differences, which can have major implications for regulation, often are of trivial significance for a toxic tort case, only serving to obfuscate the value of animal toxicology. See Silbergeld, *supra* note 8, at 374–78.



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animal and in vitro studies.<sup>17</sup> A battery of such tests, chosen for their ability to predict toxicity to humans or the environment, is performed on new chemicals. Extending animal and in vitro testing to existing chemicals has been a major societal goal in recent years as evidenced by the international agreement to test high production volume chemicals<sup>18</sup> and the European Union's recent enactment of the Registration, Evaluation, Authorisation, and Restriction of Chemicals Act ("REACH").<sup>19</sup> This extensive new legislation to regulate chemicals requires intensive toxicological testing of essentially all new and existing chemicals, including components of mixtures. It relies heavily on risk based approaches to establish priorities for testing, including a reliance on production volume as a surrogate for human dose.<sup>20</sup>

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<sup>17</sup> The reliance of standard safety assessment on testing chemicals in animals is illustrative of the similarity in response between humans and animals. It also reflects the fact that these are mostly new unmarketed chemicals so there has been no human exposure, and experimentally exposing humans raises ethical issues.

<sup>18</sup> The high production volume effort has been a joint government and industry activity that has been generally supported by the environmental movement. See Testing of Certain High Production Volume Chemicals, 65 Fed. Reg. 81,657 (proposed Dec. 26, 2000), available at <http://www.epa.gov/EPA-TOX/2000/December/Day-26/t32497.htm>; see also International Council of Chemical Associations, Welcome to the Website of the Global Initiative on High Production Volume (HPV) Chemicals, <http://www.cefic.be/activities/hse/mgt/hpv/hpvinit.htm> (last visited Apr. 20, 2008).

<sup>19</sup> The new EU legislation, the Registration, Evaluation and Authorization of Chemical Substances, known as REACH, lays a very heavy burden on industry to provide extensive toxicological testing on both new and existing chemicals, including components of mixtures. A committee of the U.S. National Research Council has recently proposed a greater emphasis on understanding the mechanism of toxicity through advances in molecular biology as a means of toxicity testing. NATIONAL RESEARCH COUNCIL, TOXICITY TESTING IN THE 21ST CENTURY: A VISION AND A STRATEGY (National Academy Press 2007).

<sup>20</sup> See Commission Regulation 1907/2006, Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), 2007 O.J. (L 396) 1. A discussion of the toxicological needs for REACH and its reliance on exposure can be found in Sven O. Hanssen & Christina Ruden, *Priority Setting in the REACH System* 90(2), in TOXICOLOGICAL SCIENCES 304-08 (2005). Further information about REACH, including its pertinence to the United States, and particularly to the amendment of our Toxic Substances Control Act, can be

### III. DOSE ISSUES RELATED TO GENERAL CAUSATION

General causation for cancer can be a particularly contentious issue in toxic tort litigation.<sup>21</sup> While dose considerations are usually considered to be pertinent to specific causation, dosage is also central to the general causation issue of whether a specific chemical or physical agent can cause a specific disease. Not surprisingly given the public and economic interest, weight of evidence approaches have been most thoroughly developed for the identification of carcinogens. However, it should be noted that the same considerations apply to diseases other than cancer.

#### *A. Weight of Evidence*

Regulatory agencies and scientific organizations routinely use “weight of evidence” processes to assess the relationship between a specific chemical or physical agent and a specific adverse outcome. These processes generally consist of an assemblage of both the available evidence<sup>22</sup> and a carefully selected internal or external expert body to review this evidence and to develop a consensus view.<sup>23</sup>

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found in the papers and presentations from the conference. Conference on A New EU Approach to Chemical Safety: Lessons for the United States, Conference on the European Union (EU) regulation providing for REACH (June 7–9, 2007) available at <http://www.ucis.pitt.edu/euce/events/policyconf/07/index.html>.

<sup>21</sup> See, e.g., *Joiner v. General Electric Co.*, 78 F.3d 524 (11th Cir. 1996) (discussing whether PCBs are a human carcinogen); *In re Agent Orange Product Liability Litigation*, 373 F. Supp. 2d 7 (E.D.N.Y. 2005) (discussing whether Agent Orange and its dioxin contaminants are human carcinogens).

<sup>22</sup> The evidence to be considered may be restricted, for example, to peer-reviewed publications.

<sup>23</sup> The contrast between a consensus conference and a toxic tort proceeding epitomizes the difficulty expert scientists have serving at the interface between science and law. Assume a reasonably mature topic with a large amount of scientific evidence developed by many scientists. One can usually describe the individual opinions of the scientist as to the weight of this evidence as falling within a bell-shaped curve—some scientists giving more overall weight, some less, but most toward the middle. The organization conducting the consensus effort, e.g., the EPA Science Advisory Board or the National Academies of

Two well-known organizations that are charged to assess the issue of whether specific chemicals or workplace situations cause cancer are the International Agency for Research on Cancer (“IARC”) of the World Health Organization, and the U.S. National Toxicology Program (“NTP”). In their deliberations, IARC and NTP have routinely incorporated both epidemiological and toxicological evidence to categorize the extent to which a chemical is likely to be a carcinogen. Both have in recent years specifically broadened the use of basic laboratory science related to understanding the mechanism of action of a potential carcinogen to help improve their categorization of carcinogens.<sup>24</sup>

The IARC process results in a formal vote of the assembled experts as to whether a specific agent is toxic. The consensus approach first occurs within four expert groups: epidemiology, animal toxicology, exposure data, and mechanistic information.

Science, will attempt to assemble a relatively small subgroup of these experts with the aim of covering the specific disciplinary expertise needed and balancing any known biases. The group dynamics among scientists usually lead to the participants coming up with a relatively centrist opinion. Scientists tend to be conservative because of the high cost associated with being identified as mistaken. In contrast, the ethical and well-trained lawyer will search the field of legitimate experts to find those at their end of the bell-shaped curve and recognizes that the opposing lawyer will be doing the same. The dynamics of the litigation process greatly inhibit discussion among the experts (and the appellate process precludes scientific discussion). It is of course true that scientific opinion does not always fit a bell shaped curve, and not all scientific experts are unbiased. It is nevertheless almost inherently impossible for the confrontational approach that characterizes tort litigation to discover that there is a consensus. This is a rationale for having judges select their own experts.

<sup>24</sup> Vincent J. Cogliano et al., *Use of Mechanistic Data in IARC Evaluations*, 49(2) ENVTL & MOLECULAR MUTAGENS 100 (2008). Note that the regulatory goal underlying IARC and NTP often frustrates the needs of the toxic tort process to have a clear understanding of general causation. Once a chemical is concluded to be a known human carcinogen for a specific cancer endpoint, there is relatively little interest in evaluating whether it causes a different tumor. Either way it will be regulated as a carcinogen. An example is benzene, a known cause of human acute myelogenous leukemia. It is highly probable that it is also a cause of other hematological cancers, but this evidence is unlikely to be considered by IARC or NTP who are moving forward with limited resources to consider the weight of evidence about other potential, but not known, human carcinogens.

Although IARC is only concerned whether the carcinogen will cause cancer, rather than with the potency of the carcinogen, dose issues are crucial in each of the working groups. Not surprisingly, the animal toxicology and mechanistic information groups look for evidence of dose response before accepting an individual report within the literature. This is also true for the epidemiology working group for which there needs to be congruence both within a given study and among all studies.

