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BAYES' LAW, SEQUENTIAL UNCERTAINTIES, AND EVIDENCE OF CAUSATION IN TOXIC TORT CASES

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Judges are the gatekeepers of evidence. Arguably, the most difficult duty for a judicial gatekeeper is to screen the reliability of expert opinions in scientific fields such as medicine that are beyond the ken of most judges. Yet, judges have a duty to scrutinize such expert opinion evidence to determine its reliability and admissibility. In toxic tort cases, the issue of causation—whether the alleged exposures actually caused the plaintiff's injury—is nearly always the central dispute, and determining admissibility of expert causation opinion is a daunting challenge for most judges. We present a comprehensive review of the courts' struggles with the screening of scientific evidence in such cases. In addition, we propose an approach to the screening of causation opinions based on probability science and logic. Central to this approach is Bayes' Law, a statistical tool that courts can use to analyze the extrinsic reliability of proffered causation testimony. We explain Bayes' Law and illustrate its potential application for evaluating the reliability of medical and scientific causation testimony.

All evidence is probabilistic. There are uncertainties attending all testimony, not only because the honesty or objectivity of witnesses may be doubtful, but also because even honest and unbiased witnesses may be mistaken in their perceptions. Reliability of causation evidence depends on both sensitivity and specificity of the tests used to determine causation. Highly sensitive tests of causation reflect an ability to identify a high percentage of those with the agent-induced disease, whereas highly specific tests of causation reflect an ability to reject a high percentage of those who have the disease, but not induced by the agent at issue. According to Bayes' Law, the reliability of causation opinion depends not only on the sensitivity and specificity of the tests employed by the causation expert, but also on the base-rate of the agent-induced disease in the population. Bayes' Law dictates that the lower the rate of the agent-induced disease in the population, the less reliable the opinion that the agent at issue in fact caused the plaintiff's disease given certain levels of sensitivity and specificity. The base-rate problem and its effect on reliability of causation opinions are overlooked by judges when scrutinizing the reliability of proffered causation evidence. In this Article, we encourage courts to consider a Bayes' Law approach to screen out, at an early stage, those claims of injury lacking reliable evidence that an injury was more likely than not caused by exposures to toxic agents.

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The goal of our Article is to provide a framework that helps the gatekeeper to screen out toxic tort claims insufficiently substantiated by the underlying scientific and medical data, and allow the factfinder to decide only those toxic tort claims for which there is reliable and relevant scientific support for each link of the causal chain, from subject exposure to the injury. Scientific substantiation of each causal link determines the reliability of an expert's opinion that the exposure more likely than not caused the plaintiff's injury.

I. INTRODUCTION

"Toxic tort" is the label applied to negligence cases in which the plaintiffs allege that exposure to harmful agents, usually chemicals, caused the onset of disease, injury, or even death in others[1] As in the norm in negligence cases, a toxic tort plaintiff has the burden of proving that the defendant's negligence caused the injury or illness. The standard of proof is the typical "preponderance of the evidence" standard applied in civil cases.[2] In a toxic tort case, the plaintiff must

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1. The phrase "toxic tort" is not amenable to precise definition, due to the fact that the term "toxic" is difficult to define. Nevertheless, we offer a practical, perhaps overly simple, definition. In this Article, "toxic tort" refers to personal injury cases in which the plaintiffs claim that exposures to chemicals or radiation caused personal injury. Hearing loss claims based on alleged exposures to noise fit this definition, but generally are not considered toxic tort cases. We discuss in this Article the so-called "trauma cancer" cases which are not strictly toxic torts, but nevertheless display features of generic toxic tort cases, most notably a chronic-type injury with a latency period between first exposure and disease onset. *See infra* note 202.

In the remainder of this Article, we use the phrase "plaintiff's injury" to include injuries, diseases, and illnesses incurred not only by the plaintiffs themselves, but also by others, usually decedents or infants. Likewise, the phrase "plaintiff's exposures" encompasses exposures of others for whose injuries the plaintiffs seek recovery.

2. *See, e.g.*, Allison v. McGhan Medical Corp., 184 F.3d 1300, 1306 (11th Cir. 1999) ("The burden of laying the proper foundation for the admission of the expert testimony is on the party offering the expert, and the admissibility must be shown by a preponderance of the evidence." (citing Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 592 n.10 (1993))). "In a negligence action, plaintiff has the burden to prove that defendant was negligent by producing evidence that will permit the trier of fact to conclude that it is more likely than not that defendant's negligence caused plaintiff's injuries, without any presumption of law one way or another." 65A C.J.S. *Negligence* § 715 (2000) (citing Vito v. Sargis & Jones, Ltd., 672 A.2d 129 (Md. Ct. Spec. App. 1996), *aff'd*, 695 A.2d 191 (Md. 1997), & Anglin v. Kleeman, 665 A.2d 747 (N.H. 1995)). In most jurisdictions, the standard of proof on the issue of causation is that the defendant's conduct "more likely than not" was a substantial factor in producing the plaintiff's injury. *See, e.g.*, Brown v. Parker-Hannifin Corp., 919 F.2d 308 (5th Cir. 1990); Sterling v. Velsicol Chem. Corp., 855 F.2d 1188 (6th Cir. 1988); Chaney v. Smithkline Beckman Corp., 764 F.2d 527 (8th Cir. 1985); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387 (D. Or. 1996); Reynard v. NEC Corp., 887 F. Supp. 1500 (M.D. Fla. 1995). A party proves a fact by a preponderance of evidence if "the scale tips, however slightly, in favor of the party with the burden of proof." *E.g.*, Ostrowski v. Atl. Mut. Ins. Co., 968 F.2d 171, 187 (2d Cir. 1992) (quoting LEONARD B. SAND ET AL., MODERN FEDERAL JURY INSTRUCTIONS ¶ 73.01, at 73–74 (1992)). Viewed from the perspective of the party not bearing the burden of proof, the "preponderance standard is . . . a tie-breaker dictating that when the evidence on an

establish that exposures to the toxic agent more likely than not caused the injury.[3]

Whether the harmful agent caused the injury or disease is the central issue in most toxic tort cases. Several factors often obscure the causal pathway between the putative exposures and the diagnosed illness. First, in contrast to injuries caused by sudden and traumatic events (for example, a broken leg caused by a fall from a ladder), injuries caused by exposure to toxic agents often develop over long periods of time.[4] The extended period from exposure to injury obscures the causal relationship, if any, between the exposure and the injuries. In addition, seldom is the injury uniquely traceable to the subject of exposure. In most toxic exposure cases, the injury at issue is one that occurs in the general population and has many possible causes, complicating the task of proving a causal link between the suspected toxic agent and the disease.[5] To make matters worse, the diagnosis of the disease is sometimes in controversy. Even the allegation of exposure to the agent may be at issue, or at least the duration and intensity of the exposure. Finally, and perhaps most basic, the question of whether the agent is capable of causing the claimed injury is disputable. A circuitous causal chain characterizes "generic" toxic tort cases.[6]

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issue is evenly balanced, the party with the burden of proof loses." United States v. Gigante, 39 F.3d 42, 47 (2d Cir. 1994).

3. *See, e.g., In re* Agent Orange Prod. Liab. Litig., 611 F. Supp. 1223, 1262 (E.D.N.Y. 1985) (concluding that toxic tort plaintiffs were required to "offer evidence that causation was more than [fifty] percent probable"); *see also* Dukes v. Ill. Cent. R.R., 934 F. Supp. 939, 944 (N.D. Ill. 1996) (observing that a plaintiff in a Federal Employers Liability Act case involving toxic exposure has a lower burden of proof of causation than a plaintiff in a common law negligence case, but "the plaintiff still bears the burden of presenting evidence from which a jury could conclude a 'probable' or 'likely' causal relationship [between the exposure and the injury] as opposed to merely a 'possible' one" (quoting Edmonds v. Ill. Cent. Gulf R.R., 910 F.2d 1284, 1288 (5th Cir. 1990))).

4. Note, *The Fairness and Constitutionality of Statutes of Limitations for Toxic Tort Suits*, 96 HARV. L. REV. 1683, 1683 n.1 (citing Stanley J. Levy, *Radiation Litigation—The Emerging Tort Field*, 1981 TRIAL LAW. GUIDE 568, 571 & n.3) ("The latency period for disease development is more than [twenty] years for victims of radiation from atomic bomb tests; for daughters of women taking DES [diethylstilbestrol], a full generation; for most cases of asbestos-related mesothelioma, [twenty-five] years; for victims of hepatic angiosarcoma caused by exposure to vinyl chloride, over [twenty years].").

5. *See* United States v. Shonubi, 895 F. Supp. 460, 517 (E.D.N.Y. 1995) (explaining that proof of causation in toxic tort cases involving latent effects and no "signature" diseases "is extremely difficult"); Steve Gold, Note, *Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence*, 96 YALE L.J. 376, 376 (1986) (noting diseases of indeterminate origin may remain latent for years, are associated with diverse risk factors, and occur without any apparent cause); *see also infra* notes 315–318 and accompanying text (discussing so-called "signature" diseases).

6. *See* Note, *Navigating Uncertainty: Gatekeeping in the Absence of Hard Science*, 113 HARV. L. REV. 1467, 1472 (2000) (defining a "generic" toxic tort case as "a case in which a complicated causal chain, a long latency period, or low levels of exposure render the argument for

A toxic tort plaintiff often will need expert medical and scientific testimony to establish the link between the subject exposure and the injury.[7] A medical expert must usually conduct a "differential diagnosis" to reliably diagnose the disease.[8] Then, the causation expert must be able to show that a sufficient dose of the toxic agent at issue, and more particularly the plaintiff's estimated dose, is capable of causing the disease in question (that is, *general causation*). Next, the causation expert must conduct a quantitative *causation analysis* (sometimes called *risk analysis*) to establish that the agent at issue is the most likely cause of the disease or injury (specific causation).[9] To conduct a valid causation analysis, the expert must apply relevant medical, toxicological, and epidemiologic principles to the facts of the case, weighing alternative potential causes of the injury to identify the most likely cause.[10]

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causation inherently weak"). Earlier, Troyen A. Brennan characterized "hazardous substances" cases. Troyen A. Brennan, *Causal Chains and Statistical Links: The Role of Scientific Uncertainty in Hazardous-Substance Litigation*, 73 CORNELL L. REV. 469, 501–02 (1988) ("First, people are exposed to [hazardous substances] in a chronic and relatively low-dose fashion. Second, exposed persons lack awareness of the toxic effect during the initial phase of the exposure. Third, the exposure is followed by a latency period before the disease or injury manifests itself. Fourth, the injury or disease at least produces chronic defects and is usually irreversible. Fifth, the hazardous substance is not left in the body in a way that firmly links the disease or injury with the substance. The paradigm of hazardous substances is the occupational or environmental carcinogen. Substances such as teratogens, certain agents that cause chronic lung disease, and heavy metals that produce neurological disease exemplify these five characteristics of hazardous substances.") (citations omitted).