Dose-response is one of Bradford Hill's<sup>25</sup> criteria for accepting an epidemiological association as causal. This is pertinent to interpreting an individual study, e.g., workers with higher exposure within a workplace are expected to have a higher level of any causally-related adverse outcome. However, often overlooked is that this criterion for interpreting epidemiological studies is not limited to interpreting individual studies; rather, it applies when evaluating the totality of the pertinent epidemiological studies. For example, a group of epidemiological studies concerning a specific agent can be stratified by dose in the individual studies, thereby providing a means to interpret the relevance of these studies to a cause and effect relationship. IARC committees often prepare a table listing all of the epidemiological studies reviewed, arranged from highest to lowest exposure. It is unlikely that a committee will accept that a chemical is known to cause cancer if there is not a reasonably strong, although not necessarily exact, relation between the extent of exposure and the observed excess risk.<sup>26</sup>

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<sup>25</sup> Bradford Hill was a physician and epidemiologist who developed a number of criteria for accepting causality. Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 PROC. OF THE ROYAL SOC'Y OF MED. 295-300 (1965).

<sup>26</sup> I am personally familiar with toxic tort cases in which the plaintiffs have alleged that exposure to benzene, a known cause of cancer of the blood system, was responsible for causing kidney cancer. The plaintiffs put forward a number of broad epidemiological studies in which there was an association between benzene-containing solvents and an increased risk of kidney cancer. Such solvents usually contain 0.1% benzene or less. However, because benzene is a known cause of blood cancers, and literally millions of workers are exposed to pure streams of benzene, a relatively large number of epidemiologic studies have been performed evaluating the mortality of these workers. As these high dose studies have not found a statistically significant increase in kidney cancer, it is

## IV. DOSE ISSUES RELATED TO SPECIFIC CAUSATION

Dose issues are central to specific causation in a toxic tort case involving exposure to chemicals at the workplace or the environment. There are two issues related to dose: 1) based upon the dose-response evaluation, what is the dose at which the adverse effect would be expected, and 2) what is the dose to the plaintiff. Approaches to these dose issues in toxic tort cases are often guided by prior judicial decisions that, to one versed in toxicology, seem uninformed about dose concepts.

Perhaps these misguided judicial approaches are the result of much of the relevant case law having been developed around pharmaceutical products or devices. One major difference between pharmaceutical agents and chemical toxins is that the dose of a pharmaceutical agent such as Vioxx or Bendectin is assumed to be that on the drug label, and someone either has or does not have a silicon breast implant or a medical device. Here, the problem is that courts attempt to transfer dose concepts from pharmaceutical products or devices to their evaluation of toxins; the inherent difference in the extent of variation in dose among those using a pharmaceutical product and a toxin makes such a transfer inappropriate.

Another major difference between environmental chemicals and pharmaceutical agents is the extent of available pre-marketing information. For a new drug, the FDA requires a clinical trial after a series of studies in laboratory animals; thus, there is a reasonably substantial amount of animal toxicology and human epidemiological data already available before the drug is marketed. This is not true for a chemical not intended for use as a drug. EPA's pre-marketing requirements under the Toxic Substances Control Act are relatively minimal by comparison. Further, as discussed below, the epidemiological gold standard of a randomized double-blind

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not consistent with usual dose assumptions to propose that the epidemiological studies of workers exposed to much lower benzene doses are indicative of a causal relation. Note that there are at least two reasons why some epidemiological studies show an association between exposure to solvents containing low levels of benzene and kidney cancer: chance variations, and a causal effect of some other component of the solvent mixture.

controlled epidemiological study cannot be achieved in epidemiological studies of the potential adverse consequences of chemical or physical agents present in the workplace or community.

For many epidemiological studies of toxic agents, dose is a binary—yes or no—determination instead of a quantitative expression.<sup>27</sup> Nevertheless, in toxic tort cases involving non-pharmaceutical chemicals present in the workplace or general environment, estimation of the dose experienced by the plaintiff, and positioning that estimate on the appropriate dose response curve for the individual plaintiff, are central to evaluating whether the plaintiff's condition more likely than not was caused by the alleged exposure.

Below, I discuss two of the approaches that are commonly used to simplify or obfuscate dose issues, one by defendants and one by plaintiffs. From a legal standpoint, defense lawyers often would like to require that there be a direct or reconstructed quantitative estimation of the actual dose; while plaintiffs often want to consider only the exposure level but not the duration component of dose.

*A. Non-Quantitative Estimation of Dose for a Toxic Tort Case*

It is appropriate under certain circumstances to admit expert testimony about sufficiency of dose without quantifying such a dose. One such circumstance is an expert's comparison of the alleged exposure of the plaintiff with that of the exposure of one or more cohorts of workers in whom there is epidemiologic evidence of an effect. The argument in essence is similar to the right of a police officer travelling at 65 mph in a 55 mph zone to ticket the driver of a car that overtakes and passes the police vehicle without direct radar evidence of the speed. While the judge might be willing to accept a defense argument concerning the exact speed of the

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<sup>27</sup> This is particularly true for the initial studies identifying most known chemical carcinogens. These were often discovered in epidemiological studies of workers in which the surrogate for dose has been qualitative estimates of high and low exposure. Quantitative exposure evaluation was subsequently added.

driver, it is clear that the driver was going more than 65 mph.

When investigating toxins, it is often difficult to come by quantitative evidence with which to prove causation. Employees who participate in epidemiological studies and experience adverse associations are generally part of a large work force; otherwise, it is difficult to observe adverse effects at the dose levels to which the workers have been subjected. A sufficiently large population that is heavily exposed can be difficult to find as large workforces tend to be well regulated through the enforcement of occupational health standards, inspections by OSHA, and the imposition of fines for failure to comply.<sup>28</sup> Further, the legacy of past heavy exposures in large worker populations can be difficult to study if there is an extended latency period before the adverse effect occurs. For example, a mesothelioma may not become manifest until decades after the initial exposure to asbestos, at which time it is difficult to perform follow up on the original cohort of workers or determine their levels of exposure.<sup>29</sup>

Smaller workforces, including the individual contractor or subcontractor, are often at a greater risk.<sup>30</sup> It is in these poorly regulated workforces that unusual and unsafe uses of chemicals tend to result in much higher individual exposures. But it is also these workforces in which exposure measurements are unlikely, and estimates of exposure are difficult to determine. Again, the passage of years between the exposure and the resultant health effect complicates estimation of specific work practices, or of the dilution factors related to ventilation of the workplace, or even the

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<sup>28</sup> A particularly problematic exception is the presence of subcontractors working among the industry's own employees. These subcontractors may not receive the same safety training or protective equipment. Michael Gochfeld & Sandra Mohr, *Protecting Contract Workers: Case Study of the U.S. Department of Energy's Nuclear and Chemical Waste Management*, 97(9) AM. J. PUB. HEALTH 1607-13 (2007).

<sup>29</sup> While this is not the place to discuss the issue, the continued failure of some judicial jurisdictions to allow the latency period to affect a statute of limitations for bringing a toxic tort case is also a reductionist approach that rejects scientific knowledge. See CARL F. CRANOR, *TOXIC TORTS: SCIENCE, LAW, AND THE POSSIBILITY OF JUSTICE* 173 (2006).

<sup>30</sup> The hobbyist working at home in an enclosed space similarly can have exposures well above those acceptable in the workplace.

extent of use of the putative causal agent.

Another complication is that there can be exposure situations in the poorly regulated workplace that are difficult to measure such as leaking valves at a particular site within the complex or the washing of hands or clothing in solvents. For example, workers are quick to observe that using an available solvent such as benzene can be an effective way to remove greasy substances from their hands or work clothes at the end of the work day, but this results in significant yet unmeasured transdermal exposure. This risky practice can and should be prevented by rigorous job training and precautionary approaches; unfortunately, these preventative measures are not usually employed at a poorly regulated work site or by a home hobbyist.