7. *See, e.g.*, Savage v. Union Pac. R.R., 67 F. Supp. 2d 1021, 1030 (E.D. Ark. 1999) ("[T]he existence of a causal connection between exposure to a certain chemical and an alleged injury requires specialized expert knowledge and testimony since such matters are not within the common knowledge of lay persons."); Joiner v. Gen. Elec. Co., 864 F. Supp. 1310, 1319 (N.D. Ga. 1994) ("When medical causation is at issue, plaintiffs must prove causation to a 'reasonable degree of medical certainty.'" (quoting Wells v. Ortho Pharm. Corp., 615 F. Supp 262, 295 (N.D. Ga. 1985))), *rev'd on other grounds*, 78 F.3d 524 (11th Cir. 1996), *rev'd on other grounds*, 522 U.S. 136 (1997); Sweeney v. Geon Co., No. 01-00-00315-CV, 2002 WL 58223, at *4 (Tex. Ct. App. Jan. 17, 2002) ("Where causation is not readily ascertainable from general experience and common sense, proving causation requires expert testimony." (citing Lenger v. Physician's Gen. Hosp., Inc., 455 S.W.2d 703 (Tex. 1970))).

8. *See infra* Part VIII.D.3 (discussing differential diagnosis).

9. *See infra* notes 296–299 and accompanying text (discussing general and specific causation).

10. A detailed description of causation analysis or risk analysis is beyond the scope of this Article. Briefly stated, risk assessment involves quantitative estimates of the probability that a certain level of exposure to a specific chemical will result in a specific disease endpoint. Of particular importance from a regulatory view is the degree of conservatism included in dose-response estimates. Regulators develop exposure standards to protect public health. As a consequence, regulators set exposure standards with a margin of safety and use conservative risk assumptions that err on the side of over-predicting the probability of an adverse outcome. Guidelines for Carcinogen Risk Assessment, 51 Fed. Reg. 33,999 (Sept. 24, 1986); RICHARD WILSON & EDMUND A.C. CROUCH, RISK-BENEFIT ANALYSIS 159–71 (2001); *see also* Hans-Olov Adami & Dimitrios Trichopoulos, *Concepts in Cancer Epidemiology and Etiology*, *in* TEXTBOOK OF CANCER EPIDEMIOLOGY 87, 105 (Hans-Olov Adami et al. eds., 2002) ("Regulatory agencies and policy makers may recommend standards, set limits, or authorize

Pursuant to the Federal Rules of Evidence (FRE) Rule 702,[11] and *Daubert v. Merrell-Dow Pharmaceuticals, Inc.*[12] and its progeny, if such proffered medical/scientific causation opinion testimony is to be admissible, then it must be reliable and relevant. Federal courts and most state courts have a gatekeeping duty to bar unreliable opinion evidence. To discharge this duty, courts hold preliminary hearings in which causation experts, if challenged by the opposing party, must demonstrate to the court that they derived their proffered conclusions from accepted methods of science.[13] A court exercising its gatekeeping duty will bar any proffered opinion testimony that fails to meet general standards of reliability and relevancy.[14] The court will not allow the trier of fact to consider opinion testimony the court has determined to be unreliable or irrelevant.[15]

In this Article we discuss an issue that to our knowledge no court has ever addressed when evaluating the reliability of an expert's proffered causation testimony in a toxic tort case. Specifically, we contend that the reliability of opinions as to the cause of a toxic tort plaintiff's injury depends on two key quantitative factors: 1) the intrinsic accuracy of the tests used by the experts to reach their opinions (that is, the sensitivity and specificity of the tests); and 2) the extrinsic rate of the agent-induced disease among those with the disease. More generally, we contend that the reliability of disease-causation opinions depends in part on what percentage of disease the subject agent causes among all

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action even when the scientific evidence is weak. These decisions serve public health objectives by introducing a wide safety margin, but they should never be confused with the establishment of causation based on scientific considerations alone."). "[R]isk is generally a function of exposure or dose. . . . [T]he process or procedure used to estimate the likelihood that humans or ecological systems will be affected adversely by a chemical or physical agent under a specific set of conditions is called *health risk assessment.*" Dennis J. Paustenbach, *Primer on Human and Environmental Risk Assessment, in* HUMAN AND ECOLOGICAL RISK ASSESSMENT: THEORY AND PRACTICE 3, 4 (Dennis J. Paustenbach ed., 2002). For a discussion of the controversies concerning risk analyses involving potential carcinogenic agents, see generally JOHN D. GRAHAM ET AL., IN SEARCH OF SAFETY: CHEMICALS AND CANCER RISK (1988).

11. FED. R. EVID. 702 ("If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.").

12. 509 U.S. 579 (1993).

13. FRE Rule 104 provides for pre-trial hearings to address questions concerning the qualifications of opinion witnesses and the admissibility of evidence. FED. R. EVID. 104.

14. *Daubert*, 509 U.S. 579 (1993).

15. *See infra* Part VIII.A (discussing the so-called *Daubert* criteria that courts apply to proffered scientific and technical testimony to determine its relevance and reliability, and, consequently, its admissibility).

people with the disease. Other things being equal, the lower the rate of the agent-induced disease among those with the disease, the less reliable the proffered causation opinion will be. Stated positively, the lower the rate of the agent-induced disease among those with the disease, the more sensitive and specific the tests employed by the expert need to be to achieve the level of reliability required for legal proof of causation. As explained below, Bayes' Law provides the statistical tool for analyzing the extrinsic reliability of proffered causation testimony.

The reliability of proffered expert medical testimony in a toxic tort case involves issues other than the sensitivity and specificity of tests and disease rates. For example, whether the subject agent is capable of causing the plaintiff's injury is often at issue. As mentioned above, it is the plaintiff's burden to establish that the agent is capable of causing the injury (general causation) as a prerequisite to establishing that the agent caused the plaintiff's injury (specific causation). Another possible uncertainty present in a toxic tort case concerns the plaintiff's specific injury. The diagnosis of the disease may be an issue either because the defendant challenges the medical expert's identification of what ails the plaintiff, or because the diagnosed ailment may be one not generally recognized in the medical community.[16] Further, the level of exposure to the toxic agent, seldom known with certainty, must be estimated either using whatever data are available or, absent data, using exposure models based on principles of dispersion, transport, chemistry, and industrial hygiene practice.[17] These exposure estimates likewise involve uncertainties. When present in a toxic tort case, each of these uncertainties compounds the overall uncertainty of a proffered opinion that the agent caused the plaintiff's injury.

This Article first describes Bayes' Law and its bearing on the reliability of causation testimony in toxic tort cases. Along the way, this Article explains important principles of epidemiology and toxicology, the sciences of disease that provide the tools to quantify risk as needed in the proposed Bayesian analysis. Next, the Article discusses the impact of other uncertainties attendant to expert opinion testimony in toxic tort

16. *See, e.g.*, Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981 (C.D. Cal. 1996) (finding that no testimony regarding "multiple chemical sensitivity" could be admitted because it is not a "physiological illness" generally accepted by the medical community).

17. For an example of an industrial hygiene expert's attempt, albeit unsuccessful, to introduce into evidence his exposure model for the purpose of estimating the plaintiff's past occupational exposures to benzene, see Castellow v. Chevron USA, 97 F. Supp. 2d 780 (S.D. Tex. 2000) (excluding the proffered exposure model testimony under *Daubert*). *See also* Leija v. Marathon Oil, No. 96-617531 (Mich. Cir. Ct. Feb. 15, 2000) (excluding as unreliable expert's proffered skin absorption model for use in estimating plaintiff's benzene dose); Austin v. Kerr-McGee Ref. Corp., 25 S.W.3d 280 (Tex. Ct. App. June 29, 2000) ("Guesses, even if educated, are insufficient to prove the level of exposure in a toxic tort case." (quoting Mitchell v. Gencorp Inc., 165 F.3d 778, 781 (10th Cir. 1999)).

cases, exploring how these uncertainties combine to make the proffered testimony less reliable. Finally, this Article suggests that judges or their appointed special masters apply a Bayesian, probabilistic approach in toxic tort cases when evaluating the reliability of proffered expert opinions pursuant to FRE Rules 104 and 702, and the holding in *Daubert*. The goal is to allow the factfinder to decide only those toxic tort claims for which there is reliable and relevant scientific support for each link of the causal chain (from subject exposure to the injury). Scientific substantiation of each causal link determines the reliability of an expert's opinion that the exposure more likely than not caused the plaintiff's injury.

II. WHAT IS BAYES' LAW?[18]

All evidence is probabilistic.[19] There are uncertainties attending all testimony, not only because the honesty or objectivity of witnesses may be doubtful, but also because even an honest and unbiased witness may be mistaken in their perception.[20] "No observation, test, or

18. We use the phrase Bayes' Law rather than Bayes' Theorem because all Bayesian and non-Bayesian theoreticians agree on the formula derived by Bayes and discussed in this Article. MASSIMO PIATTELLI-PALMARINI, INEVITABLE ILLUSIONS: HOW MISTAKES OF REASON RULE OUR MINDS 106 (Massimo Piattelli-Palmarini & Keith Botsford trans., 1994). The theoreticians disagree about the "*amount of* insight one gains from applying this formula to *all* actual cases of induction." *Id.* at 107–08; *see also* United States v. Shonubi, 895 F. Supp. 460, 485 (E.D.N.Y. 1995) (stating that the problem for the courts is not whether Bayesian analysis is valid, but rather how to make it comprehensible to the trier of fact); THE EVOLVING ROLE OF STATISTICAL ASSESSMENTS AS EVIDENCE IN THE COURTS 192 (Stephen E. Fienberg ed., 1989) [hereinafter STATISTICAL EVIDENCE] (explaining that the two most visible schools of statistical inference are the Bayesian or "subjective" approach, and the frequentist or "objective" approach, the key difference between them being how they deal with the interpretation of probability and the inferential process). The Bayesian subjectivist approach appears to be in the ascendancy. *See* David Leonhardt, *Subconsciously, Athletes May Play Like Statisticians*, N.Y. TIMES, Jan. 20, 2004, at F1 (" 'In academia, the Bayesian revolution is on the verge of becoming the majority viewpoint, which would have been unthinkable ten years ago,' said Bradley P. Carlin, a professor of public health at the University of Minnesota and a Bayesian specialist.").

19. Jonathan J. Koehler & Daniel N. Shaviro, *Veridical Verdicts: Increasing Verdict Accuracy Through the Use of Overtly Probabilistic Evidence and Methods*, 75 CORNELL L. REV. 247, 252 & n.18 (1990) (citing Laurence Tribe, *Trial by Mathematics: Precision and Ritual in the Legal Process*, 84 HARV. L. REV. 1329, 1330 n.2 (1971)). The logical positivist Alfred Ayer said that "there are no absolutely certain empirical propositions. It is only tautologies that are certain. Empirical propositions are one and all hypotheses . . . ." ALFRED J. AYER, LANGUAGE, TRUTH AND LOGIC 93–94 (1952).

20. *See* Kinsey v. State, 65 P.2d 1141, 1150 (Ariz. 1937) ("[A]ll attacks [on the truthfulness of evidence] must be reduced to one of three classes: (a) Upon the honesty and integrity of the witness; (b) upon his ability to observe accurately at the time the incident occurred; and (c) upon his accuracy of recollection of the past events.").

study is ever infallible. So the question always lurks in the background: How likely is it that this was the time the test or observation failed? The answer to that question, stated in terms of probability, lies in the statistician's way of quantifying reliability."[21]

Two basic measures of a test's or an observation's inherent reliability are "sensitivity" and "specificity."[22] To understand these terms it is helpful to keep in mind the following 2×2 grid, which illustrates the possible results of a test for the presence of a disease when applied to people known to be either diseased or disease-free.

	DISEASED	DISEASE-FREE
Positive Test Result	A True Positives	C False Positives
Negative Test Result	B False Negatives	D True Negatives

"True Positives" (A) are those persons who have the disease, and who test positive for the disease. "False Negatives" (B) are those who have the disease, but who test negative for the disease. "False Positives" (C) are those persons who are disease-free, but who test positive for the disease. Finally, "True Negatives" (D) are those persons who are disease-free, and who test negative for the disease.

Sensitivity is a measure of how well a diagnostic test detects the disease among those who are known to have the disease. It is the probability that a diseased person will have a positive test result.[23] Sensitivity is the "true positive rate" (TPR) of the diagnostic test.[24] It is equal to the number of "true positives" (that is, those with the disease who test positive) divided by the total number tested who have the disease (that is, "true positives" plus "false negatives"). In terms of the 2×2 grid shown above:

$$\text{Sensitivity} = \text{TPR} = A / (A + B).$$

Conversely, specificity is a measure of how well the test indicates that a person is free of the disease. It is defined as the probability that a disease-free individual will have a negative test result.[25]

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21. KENNETH R. FOSTER & PETER W. HUBER, JUDGING SCIENCE: SCIENTIFIC KNOWLEDGE AND THE FEDERAL COURTS 113 (1997).

22. *Id.* (citing S.H. GEHLBACH, INTERPRETING THE MEDICAL LITERATURE (1993)).

23. REBECCA G. KNAPP & M. CLINTON MILLER, CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS 36 (1992).

24. *Id.*

25. *Id.*

Specificity is the "true negative rate" (TNR) of the diagnostic test.[26] Specificity is equal to the number of "true negatives" (that is, those free of the disease who test negative) divided by the total number tested who are disease-free (that is, "true negatives" plus "false positives"). Again, in terms of the 2×2 grid shown above:

$$\text{Specificity} = \text{TNR} = D / (D + C).$$

Given the intrinsic sensitivity and specificity of the subject test, what is the overall reliability of the results when the test is applied to a population? That is, given a positive result, what is the probability that a person has the disease? Alternatively, if the result of the test is negative, what is the probability that the tested person is disease-free?[27] Intuitively, one might think that the reliability of a test result depends only on the sensitivity and specificity of the test. If, for example, a test has a sensitivity of 98%, one may think that it is 98% probable that a person with a positive test result has the disease. Similarly, if the test has a specificity of 97%, one may conclude that a person who tests negative is 97% likely to be disease-free. This intuition is simple and straightforward, but wrong!

Consider an uncommon disease with a prevalence of 100 cases out of 100,000 people; that is, in a sample of 100,000 people, 100 people are diseased and 99,900 people are disease-free. In such a population, what is the result of giving 100,000 people a test with "98% sensitivity" and "97% specificity"? Applying the proper analysis described below, the prediction is that the test will identify 98 true positives, 2 false negatives, 96,903 true negatives, and 2,997 false positives. Hence, out of the 3,095 people with a positive test result, a mere 1 in 30 (98/3,095) is in fact diseased! If treatment of the disease is expensive or has serious side effects, a medical specialist would be ill-advised to treat the 3,095 "positives" based solely

26. *Id.*

27. A number of sources contain discussions of sensitivity and specificity in the context of medical testing. *See* A.C. Equi et al., *Use of Cough Swabs in a Cystic Fibrosis Clinic*, 85 ARCHIVES OF DISEASES IN CHILDHOOD 438, 438–39 (2001) (demonstrating that cough swabs taken from cystic fibrosis children have good sensitivity for detecting infection, but poor specificity); S.H. Hussaini et al., *The Predictive Value of Transabdominal Ultrasonography in the Diagnosis of Biliary Tract Complications After Orthotopic Liver Transplantation*, 45 GUT 900 (1999) (finding transabdominal ultrasonography had 77% sensitivity and 67% specificity for detecting biliary tract complications after liver transplantation); Michael Urban et al., *Efficacy of Diagnosis of Mechanical Cholestasis by Magnetic Resonance Cholangiography*, 26 WORLD J. SURGERY 353, 353 (2002) (finding magnetic resonance cholangiography has a sensitivity of 93% and a specificity of 74% for detecting common bile duct stones).

on this test result, despite the excellent sensitivity and specificity of the test.

For comparison, consider a test with the same 98% sensitivity and 97% specificity used to test for a common disease affecting one out of two people (that is, 50,000 out of 100,000 people). Testing a sample of 100,000 people from this population would identify 49,000 true positives, 1,000 false negatives, 48,500 true negatives, and 1,500 false positives. In this case, of the 50,500 with positive test results, 97% actually have the disease, while 98% of those with a negative test result are in fact disease-free. Hence, focusing on the intrinsic sensitivity of a test while ignoring the prevalence of the disease may be a reasonable approximation of the reliability of a positive test result for very common diseases, but not for uncommon diseases.

Bayes' Law provides the method needed to calculate the overall reliability of a test result. Named for Thomas Bayes, the English theologian and mathematician who discovered the law in the mid-eighteenth century,[28] Bayes' Law holds that the reliability of a test depends not only on the intrinsic sensitivity and specificity of the test, but also the prevalence (base rate)[29] of the disease (or whatever parameter the test addresses) in the population. "Bayes' theorem tells us how to combine information about sensitivity, specificity, and base rates to arrive at an overall measure of the test, called *Predictive Value*, that accords with the lay meaning of reliability."[30] Bayes' Law, set out in encyclopedias, treatises on statistics, and in manuscripts on inductive logic,[31] is crucial for the correct determination of the reliability of causation evidence. Yet this simple formula, "truly one of the most important discoveries of the human mind,"[32] is rarely encountered in case law addressing the reliability of expert testimony.

Predictive value is the probability that a positive test result correctly indicates the presence of the disease.[33] It is the proportion of

28. *See* THOMAS BAYES, AN ESSAY TOWARD SOLVING A PROBLEM IN THE DOCTRINE OF CHANCES 5–6 (1763). This monograph is believed to be the first work to elucidate this rule.

29. "Base rates describe the frequency with which a relevant attribute occurs among members of a reference population. A base rate may also be thought of as the probability that a randomly selected member of a reference population will have the relevant attribute." Koehler & Shaviro, *supra* note 19, at 247 n.2.

30. FOSTER & HUBER, *supra* note 21, at 115.

31. PIATTELLI-PALMARINI, *supra* note 18, at 106.

32. *Id.*

33. KNAPP & MILLER, *supra* note 23, at 37. Actually, there is a "positive predictive value" (PPV) and a "negative predictive value" (NPV). The PPV is the probability that a positive test result accurately indicates the presence of the disease. *Id.* In contrast, the NPV is the probability that a negative result accurately indicates the absence of disease. *Id.* at 38. Unless otherwise indicated, this Article discusses the PPV.

truly diseased persons in the population of persons receiving a positive test result.[34] In other words, Predictive Value is equal to the number of true positives divided by the number of all persons who test positive (that is, true positives plus false positives). Once again, in terms of the 2×2 grid shown above:

$$\text{Predictive Value} = A / (A + C).$$

The predictive value is the reliability of a positive test result.

Sensitivity and specificity are, by definition, the outcomes of the test on people whose disease status is known. Hence, these test parameters are independent of the base rate, or prevalence, of the disease in the population. The sensitivity of a test is independent of the base rate because all the persons under consideration when calculating this parameter are known to have the disease. When measuring sensitivity the question is: What percentage of diseased people does the test correctly identify as diseased? It does not matter whether the base rate, or prevalence, of disease in the population is 10%, 1%, or 0.01%. Likewise, the specificity of a test does not depend on the base rate because all the persons under consideration when calculating specificity are known to be free of the disease. When measuring specificity, the question is what percentage of disease-free people does the test correctly identify as disease-free? The base rate of the disease does not affect these parameters.

The predictive value of a test, on the other hand, is dependent on the base rate of the disease. The predictive value takes into consideration all those who test positive, which includes true positives (A) who have the disease, and "false positives" (C) who are free of the disease. As the prevalence of the disease in the population decreases, the number of disease-free persons tested will increase, resulting in a greater opportunity for "false positives." Consequently, the less common the disease is in the tested population, the less reliable a positive test result will be. It follows that the reliability of a positive result (that is, the probability that a positive test result is a "true positive") is dependent on the prevalence of the disease in the test population. The relationship between predictive value and base rate is direct: as prevalence decreases, the predictive value decreases; as prevalence increases, the predictive value increases.[35]

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34. *Id.*
35. *Id.* at 40.

Richard Wilson, a professor of physics and an expert on risk assessment, provides a simple and intuitive illustration of Bayes' Law.[36] A child who says "I saw a dog running down Fifth Avenue" is very believable. If, however, the same child says "I saw a lion running down Fifth Avenue," the child in this instance is less believable. Why? Even though the child's veracity and eyesight remain the same, his report of a lion is less believable because the frequency of lions running down Fifth Avenue is much lower than the frequency of dogs running down Fifth Avenue. Given the child's report of a lion, one would seek further information (for example, was a circus in town and did its truck crash; is there an independent report of a lion escaping from the zoo?) before accepting the child's report of a lion on Fifth Avenue. While one may rely on the child's report of a dog without further inquiry, the child's report of a lion is not reliable, even though the child is equally truthful and observant in both instances. One requires application of a more sensitive and specific test (that is, further inquiry) before one is convinced that there was in fact a lion on Fifth Avenue.