It is a reasonable approach for the expert reviewing a toxic tort case to compare the plaintiff's exposure with that described in the epidemiology literature. Specifically, the expert can determine how the work practices described by the plaintiff compare with the work practices and resultant exposure of the cohorts of workers in which epidemiologic evidence of a cause and effect relationship has been reported. As an example, an individual working by him or herself in a confined workspace with an open vat of a volatile substance which splashes on their skin and clothes may have far more exposure than reported for workers in a cohort with an observed increase in cancer risk who worked in a large factory with much less opportunity for such high level exposure. A careful history of the plaintiff's workplace practices can enable an expert to assess how the plaintiff's exposure compared to that observed in cohorts in which an association between the exposure and the effect was reported.<sup>31</sup>

Note that an indirect approach to estimation of dose can be of benefit to the defense as well as the plaintiff. For example, assume John Doe claims his leukemia was caused by chronic workplace exposure to benzene at a level of 10 parts per million (ppm) in air,

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<sup>31</sup> Information about usual work practices requires expertise such as that found in practitioners of occupational medicine, occupational safety, or industrial hygiene. This expertise can be subject to usual judicial approaches to admissibility of expert opinion.



eight hours per day. Doe sues the manufacturer of a solvent mixture used in his work, alleging that it was the benzene in the solvent that caused his leukemia. Assume we know that the solvent mixture contains 0.1% benzene (1 part per thousand) and that the mixture and benzene have similar volatility. Doe's claim can be readily disposed of by estimating what dose of solvent mixture would have been required to expose him to 10 ppm benzene. To get an exposure level of 10 ppm benzene, Doe's exposure level for the solvent mixture could be approximated as 10,000 ppm, but this is well above the lethal dose of most solvents. Had he been exposed to that much solvent, Doe would have lost consciousness and died within a matter of minutes—long before he could have developed leukemia.

*B. The Potential Misuse of Dose-Based Regulatory Standards  
as Evidence in a Toxic Tort Case*

Exposure to a pollutant level that exceeds an environmental regulatory standard is often used as evidence in a toxic tort case to support the likelihood of a causal relation between the exposure and the effect. There are two major reasons why this assumption is contrary to the way dose is incorporated into regulatory standards. First, dose is concentration multiplied by duration. Occupational or environmental standards are rarely set for instantaneous exposure levels, but rather are for durations of time that are chosen to be pertinent to the health issue of concern.<sup>32</sup> For cancer-causing chemicals, the usual duration of concern is lifetime. Thus, being

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<sup>32</sup> An example of considerations related to the duration of the exposure is provided by the change in the averaging time of the ozone standard to eight hours after three decades of being at one hour. The change was based on the recognition that prolongation of the morning rush hour and travel of ozone precursors for long distances led to elevated ozone concentrations extending throughout daylight hours rather than just being a one hour peak following morning rush hour; that there were cumulative toxic effects of ozone exposure over multiple hours; and that children, who are particularly at risk to ozone, were likely to be out of doors and active for many hours during summertime high ozone days. P.J. Rombout et al., *Rationale for an Eight-Hour Ozone Standard*, 36 J. AIR POLLUTION CONTROL ASSOC. 913–17 (1986).

exposed for just a few hours to a level slightly above the concentration that would be allowed for a lifetime is of little risk consequence. Second, the dose chosen for a regulatory standard is based on societal goals for relatively low risk, usually far below the risk that would be equivalent to “more likely than not.”<sup>33</sup> For cancer-causing agents, long term environmental risk goals are usually in the range of 1/10,000 to 1/1,000,000 lifetime, although higher risk levels are sometimes accepted in setting workplace standards. For non-carcinogenic agents causing acute and/or chronic toxicity, the allowable standard usually has built in safety factors to account for uncertainties in the data and to protect susceptible individuals. The extrapolation methods used for cancer or non-cancer endpoints depend upon an understanding of the toxicological mechanisms involved in the dose response relationship.<sup>34</sup>

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<sup>33</sup> One can not directly compare a risk-related standard with “more likely than not” in that the former is based upon an absolute risk while the latter is a comparative risk. For example, the absolute risk standard might be set at one cancer among 100,000 individuals exposed for a lifetime. If the background risk was a 1% lifetime risk of this cancer among all Americans (i.e., 1,000 among 100,000 lifetime), then exposing 100,000 citizens lifetime to the minimum allowable level would lead to 1,001 cancers in this population. For any one of these individuals, the likelihood that their cancer was due to the allowable exposure level is 1/1,001—far below a “more likely than not” bright line. However, if this were a very rare cancer, such that the lifetime background incidence was only 1/100,000 Americans, then lifetime exposure at the allowable concentration would double the number of cases, one of which would be due to the chemical exposure. Risk assessors are rarely presented with the latter scenario because scientists would be unaware of the scenario even if it did exist.

<sup>34</sup> Note that the goal of environmental health science is that all decisions about regulating synthetic chemicals should be based solely on animal or in vitro data. By definition, an epidemiological study demonstrating a cause-and-effect relationship in humans represents a failure of toxicology as a preventive science. Ideally, there should be enough information about a new chemical from safety assessment in laboratory animals, and enough strength in our public health infrastructure, such that no adverse consequences from exposure to this chemical ever occur in humans.

V. SYSTEMS APPROACHES VS. REDUCTIONISM: ARE ENVIRONMENTAL HEALTH SCIENCE AND TOXIC TORT JURISPRUDENCE GOING IN DIFFERENT DIRECTIONS?

Environmental health science and toxic tort law appear to be going in opposite directions. The various disciplinary components of environmental health sciences are increasingly complex and interrelated. Boundaries between these disciplines are becoming blurred. Systems approaches are increasingly recognized as the methods by which scientific reasoning will improve our understanding of causal relations. In contrast, the American judicial system appears to be responding to the increasing breadth and complexity of environmental health science by searching for simple uni-dimensional solutions for toxic tort issues which increasingly exclude modern scientific reasoning. The *Daubert*<sup>35</sup> decision and its progeny, providing judges with the role of gatekeeper, has furthered this trend to reductionism.

The emphasis on systems approaches, in contradistinction to reductionism, is not restricted to environmental health sciences but is rather part of the scientific worldview of the early 21st Century. This reflects the maturation of the scientific community in recognizing that understanding our planet and its components requires approaches that transcend any single discipline.<sup>36</sup> It also reflects the recognition by those responsible for the funding of science that there is a growing gap between scientific advances and the applicability of these advances for the public good.

The emphasis on multi-, inter- or trans-disciplinary science is increasing, as is the emphasis on translation of science to decision makers. The breadth and depth of this emphasis is evident in the new directions taken by major science funding organizations, such

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<sup>35</sup> *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579 (1993).

<sup>36</sup> Even as seemingly narrow a field as high energy physics has been evolving toward multidisciplinary research as the norm. NATIONAL RESEARCH COUNCIL, COOPERATIVE STEWARDSHIP: MANAGING THE NATION'S MULTIDISCIPLINARY USER FACILITIES FOR RESEARCH WITH SYNCHROTRON RADIATION, NEUTRONS, AND HIGH MAGNETIC FIELDS (National Academy Press 1999).

as the National Science Foundation (“NSF”) and the National Institutes of Health (“NIH”). Similarly, the translation of science to the public is receiving greater emphasis, particularly at NIH as Congress asks for evidence that the doubling of the institute’s budget has been of value to taxpayers. This relatively new pursuit of science translation emphasizes the involvement of multiple disciplines. Increasingly, funding of new scientific research by these organizations requires teams of scientists from a broad range of disciplines. The current head of the NIH has used funds taken from each of the NIH components for competitive new interdisciplinary centers.<sup>37</sup>

As the science becomes more complex, the judicial system appears, at least in part, to have become more reductionist in its approach. An example of this reductionist approach is the search for a bright line, such as a relative risk of 2.0, which some courts use as a measuring stick by which to evaluate toxic tort claims. It is a human trait to look for some simplifying concept that cuts through a confusing mass of detail to provide answers that can be phrased as yes or no, and this trait is magnified by the extent to which one is unfamiliar or uncomfortable with the tenets of the field.<sup>38</sup>

Perhaps one of the reasons courts are becoming more reductionist in their approach to evaluating toxic torts is that judges

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<sup>37</sup> E.A. Zerhouni, *Clinical Research at a Crossroads: The NIH Roadmap*, 54(4) J. INVESTIG. MED. 171 (2006); Office of Portfolio Analysis and Strategic Initiatives, *Overview of the NIH Roadmap*, <http://nihroadmap.nih.gov/overview.asp> (last visited Apr. 20, 2008). Systems theory is not confined to laboratory sciences. Under systems theory, the socio-ecological model of human health examines cumulative effects on human health of multiple conditions, ranging from the quality of housing to the presence of disease vectors. Systems approaches also are increasingly being used for complex assessments, such as the Millennium Ecosystem Assessment for global climate change which involved over 1300 scientists providing five technical documents and six synthesis reports. Millennium Ecosystem Assessment, *Overview of the Millennium Ecosystem Assessment*, <http://www.millenniumassessment.org/en/About.aspx> (last visited Apr. 20, 2008).