Bayes' Law has real consequences. The hypothetical populations considered above illustrate the effect that the base rate of the disease has on the predictive value of a diagnostic test. Now, consider a real-life example. A published article reported the predictive value of a Human Immunodeficiency Virus (HIV) test applied to the American population.[37] As demonstrated in this study, the test for HIV is highly sensitive and highly specific, but the test applied to the general American population, in which the rate of the disease is low, produces a poor predictive value.

The screening test for HIV (the enzyme immunoassay test) has a sensitivity of 98.3% and a specificity of 99.8%.[38] What is its predictive value when used to test the presence of HIV in the general population of the United States? The answer to this question requires knowledge of the base rate of HIV in the American population, which is very low. Approximately one person in 3,000 has the virus.[39] Given this data, the authors calculated the predictive value of this highly sensitive and specific test as applied to a large population displaying this base rate of HIV infections. The expected test results shown below are for a base population of

36. Daniel M. Kammen et al., *What Is the Risk of the Impossible?*, 331A J. FRANKLIN INST. 97, 98 (1994).

37. *See* Paul D. Cleary et al., *Compulsory Premarital Screening for Human Immunodeficiency Virus*, 258 JAMA 1757, 1759–61 (1987); *see also* FOSTER & HUBER, *supra* note 21, at 116.

38. Cleary et al., *supra* note 37, at 1758.

39. FOSTER & HUBER, *supra* note 21, at 116.

3,825,368 people, in which there are 1,348 HIV-infected individuals, and 3,824,020 uninfected individuals.

	HIV-INFECTED	HIV-UNINFECTED
Positive Test Results	A True Positives 1,325 persons	C False Positives 7,648 persons
Negative Test Results	B False Negatives 23 persons	D True Negatives 3,816,372 persons

The sensitivity of the test is: A / (A + B) = 1,325 / (1,325 + 23) = 98.3%. The specificity is: D / (D + C) = 3,816,372 / (3,816,372 + 7,648) = 99.8%. Yet, despite the excellent sensitivity and specificity of this test, the predictive value is poor when applied to the American population because of the low base rate. The predictive value is: A / (A + C) = 1,325 / (1,325 + 7,648) = 14.8%. Thus, a person drawn at random from the American population who tests positive for HIV when subjected to the enzyme immunoassay test has less than a 15% probability of having the infection.[40]

As Bayes' Law dictates, a higher rate of the tested disease in the population enhances the predictive value of the HIV immunoassay test. For example, applying this test to a high-risk population of 10,000 persons with an HIV infection rate of 10% (that is, 1000 persons in the population are infected) would yield the following results:

40. The authors of this study estimated that in one year universal premarital screening in the United States would detect less than one-tenth of one percent of HIV-infected persons and would cost more than $100 million. Cleary et al., *supra* note 37, at 1757. Another real-life example of Bayes' Law's impact in the reliability of test results is provided in the Hussaini article. Hussaini et al., *supra* note 27, at 901–03. In that study, a diagnostic test called transabdominal ultrasonography had 77% sensitivity and 67% specificity for detecting biliary tract complications after liver transplantation. *Id.* Given these test parameters, the authors calculated a predictive value positive of only 26%, assuming a prevalence rate of 12.8% biliary complications in the study population. *Id.* The predictive value negative, however, was 95% in the study population, leading the authors to conclude that a normal transabdominal ultrasonography following liver transplantation makes the presence of biliary complications unlikely. *Id.* *See generally supra* note 33 (explaining "negative predictive value").

	INFECTED	UNINFECTED
Positive Test Results	A True Positives 983 persons	C False Positives 18 persons
Negative Test Results	B False Negatives 17 persons	D True Negatives 8,982 persons

The predictive value of the test in this hypothetical population is: A / (A + C) = 983 / (983 + 18) = 98.2%. Thus, increasing the background rate from 0.035%, as in the general population, to 10%, as in this hypothetical at-risk population, improves the predictive value of the test from 15% to 98%.[41]

The general form of Bayes' Law avoids the difficulty of constructing the 2×2 grids and going through the reasoning and "back calculating" as done above. The first step in deriving the general form of Bayes' Law is to put the verbal reasoning ("predictive value equals true positives divided by the sum of true plus false positives") into more precise mathematical terms.

> In words, the predictive value of a test, when applied to a population with a certain base rate of disease, equals the number of true positives revealed by the test (which is given by the base rate of the disease times the sensitivity of the test) divided by the sum of this factor (the number of true positives revealed by the test) plus the number of false positives revealed by the test (the latter factor being given by the product of the base rate of disease-free persons times [one minus the specificity of the test]).

We can express the meaning of this verbiage more compactly in symbols, using the following definitions. Let P(H) equal the numerical probability that the hypothesis, H, is correct. For example, in the hypothetical population with an HIV infection rate of 0.1 (10 percent), H is the hypothesis that an untested person has HIV, and P(H) is 0.1. In Bayesian terms, P(H) is called the "prior probability." A positive test result is evidence, E. Let P(H|E) represent the probability that the hypothesis is correct, given the evidence E. In the hypothetical population, P(H|E) represents the probability that a positive test result correctly indicates an HIV-infected per-

41. This method of calculating the predictive value of a test based on varying base rates is called "back calculating." KNAPP & MILLER, *supra* note 23, at 39–40. That is, one "back calculates" the values in the 2 x 2 grid based on published values for sensitivity and specificity of the subject test and the known prevalence of the test parameter in the population. *Id.*

son. That is, P(H|E) is the test's reliability, or predictive value, that we want to derive.

Now, let P(E|H) be the probability that E would be found if H is true. In the hypothetical population, P(E|H) is the probability that an HIV-infected person would have a positive result. In other words, P(E|H) is the sensitivity of the test. Let P(~H) designate the probability that the hypothesis is not true. For example, if the HIV-infection rate is 0.1 as in our hypothetical population, P(~H) is 0.9, the probability that an untested person is disease-free. Finally, P(E|~H) is the probability that the evidence would be found even though the hypothesis is wrong. P(E|~H) is the probability of false positives, which equals one minus the specificity of the test. Given these factors, the general form of Bayes' Law, which expresses the same relationship as the verbal description above, is:

$$P(H \mid E) = \frac{P(H) \times P(E \mid H)}{P(H) \times P(E \mid H) + P(\sim H) \times P(E \mid \sim H)}$$ [42]

Applying this formula to the hypothetical population with an HIV rate of 0.1 and subjected to the enzyme immunoassay test cited above (sensitivity 98.3%; specificity 99.8%):

$$P(H|E) = (0.1 \times 0.983) \div [(0.1 \times 0.983) + (0.9 \times 0.002)],$$

which equals 0.982, as determined by the cumbersome "back calculating" method used above.

III. BAYES' LAW AND THE COURTS

While the use of statistical evidence has burgeoned in courts,[43] the use of Bayes' Law in the judicial context is rare.[44] Yet, Bayes'

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42. To state Bayes' Law in words, see PIATTELLI-PALMARINI, *supra* note 18, at 108 ("The probability that a hypothesis (in particular, a diagnosis) is correct, given the test, is equal to: The probability of the outcome of the test (or verification), *given* the hypothesis (this is a sort of inverse calculation with respect to the end we are seeking), multiplied by the probability of the hypothesis in *an absolute sense* (that is, independent of the test or verification) and divided by the probability of the outcome of the test in an absolute sense (that is, independent of the hypothesis or diagnosis).").

43. STATISTICAL EVIDENCE, *supra* note 18, at 4.

44. *See* David H. Kaye & David A. Friedman, *Reference Guide on Statistics*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 83, 132–33 (2d ed. 2000) [hereinafter REFERENCE MANUAL] (observing that Bayesian analysis is rarely used in court,

Law applies to tests and observations of all kinds, including the testimony of witnesses in judicial proceedings. Foster & Huber provide the following hypothetical:

> Mrs. Smith witnesses an accident involving a taxi. Her eyesight has been rigorously tested; the tests establish that she can identify the color of a taxi correctly 80 percent of the time. (In other words, she says "yellow" 80 percent of the times in which the taxi really is yellow and 20 percent of the times when it is some other color.) She testifies in court: "I saw the taxi. It was yellow." How likely is it that she's right? The correct answer will almost never be "80 percent of the time."
>
> . . . Assuming that Mrs. Smith has an 80 percent chance of either correctly identifying a yellow taxi as yellow or correctly identifying a not-yellow taxi as not yellow, and that 80 percent of the taxis in the city are yellow, we find for a hypothetical group of 100 reports by Mrs. Smith the results shown [in the following grid:]

	TAXI WAS YELLOW	TAXI WAS NOT YELLOW
Mrs. Smith says yellow	64 taxis (true positives)	4 taxis (false positives)
Mrs. Smith says not yellow	16 taxis (false negatives)	16 taxis (true negatives)

> The report "it was yellow" will be correct 64 out of 68 times (94 percent). Combining good (80 percent) eyesight with a high background probability (80 percent) that a taxi is yellow pushes the probability higher . . . than one might suppose from considering eyesight alone. If every taxi in the city is yellow, Mrs. Smith's "yellow taxi" call will be right 100 percent of the time, even if Mrs. Smith is certifiably blind. But the numbers can go sour very fast. Suppose Mrs. Smith has the same 80 percent vision but she makes an "orange taxi" call. If 80 percent of the taxis in the city are in fact yellow, and 20 percent are orange, Mrs. Smith's call will be wrong exactly half

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the exception of which is paternity litigation, where genetic tests are used to determine posterior "probability of paternity").

> the time (not just 20 percent of the time, as her vision alone would suggest). If Mrs. Smith had 20 percent vision and "sees an orange taxi" in a city in which only 20 percent of the taxis are in fact orange, she will be wrong 94 percent of the time.[45]

A few courts have recognized the implications of the base-rate problem on the reliability of test data. For example, in *Gonzalez v. Metropolitan Transportation Authority*, a radio dispatcher and an instructor for a municipal bus service challenged the constitutionality of random urine tests for drugs and alcohol conducted pursuant to the Omnibus Transportation Employee Testing Act, 49 U.S.C. § 5331.[46] The plaintiffs claimed that the tests amounted to an unreasonable search in violation of the Fourth Amendment to the United States Constitution.[47] The district court granted the defendant transportation authority's motion to dismiss, but the appellate court reversed and remanded.[48] The appellate court found that the record on appeal lacked facts needed to determine whether the search in this case was reasonable.[49] Among other criteria, Fourth Amendment analysis requires a showing that the proposed invasive test effectively accomplishes the governmental objective.[50] In this regard, the appellate court discussed the base-rate problem inherent in random drug testing:

> A more complete record can also illuminate another aspect of efficacy, the Bayes' theorem problem that affects any random test given to a low incidence population. . . . Suppose the combination of errors in the tests . . . cause an error rate such that one person out of 500 gets a report of "dirty" urine when it was actually "clean." Suppose that there is a high rate of alcohol drug use among the employees . . . and on any particular day one worker in 10 has alcohol or drugs in his blood. Then with a 1/500 false positive rate, out of 1,000 tests, two will be positive even though the employee's urine was clean, and 100 will be positive correctly. Only one of the positives out of every 51 is false. Fifty out of 51 are accurate. That is a fairly effective test, in terms of reliability.