<sup>38</sup> See *infra* text accompanying footnotes 50–51 for three specific examples in which certain courts would automatically reject the scientific evidence supporting more than a doubling of risk (RR > 2.0) for an individual plaintiff.

are familiar with situations in which a bright line does exist, e.g., drunk driving statutes and speed limits. Even in these cases, however, judges recognize that there are imperfections in the measuring device.<sup>39</sup> It is hard to imagine anyone getting fined for a blood alcohol level of 6.0 mg/100 ml (the inherent variability of the measurement is at least 0.1 mg). We also all know that we can with impunity drive 57 mph in a 55 mph speed zone. Similarly, a strictly applied bright-line rule is inappropriate in toxic tort cases as the technical precision of the determination of relative risk in an epidemiological study is usually far more imprecise than a blood alcohol determination or a radar gun.

As described above, “weight of evidence” is a relatively formal approach that attempts to encapsulate the scientific judgment of the broad scientific community using all of the evidence on hand. In a toxic tort case, the basis for the judgment of an individual expert witness is subject to intense review. Lawyers insist on the expert delineating the specific scientific publications or authoritative texts on which the expert’s opinion is based, and then subjecting each source to intense scrutiny. Any limitation is highlighted, and virtually all studies have limitations. The usual scientist’s hesitancy to be absolutely certain is exploited to the fullest.<sup>40</sup> While a weight of evidence approach will consider the totality of the evidence, including limitations, the lawyer will attempt to discard every paper that is less than perfect—clearly a reductionist approach.<sup>41</sup>

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<sup>39</sup> David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 145 (2d ed., Federal Judicial Center 2000).

<sup>40</sup> Note that a scientist has little to lose by being careful about an original observation. If the scientist turns out to be correct, he or she will get full credit. If incorrect, the hesitancy will protect the scientist’s reputation. As a corollary, a vociferous assertion that their interpretation must be right runs counter to the culture of science and is not a way to favorably impress one’s colleagues.

<sup>41</sup> Using the technique of going into minute detail about every study underlying the weight of evidence, with the intention of discarding the foundation for an otherwise sound scientific conclusion, has been called “corpuscularization” when applied to regulatory law or toxic torts. Thomas O. McGarity, *On the Prospect of “Daubertizing” Judicial Review of Risk Assessment* 66 L. & CONTEMP. PROBS. 155, 155, 157 (2003); Thomas O.

There is justification for attempting to simplify science in a toxic tort case. A legal decision cannot wait for a complex scientific issue to become clarified. Further, many of the questions faced in toxic tort cases may be one of a kind—is it more likely than not that this specific exposure situation led to this specific adverse outcome in this specific individual? The judicial system certainly needs to make decisions in a timely fashion based upon the evidence at hand. However, the current process is not achieving this goal in a manner that is based on the best possible science and, accordingly, the process is unfair for both the plaintiff and defendant. Further, this attempt at simplification does not excuse the almost total disregard of the scientific discipline of toxicology.

I now discuss two examples of the law's search for simplification of environmental science and give examples of dose issues that seem to be ignored in this search.<sup>42</sup>

*A. The Havner<sup>43</sup> Rule As A Trend Toward Simplification*

The *Havner* Rule in Texas reflects the trend toward simplification when courts determine whether an epidemiological finding of more than doubling of a relative risk (RR 2.0) satisfies the “more likely than not” evidentiary rule employed in tort litigation.<sup>44</sup> The *Havner* Court found for the defendant and ruled

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McGarity, *Our Science is Sound Science and Their Science is Junk Science: Science-based Strategies for Avoiding Accountability and Responsibility for Risk-producing Products and Authorities*, 52 U. KAN. L. REV. 897, 921–22 (2004).

<sup>42</sup> I was an expert for the plaintiff in a case in which the jury's verdict was overturned by a *Havner* appeal, *Exxon Corp. v. Makofski*, 116 S.W.3d 176 (Tex. 2003), and I provided an opinion concerning summary judgment for the plaintiff in the *Parker* case. My involvement in toxic tort cases through the years, and currently, has been roughly equal for defendants and for plaintiffs.

<sup>43</sup> *Merrell Dow Pharms. v. Havner*, 953 S.W.2d 706, 716 (Tex. 1997).

<sup>44</sup> Several authors have written about the issue and the shortcomings of using  $RR > 2.0$  as a surrogate for the “more likely than not” standard. See, e.g., Sander Greenland, *Relation of Probability of Causation to Relative Risk and Doubling Dose: A Methodologic Error That Has Become a Social Problem*, 89 AM. J. PUB. HEALTH 1166 (1999); Sander Greenland & James M. Robbins, *Epidemiology, Justice, and the Probability of Causation*, 40

that the expert evidence submitted by the plaintiffs was not scientifically reliable to prove that the birth defect suffered by their child was due to the drug Bendectin. The court established a benchmark for general causation of at least two published epidemiological studies in which there was a statistically significant relative risk greater than 2.0.

The reasoning used by the *Havner* Court is straightforward. If in a given population of exposed individuals, ten individuals were expected to suffer from a specific disease without any exposure, and an epidemiological study shows that in fact there were nineteen diagnosed with the disease (a RR of  $19/10 = 1.9$ ), then for any one of these individuals it is more likely than not (10 to 9) that they belong in the group who would have contracted the disease for a reason unrelated to the exposure. However, if the epidemiological study finds that 21 were diagnosed with the disease (RR  $21/10 = 2.1$ ), then for any one of these individuals it is more likely than not (11 to 10) that they belong in the group who have contracted the disease from the exposure rather than the group who would have developed the disease without the exposure. In addition to the RR 2.0 threshold, the *Havner* rule requires that each of the two studies showing a  $RR > 2.0$  be statistically significant at the 95% level.<sup>45</sup>

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JURIMETRICS 321 (2000). This includes a study by my colleague Russel Lynn Carruth that charts the extent to which this bright line is being used for general or specific causation and considers the scientific and public health problems posed. Russel Lynn S. Carruth & Bernard D. Goldstein, *Relative Risk Greater than Two in Proof of Causation in Toxic Tort Litigation*, 41 JURIMETRICS 195 (2001). Among these problems is the healthy worker effect. Workers are much healthier than the general population for many causes of death (e.g., a major cause of lymphoma is HIV/AIDS. Intravenous drug addicts at high risk for HIV/AIDS are far less likely to be part of a chemical or petrochemical industry work force). If the workforce has a 25% lesser likelihood of dying of a specific disease than the general population (i.e.,  $RR = 0.75$ ), introduction of a chemical that doubled this risk would lead to  $RR = 1.5$  compared to the general population. There are also issues related to the biological model chosen. J. Beyea & Sander Greenland, *The Importance of Specifying the Underlying Biologic Model in Estimating the Probability of Causation*, 76(3) HEALTH PHYS. 269 (1999).

<sup>45</sup> *Havner*, 953 S.W.2d at 727 (“[A] single study would not be viewed as indicating that it is ‘more probable than not’ that an association exists.”).

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The *Havner* requirement for more than one study with a  $RR > 2.0$  also appears to take out of context epidemiologists' skeptical rule of thumb concerning risks that are not very high above normal levels. This skepticism is warranted by three common and related problems in epidemiology: the vagaries of statistical variation, the cluster fallacy, and "publication bias."<sup>46</sup> However, this rule of thumb is primarily applicable to initial unconfirmed reports that do not fit into scientific expectations based upon the totality of the information available. In applying this rule of thumb, scientists are in essence weighing the preponderance of evidence.<sup>47</sup> The *Havner*

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<sup>46</sup> The "cluster fallacy" is inherent in how the choice is made as to what is to be studied. For example, of 200 elementary schools in a city, the normal statistical distribution of childhood leukemia implies that 190 schools have levels of leukemia within the 95% statistical distribution; 5 schools have less than this 95% expectation and 5 schools have more leukemia during a specific time period. It is not unlikely that parents in one of the schools with a high incidence of leukemia will raise the alarm to public health authorities (and to newspapers). The public health authorities will do an epidemiological study confirming that the observed incidence indeed exceeds the 95% expectation, but there is no likelihood that the parents in the low incidence school will ask for a study because the lower incidence of leukemia among their children would not be noticed. Recognition of disease clusters has been the basis for discovery of new and unexpected causal relationships, such as hepatic angiosarcoma and vinyl chloride, but most clusters turn out to be chance associations. "Publication bias" is related to clustering in the sense that career considerations lead epidemiologists to prefer to pursue data that at least preliminarily show an association rather than those that do not. In part, this is due to the importance of publishing in better scientific journals and the natural reluctance of editors of these competing journals to publish negative data. If at first look there does not appear to be a publishable finding, the observation is not pursued and no scientific paper results. An overview of the issues presented by cluster investigations can be found in D. Wartenberg, *Should We Boost Or Bust Cluster Investigations?*, 6(6) EPIDEMIOLOGY 575-76 (1995).

<sup>47</sup> *Havner*, 953 S.W.2d at 716. As one example, Dimitrios Trichopoulos, a Harvard epidemiologist, reacted negatively to being quoted in an article about epidemiological evidence as saying that only a fourfold increase in risk should be taken seriously. In his letter he stated, "This is correct, but only when the finding stands in a biological vacuum or has little or no biological credibility." Dimitrios Trichopoulos, *The Discipline of Epidemiology*, 269(5229) SCIENCE 1326 (1995). He then went on to cite such epidemiological findings as the 3% difference in births of males as compared to females. *Id.*



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rule and other jurisdictions that rely solely on epidemiology strip away the animal and in vitro studies that form such a large part of the preponderance of evidence about toxic agents.

It is understandable that judges want to provide a simplified way to interpret the maze of science related to toxic agents. There are good reasons to do so, particularly given the crowded court calendars and high cost of toxic tort litigation. Extrapolation among scientific findings can be difficult, but the reductionism involved in the *Havner* rule goes well beyond what is needed to prevent obfuscation by experts waving scientific evidence as a flag rather than weighing it as an aid in the understanding of judges and juries.

Below are three hypothetical examples that are fully consistent with either the “more likely than not” or “preponderance of proof” rationale for a doubling of a relative risk, but such examples would be excluded from consideration in Texas because of the failure to exceed either the  $RR > 2.0$  or the 95% statistical significance test. Two of the examples refer to dose, which, as noted earlier, is defined as concentration multiplied by the duration of exposure.<sup>48</sup>

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As another example, the relation of cigarette smoking to cancers other than lung cancer is often characterized by statistically significant relative risks less than 2.0. The risk of bladder cancer in European men after 20 years of smoking is reported by World Health Organization scientists as an odds ratio of 1.96 with a 95% confidence interval of 1.48 to 2.61. P. Brennan et al., *Cigarette Smoking and Bladder Cancer in Men: A Pooled Analysis of 11 Case-Control Studies*, 86(2) INT. J. CANCER 289 (2000).

One can derive another hypothetical from the latter study similar to Example 2 below. Assume that in this study of bladder cancer and cigarette smoking the average extent of smoking was one pack a day for the 20-year period. Also assume a plaintiff with bladder cancer could demonstrate that he smoked two packs a day for 20 years; that, as well known, other effects of smoking were roughly twice as high in those who smoked two packs as compared to one pack a day; and that there was ample literature demonstrating that the more one smoked, the more carcinogens are found in the urine having first passed through the bladder. Further, the plaintiff had no other competing causes of bladder cancer and the plaintiff’s age-related risk was no different than reported in the study. From a toxicologist’s viewpoint, based on this set of facts it is obvious that a two pack a day smoker for twenty years has more than a doubling of risk of bladder cancer. Notwithstanding, this case would be precluded in a jurisdiction requiring  $RR > 2.0$  for general causation.

<sup>48</sup> The difference in how toxicological scientists and the Texas Supreme

The third example relates to statistical significance.<sup>49</sup>

*Example 1. Dose Dependency: The Effect of Duration*

Assume that there is a common workplace process that consistently exposes workers to 10 parts per million (ppm) of chemical XYZ in the air throughout the workday, and that chemical XYZ is supplied by a chemical company that allegedly should have communicated about XYZ's potential for risk. XYZ is found to produce a specific adverse effect in laboratory animals in a dose dependent fashion. These findings in laboratory animals lead to two studies of cohorts of exposed workers which show that there is an 80% higher incidence of this adverse effect than expected (i.e., RR 1.8), and that in each study the increase in risk is statistically significant at the 95% level. The average duration of exposure in the workers is fifteen years. In subsets of workers exposed for periods greater than thirty years, there is, as expected, twice the relative risk than observed in those exposed for fifteen years (i.e, a 160%

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Court view dose is evident from *Borg-Warner Corp. v. Flores*, 232 S.W.3d 765 (Tex. 2007), a recent Texas Supreme Court decision extending *Havner*. In this decision the court repetitively referred to the "dose makes the poison" as a major rationale for reversing a lower court finding in favor of a plaintiff exposed to asbestos while working on brake lining. *Id.* at 770. *See also* Parker v. Mobil Oil Corp., 793 N.Y.S.2d 434 (N.Y. App. Div. 2005), *aff'd*, 857 N.E.2d 1114 (N.Y. 2006), *reh'g denied*, 861 N.E.2d 104 (N.Y. 2007); *but see* Chapin v. A&L Parts, Inc., 732 N.W.2d 578 (Mich. Ct. App. 2007); Laura S. Welch, *Asbestos Exposure Causes Mesothelioma, But Not This Asbestos Exposure: An Amicus Brief to the Michigan Supreme Court*, 13 INT'L. J. OCCUPATIONAL & ENVTL. HEALTH 318 (2007). As noted by John S. Gray, "Some" is No Longer Enough in Texas Toxic Tort Cases, 45 HOUSTON LAW. 54 (2007), the Texas court in *Borg-Warner Corp. v. Flores* required that there be epidemiological findings specifically for brake lining workers. 232 S.W.3d at 7. They further require that if there are multiple defendants contributing to the asbestos levels, only those whose dose is a substantial factor can be held liable. *Id.* at 4; *see also* Richard O. Faulk & Joy E. Palazzo, *Texas High Court Heightens Scientific Evidence Standards*, 22 LEGAL BACKGROUNDER 1 (2007).

<sup>49</sup> What is unrealistic about these examples is the absence of any mechanistic data about XYZ that would help interpret the epidemiologic data. Such data would exist, or be rapidly obtained after XYZ was reported to be a potential human toxin, but would not be admissible in these instances.

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higher incidence which is equivalent to RR 2.6, i.e., more than a doubling of risk), but because the groups are small, the findings are not statistically significant for these subsets. Under *Havner*, the workers with the longer exposure would not be able to sue, despite the evidence from laboratory animals of dose dependency and the reasonable expectation that doubling the duration of exposure would double the risk such that it would be greater than 2.0.