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45. FOSTER & HUBER, *supra* note 21, at 116–17 (citation omitted) (adapting the taxicab hypothetical from a hypothetical by Amos Tversky and Daniel Kahneman).

46. 174 F.3d 1016, 1018 (9th Cir. 1999).

47. *Id.*

48. *Id.* at 1024.

49. *Id.* at 1021.

50. *Id.* at 1022.

> But if the workers are generally "clean," the reliability of the test goes way down. Suppose on a particular day only one worker in 500 has ingested drugs or alcohol. Then with a 1/500 false positive rate, out of 1,000 tests, 2 will be correct positives and 2 will be false positives. Half the employees who get a "dirty" urinalysis are unjustly categorized. A positive result is as likely to be false as true on so clean a population, even though the test is identical to the one that was quite effective for a population with a higher incidence of drug and alcohol usage.[51]

Bayesian analysis provides "[t]he most prominent general account of scientific reasoning . . . ."[52] Nevertheless, Bayesian analysis has rarely made it to the courtroom, no doubt due in part to the fact that "people do not naturally engage in Bayesian calculations . . . ."[53] It is time for courts to recognize Bayes' Law and require expert witnesses to apply this prominent scientific reasoning to causation testimony in toxic tort cases.

IV. BAYES' LAW AND EVIDENCE OF CAUSATION IN TOXIC TORT CASES

"Statisticians understand this 'base-rate' problem very well. After *Daubert*,[54] judges must grasp it too. This is absolutely fundamental to the evaluation of the reliability of a claim based on an observation or a test of any kind."[55] This Article now turns to the implications of Bayes' Law in the context of a toxic tort claim.

In a toxic tort case, it is the plaintiff's burden to prove that the exposure more likely than not caused the injury.[56] In most toxic exposure cases, medical testimony is required to establish the link

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51. *Id.* at 1023. Note that the court assumes in both scenarios—the "dirty" population scenario and the "clean" population scenario—that the sensitivity of the drug test is 100%, that is, that there are no "false negatives."

52. PHILIP KITCHER, THE ADVANCEMENT OF SCIENCE: SCIENCE WITHOUT LEGEND, OBJECTIVITY WITHOUT ILLUSIONS 291 (1993).

53. *Id.* at 292. Justice Oliver Wendell Holmes, Jr., admonished that in law "the man of the future is the man of statistics and the master of economics." Oliver W. Holmes, *The Path of the Law*, 10 HARV. L. REV. 457, 469 (1897).

54. *See infra* Part VIII.A (discussing a court's gatekeeping duty to exclude unreliable scientific and technical opinions following the *Daubert* decision and its federal court and state court progeny).

55. FOSTER & HUBER, *supra* note 21, at 121.

56. *See* cases cited *supra* note 3.

between the exposure and the injury.[57] To meet the plaintiff's burden of proof, the medical expert must be able to offer reliable and relevant testimony that the exposure more likely than not caused the plaintiff's injury.

Most diseases, however, also occur in the general population among those who were not exposed to a particular toxic agent. With few exceptions, the mere fact that the disease follows the exposure does not prove that the exposure caused the disease.[58] Most diseases have numerous risk factors with a range of probabilities from "established" to "possible" to "suspected," while other diseases are "idiopathic," that is, causes unknown. The plaintiff's causation expert must be able to demonstrate that the exposure more likely than not caused the disease using a process of causation analysis whereby the expert considers and eliminates the other potential causes of the disease.[59]

Bayes' Law, though abstract, is crucial in the context of disease causation analysis. Just as Bayes' Law dictates the predictive value of a diagnostic test, it likewise dictates the predictive value, or reliability, of disease causation analyses. The reliability of such causation opinions is undeterminable without knowing the base rate of the disease in the relevant population, and without knowing how to apply Bayes' Law. Yet courts have continually failed to consider the impact that Bayes' Law has on the reliability of causation opinions.

To illustrate, suppose a causation expert offers an opinion that an individual contracted disease "P" as a consequence of her exposure to substance "Q." What is the reliability of this opinion? In part, the reliability of this causation opinion depends on the base rate of Q-induced disease among those with disease P. In other words, the issue is to what extent is exposure to agent Q responsible for disease P in the population? In this context, we modify the labels of the familiar 2×2 grid to read:

57. *See* cases cited *supra* note 7.

58. *See infra* notes 315–318 and accompanying text (discussing "signature diseases" believed to be usually or always caused by a given toxic agent).

59. One should not confuse medical causation analysis with the related process of differential diagnosis. *See infra* Part VIII.D.3.a.

	DISEASE P INDUCED BY AGENT Q	DISEASE P NOT INDUCED BY AGENT Q
Causation Claimed	A True Positives	C False Positives
No Causation Claimed	B False Negatives	D True Negatives

An expert's causation analysis must have sufficient sensitivity and specificity to render the predictive value of the analysis accurate "within a reasonable degree of medical certainty," given the rate of agent Q-induced disease among those with disease P in the population. To establish causation within a reasonable degree of medical certainty, *the causation analysis must have a predictive value greater than 50%*, indicating that the test is able to establish that it is more likely than not that the exposure to agent Q caused disease P. As discussed above, the predictive value depends not only on the sensitivity and specificity of the expert's test, but also on the rate of the non-agent-induced disease in the population. As Bayes' Law dictates, the lower the base rate of the agent-induced disease among those with the disease, the poorer the reliability (predictive value) of the medical expert's causation analysis.

The initial inquiry concerns the sensitivity and specificity of the medical expert's causation analysis. Focusing on the proffered causation opinion of the plaintiff's causation expert, we may assume that the plaintiff's expert's causation analysis has a sensitivity of 100%. In other words, there will be no "false negatives" in the plaintiff's expert's causation analysis because the expert will opine that all the plaintiffs with disease P got the disease due to exposures to agent Q. Certainly, the plaintiff's attorneys will not retain an expert who will undermine their client's case by disputing the plaintiff's causation theory. When it comes to sensitivity, one may assume that plaintiffs' retained experts are perfect: they will identify all diseases caused by the subject agent. The crucial issue thus becomes the *specificity* of the plaintiff's expert's causation analysis. It is the plaintiff's expert's ability to identify "true negatives" and minimize "false positives" that will determine whether the causation analysis is reliable. Ultimately, the question to ask is the following: What specificity must the plaintiff's expert's causation analysis achieve to obtain the requisite predictive value of greater than 50%?

To arrive at a formula for determining the requisite specificity, consider again the now familiar grid:

	FRACTION OF DISEASE P INDUCED BY AGENT Q	FRACTION OF DISEASE P NOT INDUCED BY AGENT Q
Causation Claimed	A True Positives	C False Positives
No Causation Claimed	B False Negatives	D True Negatives

Remember that the formula for sensitivity is A / (A + B). Assuming that the expert's causation analysis has a sensitivity of 100%, there are no "false negatives," which means that B = 0.

It may be preferable to express A, B, C and D as "rates" rather than numbers of people. If B equals 0, then A, the group of "true positives," is equal to the fraction of disease P induced by agent Q. For example, if agent Q causes one case in a thousand cases of disease P in the population, then A = 0.001 and B = 0, assuming the expert's sensitivity equals 100%.

Next, consider the formula for predictive value A / (A + C). The expert's specific causation analysis needs a predictive value of greater than 50% for legally sufficient proof of causation. Setting the predictive value greater than 0.5, which is the minimum required, means that A / (A + C) > 0.5. Solving for A:

$$A > 0.5\ (A + C)$$
$$0.5A > 0.5C$$
$$A > C.$$

To achieve a predictive value of greater than 0.5, the "true positive rate" (A) must exceed the "false positive rate" (C), assuming a sensitivity of 100% (that is, B = 0). For a predictive value equal to 0.5, A must equal C.

Finally, consider the formula for specificity: D / (D + C). As discussed in the preceding paragraph, if one assumes 100% sensitivity and a predictive value equal to 0.5, then A = C. Since A + B + C + D = 1, and in this hypothetical B = 0, then D = 1 – (A + C), which equals 1 – 2A. The specificity formula, D / (D + C), becomes

$(1 - 2A) / (1 - 2A + A) = (1 - 2A) / (1 - A)$. Since A equals the proportion of disease P in the population caused by agent Q background rate, we will set A equal to "x." The formula for the required specificity to achieve a predictive value of 0.5 is therefore:

$$\text{Required Specificity} = (1 - 2x) / (1 - x).$$

As seen by this formula, the specificity required to exceed 50% predictive value will depend on the value of "x," the fraction of cases of disease P known to be caused by agent Q. The lower the fraction of the agent-induced disease among those with the disease (that is, as x becomes smaller), the greater the specificity of the expert's causation analysis must be to achieve the requisite predictive value. The following table displays the specificity required to equal 50% predictive value for rates of disease caused by the agent in the reference population up to 0.5, assuming 100% sensitivity of the expert's specific causation analysis. The table illustrates that, as x becomes smaller, the expression "$(1 - 2x) / (1 - x)$" approaches "$(1 - x)$." Note that in the limiting case of $x = 0$, which indicates that agent Q does not cause any cases of disease P, the required specificity becomes 1.0 (that is, the expert's specificity must be 100%), forcing the expert to conclude that agent Q did not cause disease P in the subject individual.