*Example 2. Dose Dependency: The Effect of Concentration*

Assume that chemical XYZ had been found to be particularly useful by a small business owner specializing in restoring antique cars. He has used XYZ almost every work day for fifteen years in his poorly ventilated shop before developing the specific adverse effect now shown in epidemiological and animal studies to be causally related to chemical XYZ. An expert industrial hygienist has estimated that daily workplace exposure averaged 100 ppm, which is ten times higher than that in the much larger workplaces on which cohort studies are based. A physician toxicologist reviewing the dose-response data is prepared to testify that in keeping with this dose response data, the risk for an individual exposed at the workplace to 100 ppm daily for fifteen years is ten times higher than the 80% increase observed in the cohort of workers exposed to 10 ppm for an average of fifteen years (as a simplification, this would be equivalent to an 800% increase in risk or RR 9.0).

If the exposure and the dose response estimations are correct, it is far more likely than not that this individual is suffering from the adverse effect due to exposure to XYZ. Notwithstanding this scientific determination, the plaintiff cannot present his claim before a jury in a Texas state court or in any other jurisdiction that requires dose-specific epidemiological evidence of  $RR > 2.0$  for general causation.<sup>50</sup>

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<sup>50</sup> An individual's anachronistic exposure to a very high chemical dose is often the basis for human harm, but is usually too rare for an epidemiologic study.

*Example 3. Statistical Inconsistency*

Assume that there are only two epidemiologic studies on chemical XYZ in cohorts of workers. The first study, in a large cohort, reported a statistically significant  $RR > 2.0$ . The second study, despite a relative risk of 6.3, has a smaller cohort size and 95% confidence intervals of 0.9–16.8, (i.e., it is not statistically significant at the 95% level). The plaintiff's claim would fail the *Havner* test as there would be only one study that is statistically significant at the 95% level. A researcher could calculate a 50% confidence limit as well as a 95% confidence limit from the data in the second study, however. A 50% confidence limit is basically the range within which 50% of the likely outcomes would fall. If the lower limit of the 50% confidence limit was above 2.0, it is consistent with "more likely than not" (i.e., more than half the expected outcomes are above a relative risk of two). Requiring a plaintiff present scientific evidence with  $RR > 2.0$  and statistical significance at the 95% level is in reality more strict than "more likely than not," even if one were to accept that an epidemiological finding of  $RR > 2.0$  is an appropriate criterion. It also seems contradictory to insist that the science used in a toxic tort case should conform to a nineteen to one ratio of certainty (which essentially is a 95% confidence level), while at the same time focusing on "more likely than not."

*B. The Parker<sup>51</sup> Rulings: Struggling With Chemical Risk*

The *Parker* litigation<sup>52</sup> is an example of decisions from two levels of the New York State judiciary that appear to run counter to how toxicological scientists consider dose issues in cause and effect relationships, although the higher court overruled the lower court on one of these issues. Both the trial court and the appellate

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<sup>51</sup> *Parker v. Mobil Oil Corp.*, 793 N.Y.S.2d 434 (N.Y. App. Div. 2005), *aff'd*, 857 N.E.2d 1114 (N.Y. 2006), *reargument denied*, 861 N.E.2d 104 (N.Y. 2007).

<sup>52</sup> *Id.*

court implement reductionist approaches in the sense that neither court permits an expert to bring to court the full range of scientific evidence that would appropriately and logically be used in forming an expert opinion. In *Parker*, the plaintiff had worked for seventeen years as a gas station attendant and claimed that he had a particularly high level of exposure to gasoline due to his work practices which led to his developing acute myelogenous leukemia.<sup>53</sup> Gasoline is a blend of chemicals that in its usual formulation always contains benzene. There was no argument on general causation as benzene is a known cause of this disease. The Appellate Division of the New York Supreme Court granted a motion from the defendants to dismiss the complaint, primarily because the plaintiff's expert reports had failed to quantify the exposure beyond claiming it was higher than that observed in cohorts of petroleum refinery workers. On appeal, the New York Court of Appeals rejected the Appellate Division's requirement that the amount of exposure must be quantified exactly.<sup>54</sup> Notably, the Court of Appeals nonetheless found for the defendants based on the failure of the plaintiff to show epidemiological evidence that exposure to gasoline causes leukemia.<sup>55</sup>

If the court's finding was carried to its logical conclusion, one could never assign causation to any benzene source except to pure benzene and to a specific benzene-containing mixture for which there is already epidemiological evidence. Industry would be able to market any benzene mixture for which there is now no epidemiological evidence without fear of toxic tort litigation because the specific mixture had not been studied.<sup>56</sup>

Benzene exposure leading to health effects historically has been to benzene in mixtures. This is in part because commercial grade benzene usually had substantial amounts of related hydrocarbon solvents that traveled with benzene during the crude refinery processes of the past. Thus, in the past, compounds such as

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<sup>53</sup> *Id.* at 442.

<sup>54</sup> *Id.* at 438.

<sup>55</sup> *Id.* at 438–39.

<sup>56</sup> Gasoline is a blend that contains various amounts of benzene; usually 1–2% in the United States but up to 5% in other countries.

toluene, ethyl benzene, xylenes and cumene—none of which cause leukemia—were often heavily contaminated by benzene. The extent of contamination in the past led to the erroneous belief that toluene was also a cause of bone marrow damage—the hallmark of benzene toxicity. In addition to the vagaries of the refinery processes, the level of benzene in these aromatic mixtures also depended on commercial needs. For example, removal of toluene from benzene becomes more commercially viable during wartime when toluene is used as a base for the production of trinitrotoluene (“TNT”).

There was never any question that Parker was exposed to benzene, and there was never any question that benzene is a cause of acute myelogenous leukemia. Instead of considering whether the dose of benzene was sufficient under the circumstances of Parker’s work practices, the court acknowledged that benzene was a medically probable cause of his leukemia but nevertheless enforced a requirement for epidemiology that cannot conceivably be performed under the circumstance in which the plaintiff alleges he was exposed.<sup>57</sup> There simply are not enough individuals with this particular work practice to ever be sufficient for an epidemiological study.<sup>58</sup>

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<sup>57</sup> “Key to this litigation is the relationship, if any, between exposure to gasoline containing benzene as a component and AML.” *Parker v. Mobil Oil Corp.*, 857 N.E.2d 1114 (N.Y. 2006) (emphasis in original). The court in *Parker* cited two other cases recognizing that an expert may not need to establish an exact number for the dosage at which a substance is toxic and the amount of exposure the plaintiff experienced. *Id.* at 1121 (citing *McClain v. Metabolife Intl., Inc.*, 401 F.3d 1233, 1241 n.6 (11th Cir. 2005); *Wright v. Willamette Indus., Inc.*, 91 F.3d 1105, 1107 (8th Cir. 1996)).

<sup>58</sup> I am not arguing that exposure to benzene in gasoline is or is not a reasonable medical probable cause of blood cancers. My short letter opinion on the *Parker* case was solely limited to whether the defense’s request for summary judgment was justified. I did not opine on whether it was more likely than not that the plaintiff’s exposure was the cause of his leukemia. My three arguments in favor of letting the case go to a jury were that the description of the plaintiff’s exposure, including dermal exposure, would lead him to have higher exposure than observed among gasoline refinery workers; that there was at least some epidemiological evidence of a more than doubling of risk in these workers for which I cited one study; and that the plaintiff was relatively unique in having a

While recognizing that I am arguing as a toxicologist and not a legal expert, it nonetheless seems that the burden of proof should be on the defense to argue that, per unit dose, benzene in gasoline is any less likely to be a cause of leukemia than benzene in any other mixture. Instead the burden of proof is now on the plaintiff to demonstrate epidemiological evidence that benzene in a specific mixture is a cause of leukemia, despite the fact that benzene itself is fully accepted as a cause of leukemia. In essence, the action of the court was to replace a scientific argument concerning dose and specific causation. The court did so with a requirement for an epidemiological study to prove general causation before being able to consider specific causation.<sup>59</sup>

#### VI. THE EXCLUSION OF ANIMAL TOXICOLOGY AND MECHANISTIC INFORMATION FROM TOXIC TORTS: LEGAL REDUCTIONISM

To a toxicologist, the reductionist tendency of the law that is most difficult to understand is the often seemingly dismissive attitude of toxic torts jurisprudence to the science of poisons. The failure to consider toxicology does a disservice to defendants as well as plaintiffs. It is quite possible to construct a large reference list of agents that have been epidemiologically associated with

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history of radiation exposure. Atom bomb survivors who developed leukemia are reportedly more likely to have workplace benzene exposure than those who did not develop leukemia. Toranosuke Ishimaru, *Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki*, 93(3) AM. J. EPIDEMIOLOGY 157-65 (1971).