FRACTION OF DISEASE P CASES KNOWN TO BE CAUSED BY AGENT Q (x)	SPECIFICITY REQUIRED FOR PREDICTIVE VALUE OF 0.5 $(1-2x)/(1-x)$
0.001	0.999
0.01	0.99
0.05	0.95
0.1	0.89
0.15	0.82
0.2	0.75
0.25	0.67
0.3	0.57
0.35	0.46
0.4	0.33
0.45	0.18
0.5	0

As seen in this table, if agent Q at the estimated dose causes 1 percent of disease P cases, then the plaintiff's causation expert must use methods able to identify more than 99% of disease P cases whose diseases were not caused by the exposure to agent Q to

achieve a predictive value exceeding 50%. In comparison, if agent Q causes 10% of disease P cases, the expert's specificity must exceed 0.89. That is, the applied causation analysis must identify more than 89% of such persons whose diseases were not caused by the agent at the estimated dose to achieve a mere 50% predictive value. Further increasing the percentage of agent Q-induced disease to 50% of persons with disease P who were similarly exposed, then the mere presence of the disease in any random individual is more likely than not due to exposure to agent Q (absent evidence to the contrary). Consider the following finding:

> Tests that purport to identify things that are common to begin with are likely to yield correct results—whatever their inherent quality, they are reliable because external circumstances make them so. Thus, if a test shows that an individual suffered from chickenpox during childhood, she probably did; we don't have to know anything at all about the test to assert that it is quite "reliable." In a case like this, it hardly matters how good your "scientific eyesight" happens to be. If you consult a psychic or a soothsayer you will do nearly as well.[60]

The same statistics apply to defendants' medical causation testimony, but in reverse. While the plaintiff's medical experts' tests will have 100% sensitivity (that is, no "false negatives"), the defendant's causation experts will achieve 100% specificity (that is, no "false positives"). Certainly, defense attorneys will not retain experts who will confirm the plaintiff's causation theory where arguably no causation exists. If the base rate of agent Q-induced disease P is 1% among persons similarly dosed with agent Q, then the fraction of disease P cases not caused by agent Q among such persons is 99%. In such a case, the defense expert's opinion that the plaintiff's injury was not caused by the agent at issue are highly reliable, amounting almost to certainty, no matter how crude the tests they apply. To borrow a phrase, a psychic or soothsayer will do nearly as

60. FOSTER & HUBER, *supra* note 21, at 117–19. As an illustration, suppose that a blindfolded person is asked to guess whether a flipped coin shows heads or tails. Though the response is a pure guess, it is nevertheless "reliable" as long as 0.5 or greater probability of a correct answer is considered reliable. On the other hand, the same blindfolded person's guess as to what side of a six-sided die is showing is unreliable (that is, less likely than not to be accurate), not because her guessing is worse, but because of the extrinsic circumstance that the odds of any given side of the die showing is only one out of six.

well.[61] In contrast, if the fraction of agent Q-induced disease exceeds 50% among persons with disease P who were similarly exposed, then the burden should shift to the defendant's experts to conduct causation analyses evidencing that there are alternative, more likely causes of disease P in the plaintiff.

To apply Bayes' Law to the proffered causation opinions in a toxic tort case, it is essential to have information concerning the base rate of the agent-induced disease in the appropriate population. The science of epidemiology can be the source of that information.

V. EPIDEMIOLOGY AND THE RATE OF AGENT-INDUCED DISEASE

A. Principles of Epidemiology

What are the rates of diseases caused by various agents? The discipline of epidemiology addresses this question.[62] "Epidemiology" is a branch of science and medicine that strives to "observe the effect of exposure to a single factor upon the incidence of disease in two otherwise identical populations."[63] Epidemiology focuses on the question of general causation, (i.e., whether a substance is capable of causing a particular disease) as opposed to specific

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61. *See* Note, *supra* note 6, at 1472 n.32 ("Extremely precise tests are needed to 'prove' the presence of highly unlikely results, whereas crude tests can accurately predict substantially probable results." (citations omitted)). Adami & Trichopoulos put it this way:

> When the relative risk is higher than 1 but less than 2, the individual who has been exposed and has developed the disease is more likely than not to have developed the disease for reasons not entirely due to the exposure. For instance, if the risk of a light-smoking 55-year-old man of suffering a first heart attack in the next 5 years is 6%, and that of a same-age nonsmoking man is 4% (relative risk 1.5), only 33% of the smoker's risk (that is, one-third of the total 6%) can be attributed to his smoking. When the relative risk is higher than 2, a particular individual who has been exposed and has developed the disease under consideration is more likely to have developed the disease because of the exposure.

Adami & Trichopoulos, *supra* note 10, at 109.

62. The related discipline of "health risk assessment" also addresses disease risks associated with toxic substances. *See generally* HUMAN AND ECOLOGICAL RISK ASSESSMENT: THEORY AND PRACTICE (Dennis Paustenbach ed., 2002).

63. DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 945 (3d Cir. 1990) (quoting Bert Black & David E. Lilienfield, *Epidemiological Proof in Toxic Tort Litigation*, 52 FORDHAM L. REV. 732, 755 (1984)).

causation (i.e., whether the substance caused the disease in a specific individual).[64]

To establish that a given substance is capable of causing development of a particular disease, a scientist might in theory obtain reliable information by engaging in experimental studies with human beings. For example, to determine whether exposure to a certain level of a suspected toxin is associated with a particular disease, the scientist might compare two randomly selected groups of people. One of the groups would be exposed to certain doses of the toxin over a prescribed length of time and the other group would not. For obvious ethical reasons, however, experimental studies with human beings are proscribed where the subject chemical agent is known or thought to be toxic.[65]

Instead, epidemiologists use observational methods rather than experimental methods to study persons exposed to a suspected toxic substance.[66] Epidemiologists seek to determine whether an association exists between exposure to the chemical and the development of a disease. These epidemiological studies use "statistical methods to detect abnormally high incidences of disease in a study population and to associate these incidences with unusual exposures to suspect environmental factors."[67]

In many toxic tort cases, courts have emphasized the critical role that epidemiological evidence plays in causation issues. If general causation is at issue, it is important to have epidemiological evidence to support expert opinions that an alleged exposure caused

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64. Michael D. Green et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL, *supra* note 44, at 333, 381; *see also* Merrell Dow Pharms., Inc., v. Havner, 953 S.W.2d 706, 715 (Tex. 1997) ("[E]pidemiological studies cannot establish that a given individual contracted a disease or condition due to exposure to a particular drug or agent." (citing Michael Dore, *A Commentary on the Use of Epidemiological Evidence in Demonstrating Cause-In-Fact*, 7 HARV. ENVTL. L. REV. 429, 431–35 (1983); Gold, *supra* note 5, at 380).

65. Ethyl Corp. v. EPA, 541 F.2d 1, 26 (D.C. Cir. 1976); Green et al., *supra* note 64, at 338–39.

66. *See* Khristine L. Hall & Ellen K. Silbergeld, *Reappraising Epidemiology: A Response to Mr. Dore*, 7 HARV. ENVTL. L. REV. 441, 441 (1983) ("Because most diseases occur naturally at some background rate, studying large groups of people offers one of the few opportunities (apart from using human beings as experimental subjects) to demonstrate a relationship between exposure and disease." (citing GARY D. FRIEDMAN, PRIMER ON EPIDEMIOLOGY (2d ed. 1980))).

67. *In re* Agent Orange Prods. Liab. Litig., 611 F. Supp. 1223, 1231 (E.D.N.Y. 1985) (quoting Dore, *supra* note 64, at 431); *see also* Gen. Elec. Co. v. Joiner, 522 U.S. 136, 144 n.2 (1997) ("Epidemiological studies examine the pattern of disease in human populations."); *In re* Swine Flu Immunization Prods. Liab. Litig., 508 F. Supp. 897, 907 (D. Colo. 1981) ("Where . . . the exact organic cause of a disease cannot be scientifically isolated, epidemiologic data becomes highly persuasive."), *aff'd sub nom.* Lima v. United States, 708 F.2d 502 (10th Cir. 1983).

the plaintiffs' injuries. As stated in *Conde v. Velsicol Chemical Corp.*, a pesticide poisoning case:

> Epidemiologic studies are the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease. When an expert does not rely on the primary methodology for establishing causation, then that places a burden on the expert to explain his choice of methodologies and to explain why the evidence from those methodologies should be considered reliable in the face of generally accepted medical and scientific opinion to the contrary.[68]

In accord, the district court in *Porter v. Whitehall Laboratory, Inc.*, stated: "A long series of federal cases supports the legal principle that an expert medical opinion must have an epidemiological or scientific foundation to support a reasonable finding of fact."[69]

It is important to understand a basic consequence of epidemiology's observational nature: *epidemiology cannot prove causation.*

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68. 804 F. Supp. 972, 1025–26 (S.D. Ohio 1992) (citation omitted).

69. 791 F. Supp. 1335, 1347 (S.D. Ind. 1992); *see also* Allen v. Pa. Eng'g Corp., 102 F.3d 194, 195 (5th Cir. 1996) (holding that an expert's proffered causation opinion was unreliable because, among other reasons, there was no epidemiologic support); *In re* Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124, 1128 (2d Cir. 1995) (stating that epidemiological evidence is indispensable in toxic tort cases where direct proof of causation is lacking); Perry v. United States, 755 F.2d 888, 892–93 (11th Cir. 1985) (upholding trial court's finding that witnesses were unable to establish causation without "the crucial statistical connection" between the agent and the disease); Cloud v. Pfizer, 198 F. Supp. 2d 1118, 1133–34 (D. Ariz. 2001) ("[C]ase reports do not provide reliable scientific evidence of causation . . . [because] they are merely compilations of occurrences . . . ."); Lennon v. Norfolk & W. R.R., 123 F. Supp. 2d 1143, 1153 (N.D. Ind. 2000) ("[Medical case reports] are not reliable, because normally such reports 'record nothing more than a temporal association between an exposure and a particular occurrence,' and are therefore less reliable than epidemiological studies, because '[e]pidemiologists use their population studies to eliminate the chance associations and confounding factors, which inherently infect anecdotal reports, to determine whether a statistically significant positive association exists.'" (citation omitted)); Chambers v. Exxon Corp., 81 F. Supp. 2d 661, 665 (M.D. La. 2000) (holding that plaintiffs' causation theory lacked scientific reasoning because experts failed to produce a single positive peer-reviewed epidemiologic study); Nelson v. Am. Home Prods. Corp., 92 F. Supp. 2d 954, 969 (W.D. Mo. 2000) (excluding plaintiff's causation experts' opinions based on anecdotal case reports postulating hypothesis that drug may cause blindness because such case reports "do not demonstrate a causal link sufficient for admission to a finder of fact in court"); Wade-Greaux v. Whitehall Lab., Inc., 874 F. Supp. 1441, 1483 (D.V.I. 1994) (finding that statistically significant epidemiologic findings provide the only reasonably conclusive data concerning associations of diseases and potential causes in humans), *aff'd*, 46 F.3d 1120 (3d Cir. 1994); Cadarian v. Merrell Dow Pharms., Inc., 745 F. Supp. 409 (E.D. Mich. 1989) (finding epidemiological studies required to confirm plaintiffs' other evidence on causation). *But see* Heller v. Shaw Indus., Inc., 167 F.3d 146, 154 (3d Cir. 1999) (considering epidemiologic evidence less important so long as the "temporal relationship" between the alleged exposure and the injury is "valid and strong"); *see also infra* Part VIII.D.3.b.

Causation is a judgment issue for epidemiologists and other scientists interpreting the epidemiological data.[70] A finding of causality "requires judgment and searching analysis" informed by scientific expertise.[71]

Through epidemiological studies, scientists can assess the existence (and strength) or absence of an association between an agent and a disease. But "*an association is not equivalent to causation.*"[72] Association is a term used to describe the statistical relationship between exposure to a chemical agent and the onset of a disease that occurs more frequently than one would expect by chance.[73] Establishing an association does not necessarily mean that there is a *causal* association between the exposure and the disease.[74] Causation, by comparison, constitutes an association between two events in which one event is a necessary link in a chain of events that results in the effect.[75] Although epidemiology cannot prove causation, epidemiologists and other scientists rely on epidemiologic data in making judgments as to the probability of a causal connection.[76]

In the event an epidemiological study finds an association between exposure to a substance and a disease, scientists can analyze the study to consider whether the reported association reflects a cause-and-effect relationship or, alternatively, is a spurious finding.[77] "[R]esearchers first look for alternative explanations for the association, such as bias or confounding factors . . . ."[78] The primary types of biases are selection bias and information bias. "Selection bias occurs when the exposed group is selected in a way that makes it more or less susceptible to disease for reasons independent of exposure."[79] Of similar concern is information bias, which occurs when the participants in the study provide incorrect information about either exposure or health effects. One form of information bias is "recall bias," a phenomenon recognized by

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70. Green et al., *supra* note 64, at 374.

71. *Id.* at 375.

72. *See, e.g.*, Norfolk & W. Ry. Co. v. Ayers, 538 U.S. 135, 173 (2003) ("Correlation is not causation.") (Kennedy, J., dissenting); Green et. al., *supra* note 64, at 336.

73. Green et al., *supra* note 64, at 348, 387.

74. *Id.* at 348.

75. *Id.* at 374, 388–89.

76. *Id.* at 374; *see also* Dore, *supra* note 64, at 434 (asserting that epidemiologic studies cannot, standing alone, establish causation).

77. Green et al., *supra* note 64, at 374–75.

78. *Id.* at 374.

79. Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substance Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 NW. U. L. REV. 643, 649 (1992).

epidemiologists.[80] That is, epidemiologists know that people who have a given disease are motivated to "recall" a putative exposure to a suspect causative agent, while those free of the disease are not so motivated to recall all possible exposures.[81] Another type of information bias occurs when an interviewer whose "awareness of the identity of cases and controls . . . may influence the structure of the questions and the interviewer's manner, which in turn may influence the response."[82]

Although epidemiologists cannot control such variables as the genetic background or lifestyle choices of their human subjects, or the amount and duration of their exposure to the studied substance,[83] they have systematic methods for assessing the characteristics of the people in the study and their risk of disease to avoid bias and errors.[84] For example, to eliminate one source of information bias, whenever possible an interviewer should conduct "blind" interviews without prior knowledge of whether the interviewee is a case or a control.[85]

Further, even when a statistical association exists, and no bias is present, the association may be the result of some other confounding factor, or a so-called "confounder." A confounder is a factor that is both a risk factor for the disease and is associated with the exposure of interest.[86] As an example, assume a study finds that individuals with gray hair have a higher rate of death than those with another hair color. Instead of hair color impacting death, however, the test results might be explained by the confounding factor "advanced age." Perhaps a better example, relating more to the issue of toxic exposures, is the positive association between the use of suntan lotion and the risk of skin cancer, not because the exposure (suntan lotion) causes skin cancer, but because both skin cancer and use of suntan lotion are associated with the confounder "sunbathing" and exposure to the sun's cancer-causing ultraviolet rays. As these examples illustrate, when researchers find an association between an agent and disease, they must first determine whether

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80. Green et al., *supra* note 64, at 365 ("Research has shown that individuals with disease (cases) may more readily recall past exposures than individuals with no disease (controls); this creates a potential for bias called recall bias.")

81. *Id.*

82. DAVID E. LILIENFELD & PAUL D. STOLLEY, FOUNDATIONS OF EPIDEMIOLOGY 237 (3d ed. 1994).

83. Green et al., *supra* note 64, at 339.

84. *Id.* at 354–55.

85. LILIENFELD & STOLLEY, *supra* note 82, at 237.

86. Green et al., *supra* note 64, at 369–72, 389.

the association is causal, or the result of confounding or other weaknesses in the study design.[87]

After the researchers have analyzed the epidemiological study for selection and information biases, researchers then consider generally accepted guidelines for evaluating whether the association between exposure to a substance and a disease may be causal.[88] One generally accepted set of criteria used to evaluate epidemiologic findings is known as the Bradford Hill criteria.[89] As set forth in *Amorgianos v. National Railroad Passenger Corp.*,[90] the Bradford Hill criteria are:

1. Strength: How strong is the association between the suspected risk factor and the observed outcome?;
2. Consistency: Does the association hold in different settings and among different groups?;
3. Specificity: How close is the association between the specific exposure factor and the specific health outcome (that is, how unique is the quality or quantity of the response)?;
4. Temporality: Does the hypothesized cause precede the effect?;
5. Biological plausibility: Does the apparent association make sense biologically?;
6. Coherence: Is the association consistent with what is known of the natural history and biology of the disease?;
7. Experimental verification: Does any experimental evidence support the hypothesis of the association?;

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87. *Id.* Another interesting example of confounding is the finding that, with the exception of very heavy drinkers, the more alcohol people drink, the more money they make. Christopher Auld, *Smoking, Drinking and Income*, 40 J. HUM. RESOURCES 505 (2005). This association likely is the result of confounding rather than causal; perhaps wealthier men are able to afford more alcohol, or alcohol consumption helps some men deal with more stressful, higher-paying careers, two examples of "reverse causality."

88. *See* Smith v. Ortho Pharm. Corp., 770 F. Supp. 1561, 1575–76 (N.D. Ga. 1991) (discussing criteria epidemiologists apply when making a judgment as to whether associations are causal); *see also* Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001) (observing that a finding of an association between exposure and disease is not in itself proof of causal association, and that epidemiologists instead turn to certain criteria "to determine whether a statistical association is indeed causal"), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

89. The criteria were named after Sir Austin Bradford Hill after he discussed them in his article, *The Environment and Disease: Association or Causation?*, 58 PROC. ROYAL SOC'Y MED. 295 (1965).

90. 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

8. Biological analogy: Are there examples of similar risk factors and similar outcomes?; and
9. Dose-Response relationship: Has a dose-response relationship been established (that is, does the magnitude of the response increase as the magnitude of the dose increases)?[91]

These criteria are to be applied flexibly. As one scholar noted, "[t]here is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines."[92] For present purposes, the following is a brief exposition of these criteria in the context of toxic tort litigation.

1. Strength and Significance of the Association—The stronger the association, the stronger is the support for a causal link. "A strong association is not easily explained by potential sources of bias or confounding and hence it is more likely to be causal than is a weak association, which could more easily be the result of confounding or bias."[93]

Epidemiologists measure the strength of an association by the magnitude of its effect. That is, the higher the rate of the disease among the exposed population relative to the reference population, the stronger is the association. Epidemiologists use "relative risk" (RR) or "odds ratio" (OR) to measure the strength of the association between exposure and disease.[94] The RR is the ratio of the risk of disease among the group exposed to the chemical agent compared with the risk of disease among the unexposed group.[95] An RR of 1.0 indicates no association, while a relative risk of 2.0 indicates that the risk of developing a disease in the exposed group is two times higher than the risk of developing that disease in the unexposed group.[96] The OR is similar to the RR except that the OR

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91. These criteria can be explained in somewhat different language. *See* Green et al., *supra* note 64, at 375; Black & Lilienfeld, *Epidemiological Proof in Toxic Tort Litigation*, 52 FORDHAM L. REV. 732, 762–63 (1984). Alfred S. Evans has updated these criteria and set forth his "unified concept" of the criteria for causation. Alfred S. Evans, *Causation and Disease: The Henle-Koch Postulates Revisited*, 49 YALE J. BIOLOGY & MED. 175 (1976).

92. Green et al., *supra* note 64, at 375. The criterion of temporality, in contrast to the other criteria, is essential. That is, exposure to the agent must precede the injury, or no causal inference is possible. *See infra* Part V.A.2.

93. ISABEL DOS SANTOS SILVA, CANCER EPIDEMIOLOGY: PRINCIPLES AND METHODS 297 (1999).

94. Green et al., *supra* note 64, at 376.

95. *Id.* at 348–49.

96. Generally, epidemiologists consider an RR of 2.0 or less as indicative of a weak association. *See* Ernst L. Wynder, *Guidelines to the Epidemiology of Weak Associations*, 16 PREVENTIVE MED. 139 (1987). Dr. Marcia Angell, Editor of the New England Journal of Medicine, has stated: "As a general rule of thumb, . . . we are looking for a relative risk of three or more [before accepting a paper for publication], particularly if it is biologically

is used in case-control mortality studies. The OR expresses the likelihood of the exposure being higher in the disease cases versus the non-disease controls. An OR of 1.0 results when the exposure was equally likely among the cases (diseased) and the controls (non-diseased). The higher the RR or OR, the stronger or more powerful is the association between exposure and probability of having the disease.[97]

The RR or OR found in an epidemiology study is crucial in the legal context. The standard of proof on the issue of causation is by a preponderance of the evidence,[98] that is, that the defendant's conduct "more likely than not" caused the plaintiff's injury. In epidemiological terms, this standard of proof requires an RR or OR greater than 2.0. As explained in *Hall v. Baxter Healthcare Corp.*:

> The threshold for concluding that an agent was more likely the cause of a disease than not is relative risk greater than 2.0.

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implausible or if it's a brand-new finding." Gary Taubes, *Epidemiology Faces Its Limits*, 269 SCIENCE 164, 168 (1995) (quoting Marcia Angell, Editor-in-Chief, New England Journal of Medicine). "Robert Temple, director of drug evaluation at the Food and Drug Administration, puts it bluntly: 'My basic rule is if the relative risk isn't at least three or four, forget it.'" *Id.*; *see also* Melissa Moore Thompson, *Causal Inference in Epidemiology: Implications for Toxic Tort Litigation*, 71 N.C. L. REV. 247, 253, 289 (1992) (arguing that a strong association requires a risk ratio of 8.0 or greater, though moderate associations between 3.0 and 8.0 could suffice to show causation if coupled with other factors). For comparison, there is a strong association, and therefore a long-recognized causal association, between bladder cancer and occupational exposures to aromatic amino compounds used in dye and leather industries. *See* Gold, *supra* note 5, at 399 n.116 (citing W.C. HUEPER, OCCUPATIONAL AND ENVIRONMENTAL CANCERS OF THE URINARY SYSTEM 119, 156 (1969)). Reported RRs found in epidemiologic studies of workers exposed to these compounds have ranged from 30 to 47 in earlier studies, and 8.7 to 17 in later studies (after improved production methods reduced exposures). *Id.*

97. *See* Landrigan v. Celotex Corp., 605 A.2d 1079, 1085 (N.J. 1992) ("The relative risk of lung cancer in cigarette smokers as compared to nonsmokers is on the order of 10:1, whereas the relative risk of pancreatic cancer is about 2:1. The difference suggests that cigarette smoking is more likely to be a causal factor for lung cancer than for pancreatic cancer."). The following example provides a brief explanation as to why a larger RR or OR evinces causality:

> Prospective [cohort] studies have shown that the death rate from lung cancer among cigarette smokers is approximately 10 times the rate in non-smokers .... To account for such a high relative risk in terms of an indirect association would require that an unknown causal factor be present at least 10 times more frequently among smokers ... than among non-smokers. Such a confounding factor should be easily detectable, and if it cannot be detected or reasonably inferred, the finding of such a strong association makes a conclusion concerning causality more probable.