<sup>59</sup> This is similar to arguing that there is a need for an epidemiologic study demonstrating that a Chevrolet can cause trauma if it runs into a pedestrian if prior studies only involved Fords. When it comes to damaging a human, automobiles are automobiles, and benzene is benzene. Both products have the potential, but the extent of damage, if any, depends upon the circumstances. In this case the court prevented the jury from hearing the circumstances. Two authors that take up the issue of jury exclusion are CARL F. CRANOR, *Judge-Jury Responsibilities and the Right to a Jury Trial*, in TOXIC TORTS: SCIENCE, LAW, AND THE POSSIBILITY OF JUSTICE 70, 70-71 (2006) and Michael H. Gottesman, *From Barefoot to Daubert to Joiner: Triple Play or Double Error?*, 40 ARIZ. L. REV. 753, 776 (1998).

virtually any disease, and these lists are readily accessible to the plaintiffs' bar.

The body of studies associating specific agents with a number of different diseases reflects the many epidemiological studies that attempt to uncover previously unobserved relationships by searching for associations among large databases. These are often called "hypothesis generating" studies. Such studies are highly appropriate in that they contribute to developing further studies aimed at specifically exploring the possible cause and effect relationship generated in the initial study. However, hypothesis generating studies have the inherent weakness that some statistically significant association will occur when there are enough questions being asked. For example, a common approach is to start with the diagnoses in a given hospital population, or the causes of mortality stated on death certificates in a given geographical location, and relate these to the occupation of the hospital patient or the potential environmental factors associated with a geographical location. There are many different diseases, many different occupations, and many different localized environmental factors. Using a standard statistical approach in which in essence one chance variation out of 20 is reported as statistically significant, it is inevitable that some associations of some disease with some chemical will be noted.

Many studies retrospectively look at what has happened in the past. Testing the hypotheses generated in such studies can be done in a number of ways, including further epidemiological studies. A more probable response, which is far quicker and far less expensive, are toxicological studies in laboratory animals searching for the same effect, or mechanistic studies aimed at determining if there is a likely pathway by which the chemical causes the putative effect, rather than just a statistical association with no causality.<sup>60</sup>

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<sup>60</sup> An example of both a hypothesis-evaluating and hypothesis-generating study is the Agricultural Health Study, a large scale study of the health of farmers by the National Cancer Institute. M.C. Alvanja et al., *The Agricultural Health Study*, 104(4) ENVTL. HEALTH PERSP. 362 (1996). The study is aimed at testing the cancer risk of American farmers and follows a number of smaller studies that have reported an increased risk of non-Hodgkin's lymphoma and other cancers. Over 80,000 farmers are being followed prospectively, with careful



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It is appropriate to fully depend upon studies in humans if there is direct epidemiological evidence of the tort and there are no competing causes in the individual for exposure to the agent or risk factors for the disease. In most instances there is little or no direct epidemiological evidence related to the plaintiff's exposure. Instead inferences that often depend upon an analysis of all of the pertinent information for scientific acceptability must be made from the existing epidemiological literature.

In epidemiology, the gold standard has long been the randomized double blind control trial. This standard, although difficult, can be achieved when testing drugs or other therapeutic approaches. However, it cannot be achieved in epidemiological studies of chemicals in the workplace or general environment. Inevitably, such studies are observational studies with various degrees of strengths, but all requiring some degree of inference or extrapolation. While it is true that animal toxicology always requires extrapolation across species, it is also true that animal toxicology can be rigidly controlled in a way that is not possible in epidemiological studies of the workplace or the general community.<sup>61</sup>

A classic cohort epidemiological study will often describe a

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attention to present and past exposures to pesticides and other chemical and biological agents common to agricultural activities. A comprehensive health and exposure questionnaire has been developed that seeks information on multiple health endpoints. The prospective study should have ample power to test hypotheses related to farmers and cancer, but the questionnaire inevitably leads to hypothesis-generating studies. See George M. Gray et al., *The Federal Government's Agricultural Health Study: A Critical Review with Suggested Improvements*, 6(1) HUM. & ECOLOGICAL RISK ASSESSMENT 47 (2000). For example, there are 800 possible associations in a study evaluating 20 different pesticides and 40 different health endpoints. It is inevitable that there will be statistically significant associations between a specific pesticide and a specific health endpoint that occur by chance alone. Statistical correction factors are used to approach this problem, but as the goal is the generation of hypotheses rather than the assignment of causation, it is not inappropriate that the association be reported and left for others to explore whether true causality exists. This will often depend upon animal toxicology and mechanistic studies.

<sup>61</sup> See discussion in Joseph V. Rodricks, *Evaluating Disease Causation in Humans Exposed to Toxic Substances*, 14 J.L. & POL'Y 39 (2006).

relatively large number of workers of whom usually only a small percent suffer from the disease of interest. Further, not all of the cohort is substantially exposed to the agent of concern.<sup>62</sup> This is in contrast to a drug trial in which everyone in the treatment group receives the same dose of a drug and everyone in the control group receives a placebo.

Toxicological research focusing on the mechanism of action of chemicals can also be useful in clarifying medical nomenclature—an issue that can present a problem to judges and juries. In the field of medicine, the nomenclature of disease is usually based on what is observable. One example is asthma, the diagnosis of which depends primarily upon whether an individual has the particular type of breath sound known as a wheeze. In essence, asthma is purely a descriptive term depending upon a physical sign. Wheezing reflects the narrowing of major airways within the lung and is a final common denominator of many different types of extrinsic causes and intrinsic susceptibilities.

Advances in molecular biology will allow us to discard the term asthma and use diagnostic terms that describe the direct intrinsic or extrinsic causes of lung disease that is accompanied by wheezing. The opposite occurs for other diseases, such as leukemia, for which

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<sup>62</sup> Classic epidemiological studies evaluating the mortality of a petrochemical or chemical industry workforce can underestimate true effects at the work site both by including workers whose exposure is relatively minimal, e.g., those working in the cafeteria or in accounts payable, and by excluding those who may have high exposure but who work for subcontractors rather than the industry, e.g., maintenance workers who clean up after product spills, or as in a recent Delaware case, millwrights who replace leaky valves. *Texaco to Pay Worker's Widow \$2.84 Million*, DELAWARE ONLINE, 2007, available at <http://www.delawareonline.com/apps/pbcs.dll/article?AID=/20071106/NEWS/711060390>.

Some of the problems of cohort studies can be approached by nested case control studies. For example, in a study of refinery workers whose overall relative risk was slightly less than 1.0, a nested case control study found that for those who did develop leukemia there was more than a doubling of risk that they were exposed to higher rather than lower doses of benzene at the workplace. L. Rushton & M.R. Alderson, *A Case-Control Study to Investigate the Association Between Exposure to Benzene and Deaths from Leukemia in Oil Refinery Workers*, 43 BRIT. J. CANCER 77 (1981).

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nomenclature tends to split diseases that are closely related. The recognition of different subtypes of leukemia is abetted by the ready availability of blood or bone marrow which allows microscopic observation of multiple samples as the disease progresses—something that, at least until recently, has been unusual for cancers of most other organs for which a biopsy is a relatively major procedure. Thus, differences in morphology could readily be related to differences in clinical course or outcome. Yet with the use of modern molecular biology, we find that there are overlapping molecular characteristics between such disorders as acute myelogenous leukemia, the form more commonly observed in adults, and acute lymphoblastic leukemia, the form more commonly observed in children. This is not surprising as both the lymphocytic and myelocytic cell series derive from a common pluripotential cell. If the mutation that leads to cancer occurs sufficiently early in the differentiation process, the cancer will have characteristics of both cell series.<sup>63</sup>

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<sup>63</sup> The medical literature also tends to be confusing for toxic tort litigation because of the organizational structure of medical specialties and their journals. For example, a relatively minor brain tumor type is a solitary lymphoma. The patient will usually present to a neurologist for the evaluation of symptoms related to a space-occupying lesion in the central nervous system. After biopsy demonstrating a lymphoma, and further evaluation that shows that the lymphoma is localized to the one location in the brain, the neurologist will identify the patient as suffering from a Primary Central Nervous System Lymphoma (“PCNSL”). In terms of nomenclature, PCNSL merely identifies the anatomical location of a tumor type. To a hematologist who might be called upon to prescribe the appropriate chemotherapy for this localized lymphoma, the primary concern will be which pathological subtype of lymphoma cells and organizational structure are present as this will guide treatment, e.g., B-cell or T-cell; follicular or diffuse, etc. Lymphomas are discussed or classified in the hematological literature in terms of pathological subtype. For example, see the Revised European-American Lymphoma Classification which lists about 40 lymphoma subtypes in terms of morphology, phenotype and genotype, without mentioning PCNSL. THOMAS J. KIPPS, *WILLIAMS HEMATOLOGY* 1316–17 (7th ed. 2006).

In terms of toxic torts, a hematologist convinced that benzene can cause lymphoma would reason that the location of the lymphoma is of little consequence as lymphocytes are diffusely present within the body, are known to move from organ to organ, and localized lymphomas are not unusual in almost

Also favorable to the defendant is the use of mechanistic understanding to discard a presumed cause and effect relationship. For example, saccharin has been downgraded by the National Toxicology Program from its previous listing as reasonably anticipated to be a human carcinogen.<sup>64</sup> A major reason for this change was the finding of a mechanism to explain why bladder cancer was observed in laboratory animals exposed to saccharin. This mechanism was one that had a threshold, permitting regulators to move away from a no-threshold model for carcinogens. The dose to exceed the threshold was well above any reasonable expectation in humans consuming saccharin.<sup>65</sup>

Another example of using mechanistic principles to downgrade an epidemiological finding comes from a recent IARC review of formaldehyde. A long term follow up of a formaldehyde-exposed cohort by an excellent group of epidemiologists found a statistically significant increase in leukemia incidence. However, based on mechanistic grounds, it was difficult to conceive of a mechanism by which exposure to formaldehyde could cause leukemia. Despite the “strong evidence” in human studies, IARC

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any part of the body; although of particularly great consequence within the limited space of the skull. In contrast, a defense lawyer would take the reductionist approach of insisting that there be epidemiological evidence linking benzene specifically to PCNSL and would likely ask the court to discard any evidence linking benzene to lymphoma as not being sufficiently specific to the disease.

<sup>64</sup> See National Toxicology Program: Department of Health and Human Services, Report on Carcinogens, “Saccharin” (2005), available at <http://ntp.niehs.nih.gov/INDEX.CFM?OBJECTID=BE49AE97-F1F6-975E-77FE65CCD04657CF> (last visited Mar. 22, 2008).

<sup>65</sup> Joe G. Hollingsworth & Eric G. Lasker, in a review of *Daubert* avowedly from a defense lawyer’s perspective, claims that the downgrading of the saccharin decision shows the failure of toxicology to be borne out. Joe G. Hollingsworth & Eric G. Lasker, *The Case Against Differential Diagnosis: Daubert, Medical Causation Testimony, and the Scientific Method*, 37(1) J. HEALTH L. 90 (2004). Indeed, the opposing opinion is much more accurate. The fact that a previous weakly positive epidemiological study was not replicated likely would not have been enough to overcome the usual regulatory resistance to downgrading a potential human carcinogen without the new information on mechanism. See L. B. Ellwein & S. M. Cohen, *The Health Risks of Saccharin Revisited*, 20(5) CRIT. REV. TOXICOL. 311–26 (1990).

classified the overall evidence that formaldehyde caused leukemia as “not sufficient.”<sup>66</sup> Similarly, evidence of cancer in laboratory animal studies can be scientifically discounted as has occurred for the finding that exposure of male rats to gasoline causes kidney cancer through a mechanism not operative in humans.<sup>67</sup>

Mechanistic understanding also helps with interpreting latency periods between exposure and disease. The latency period is a particularly important point for understanding cancer caused by chemicals as such periods can be too short or too long to be consistent with the known biological processes involved in the causation of disease. Some examples are obvious because they are within the experience of a layperson. For instance, one can readily reject a plaintiff’s allegation that someone hit them in the eye two weeks before the plaintiff first noted a black eye. It would hardly be necessary for an expert to convince a jury by giving scientific testimony about the biological mechanisms that convert trauma into skin discoloration. In other situations, however, understanding of the mechanism underlying the disease process, coupled with the existing epidemiological literature concerning latency periods, is a

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<sup>66</sup> “The working group also found . . . ‘strong but *not sufficient* evidence’ for leukaemia. The finding for leukaemia reflects the epidemiologists’ finding of strong evidence in human studies coupled with an inability to identify a mechanism for induction of leukaemia, based on the data available at this time.” Press Release, World Health Organization’s International Agency for Research on Cancer, IARC Classifies Formaldehyde as Carcinogenic to Humans (June 15, 2004), available at [http://www.iarc.fr/ENG/Press\\_Releases/archives/pr153a.html](http://www.iarc.fr/ENG/Press_Releases/archives/pr153a.html). See also Vincent J. Coglianò et al., *Meeting Report: Summary of IARC Monographs on Formaldehyde, 2-Butoxyethanol, and 1-tert-Butoxy-2-Propanol*, 113(9) ENVTL. HEALTH PERSP. 1205–08 (2005).

<sup>67</sup> In yet another example of more inclusiveness of toxicology data, an Institute of Medicine (“IOM”) committee has recently recommended additional consideration of the non-epidemiological database and of dose in the evaluation process used to classify the scientific basis for presumptive disability decisions made by the Veterans Administration. This would be a change from the previous process in which the IOM classification was almost totally based upon epidemiological findings. INSTITUTE OF MEDICINE, COMMITTEE ON EVALUATION OF THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS FOR VETERANS, IMPROVING THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS FOR VETERANS (Jonathan M. Samet & Catherine C. Bodurow eds., 2008).

valuable part of evaluating a potential toxic tort.

#### CONCLUSION

Much of the legal commentary concerning science reflects the issue of how to fairly bring the state of the art into the courtroom. Supreme Court Justice Stephen Breyer commented, “A judge is not a scientist and a courtroom is not a scientific laboratory,” but judges “must aim for decisions that, roughly speaking, approximately reflect the scientific state of the art.”<sup>68</sup> The core understanding of dose issues related to toxic torts reflects a scientific state of art that is at least 500 years old.<sup>69</sup> Unfortunately, as judges attempt to simplify complex issues related to causality, there are too many instances in which relatively simple and straightforward scientific understanding concerning dose is being discarded or obfuscated.

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<sup>68</sup> *Justice Breyer Calls for Experts To Aid Courts in Complex Cases*, N.Y. TIMES, Feb. 17, 1998, at A17.

<sup>69</sup> Michael A. Gallo, *History and Scope of Toxicology*, in CASARETT & DOULL’S TOXICOLOGY: THE BASIC SCIENCE OF POISONS 3–11 (Curtis D. Klaassen ed., 5th ed. 1996).