SILVA, *supra* note 93, at 297.

98. Hansen v. Hansen, 958 P.2d 931, 934–35 (Utah Ct. App. 1998) (citing Johns v. Shulsen, 717 P.2d 1336, 1338 (Utah 1986)).

> Recall that a relative risk of 1.0 means that that agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other background causes. Thus, a relative risk of 2.0 implies a 50% likelihood that an exposed individual's disease was caused by the agent.[99]

Scientists use the concept of a "confidence interval" as the means by which an epidemiologist can express statistical confidence in a specific finding of relative risk. For instance, if the RR in a study is found to be 2.0, the epidemiologist can use statistical methods to estimate the range of numeric values above and below 2.0 in which RR would likely fall in numerous repeat studies.[100] "The width of the confidence interval provides an indication of the precision of the point estimate or relative risk found in the study . . . ."[101] The confidence interval should be expressed with estimated 95% accuracy, that is, as a range in which the RR will fall ninety-five times out of one hundred replications of the study.[102]

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99. 947 F. Supp. 1387, 1403 (D. Or. 1996); *see also* Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1321 (9th Cir. 1995) ("For an epidemiological study to show causation under a preponderance standard, 'the relative risk of [the condition] arising from the epidemiological data . . . will, at a minimum, have to exceed "2".'" (quoting DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 958 (3d Cir. 1990))); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981, 1000 (C.D. Cal. 1996) (arguing that relative risk of less than 2.0 tends to disprove legal causation); *Hall*, 947 F. Supp. at 1403 (requiring breast implant plaintiffs to demonstrate that exposure to breast implants more than doubled the risks of their injuries, which in epidemiologic terms requires a relative risk of more than 2.0.); Marder v. G.D. Searle & Co., 630 F. Supp. 1087, 1092 (D. Md. 1986) ("[A risk ratio of two is] an important showing for plaintiffs to make because it is the equivalent of the required legal burden of proof—a showing of causation by the preponderance of the evidence."), *aff'd sub nom* Wheelahan v. G.D. Searle & Co., 814 F.2d 655 (4th Cir. 1987); Manko v. United States, 636 F. Supp. 1419, 1437 (W.D. Mo. 1986) (stating that exposure to a substance is "more likely than not" a cause of the disease when the risk ratio is greater than two), *aff'd in relevant part*, 830 F.2d 831 (8th Cir. 1987); Cook v. United States, 545 F. Supp. 306, 308 (N.D. Cal. 1982) ("[A risk ratio of two would] sustain[] . . . plaintiff's burden of proof on causation."). It is important to understand that, while epidemiologic studies demonstrating relative risks less than 2.0 may not be sufficient in some cases to reach a finding of specific causation, such studies consistently showing a small but elevated relative risk may in the aggregate be sufficient to establish general causation. *See infra* Part V.A.3. The association may be weak, but still causal. *Id.*; *see also* Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 718 (Tex. 1997) (recognizing that high relative risks do not prove causal associations, and low relative risks do not disprove causal associations). In terms of the Bradford Hill Criteria, the "strong association" criterion may be lacking if the epidemiology studies demonstrate relative risks of less than 2.0. Such relative risks consistently found among exposed subjects across many epidemiology studies, however, may satisfy the "consistency" criterion and help establish general causation if the evidence fulfills other criteria.

100. REFERENCE MANUAL, *supra* note 44, at 173.

101. *Id.*

102. Black & Lilienfeld, *supra* note 91, at 757. One should not confuse the ninety-five percent significance level with the plaintiff's burden of proof in a civil case.

Many courts require that epidemiologic studies submitted in support of a claim of injury demonstrate statistically significant results.[103]

With regard to statistical significance, it is important to note that there is an important difference between the standard practice in epidemiology as compared with the standard practice in laboratory sciences. Laboratory scientists routinely discuss non-statistical and systematic errors in great detail, and usually provide a quantitative measure of these errors in the confidence interval assigned to the results. In contrast, epidemiologists may at times discuss non-statistical errors in the text of published studies, but do not make any quantitative estimates of the size of these errors. Thus, the "confidence intervals" in epidemiology studies capture only random

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> A common error made by lawyers, judges, and academics is to equate the level of alpha[, the level of statistical significance,] with the legal burden of proof. Thus, one will often see a statement that using an alpha of .05[, equal to a 95% confidence limit,] for statistical significance imposes a burden of proof on the plaintiff far higher than the civil burden of a preponderance of the evidence[, that is, greater than 50%].
>
> This claim is incorrect, although the reasons are a bit complex and a full explanation would require more space and detail than is feasible here. Nevertheless, we sketch out a brief explanation. First, alpha does not address the likelihood that a plaintiff's disease was caused by exposure to the agent; the magnitude of the association bears on that question. Second, significance testing only bears on whether the observed magnitude of association arose as a result of random chance, not on whether the null hypothesis is true. Third, using stringent significance testing to avoid false positive error comes at a complementary cost of inducing false negative error. Fourth, using an alpha of .5 would not be equivalent to saying that the probability the association found is real is 50 percent, and the probability it is a result of random error is 50 percent. Statistical methodology does not permit assessments of those probabilities.

Green et al., *supra* note 64, at 358 n.67 (citations omitted)

103. *See, e.g.*, Oran v. Stafford, 226 F.3d 275, 284 (3d Cir. 2000) (stating that drug companies need not disclose isolated reports of illnesses suffered by users of its drugs until reports provide statistically significant evidence of causal association); Boughton v. Cotter Corp., 65 F.3d 823, 834–35, 835 n.20 (10th Cir. 1995) (affirming trial court's holding that plaintiffs' fear of contracting cancer was not supported by evidence where epidemiology study results did not reach statistical significance); DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941 (3d Cir. 1990) (considering the fact that the scientific community declined to give weight to statistically non-significant studies); Brock v. Merrell Dow Pharms., Inc., 874 F.2d 307, 312–13 (5th Cir. 1989) (rejecting plaintiffs' claims due to the lack of statistical significance in available epidemiology studies); Hollander v. Sandoz Pharms. Corp., 95 F. Supp. 2d 1230, 1236 (W.D. Okla. 2000) (recognizing that plaintiffs' experts did not rely on epidemiology studies showing statistically significant results); Joiner v. Gen. Elec. Co., 864 F. Supp. 1310 (N.D. Ga. 1994) (holding that study results were not statistically significant and, therefore, could not support plaintiff's position that a chemical "more likely than not" promoted his cancer), *rev'd on other grounds*, 78 F.3d 524 (11th Cir. 1996), *rev'd on other grounds*, 522 U.S. 136 (1997).

errors due to the number of study subjects. The true confidence interval, capturing all possible sources of systematic and random errors, is much larger.[104]

A statistically significant association, even at the 95% confidence level, does not prove that there is a true, causal association. The association may be false, due to confounders or bias in the study.[105] Even if the association is true, it may not be causal. For example, just because gray hair is associated with death rate does not mean that gray hair causes death.[106] Statistical significance tests the likelihood that an RR above or below 1.0 likely represents an association (ignoring bias, confounders, and other types of errors) or random error.[107] Even an RR that is statistically significant at the conventional 95% confidence level does not prove a "true" association, let alone causation. For example, an RR that is statistically significant at the 95% confidence level will occur, due to chance alone, one time out of every 20 statistical tests. A causation determination begins with statistically significant findings and continues with application of the remaining Bradford Hill criteria.

2. Temporal Relationship—Unlike the other Hill criteria, temporality is a prerequisite for a finding of causation. That is, unless the exposure precedes the injury, there can be no causal link between the exposure and the injury.[108] On the other hand, the mere fact that the injury follows the exposure is insufficient to establish a causal link.[109]

3. Consistency with Other Research—The validity of scientific conclusions is often based upon the replication of research findings. Likewise, consistency among epidemiologic studies is an important factor in making a judgment about causation. As one scholar notes:

> The need to replicate research findings permeates most fields of science. In epidemiology, research findings often are replicated in different populations. Consistency in these findings is an important factor in making a judgment about causation.

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104. *See generally* Alexander I. Shlyakhter, *An Improved Framework for Uncertainty Analysis: Accounting for Unsuspected Errors*, 14 RISK ANALYSIS 441 (1994) (quantifying overconfidence in reliability of uncertainty estimates, and suggesting that estimated uncertainties be inflated by default safety factors to account for unsuspected uncertainties).

105. Green et al., *supra* note 64, at 354–55.

106. *Id.* at 369.

107. *Id.* at 355–59.

108. *Id.* at 376 (citing Carroll v. Litton Sys., Inc., No. B-C-88-253, 1990 U.S. Dist. LEXIS 16833, at *29 (W.D.N.C. Oct. 29, 1990)); *see also* SILVA, *supra* note 93, at 296 ("For an exposure to be the cause of a disease, it has to precede its biological onset.").

109. *See infra* note 399 and accompanying text (discussing the *post hoc, ergo propter hoc* fallacy).

> Different studies that examine the same exposure-disease relationship generally should yield similar results. While inconsistent results do not rule out a causal nexus, any inconsistencies signal a need to explore whether different results can be reconciled with causality.[110]

"Repeated demonstration of an association of similar direction and magnitude in several studies, undertaken by different investigators in different population groups, increases confidence in a genuine causal basis . . . ."[111] Conversely, "[c]ausality can never be inferred on the basis of one or even a handful of epidemiologic studies . . . ."[112] Many courts require consistency among epidemiology studies before opinions concerning causation based on these studies can reach the jury.[113]

4. Biological Plausibility—Does the theory that the agent can cause the injury make biological sense? Biological plausibility of a hypothetical causal relationship strengthens the inference that a causal association exists. A known or generally accepted mechanism by which the agent, at the doses in question, may cause the injury is one factor favoring a causal link.[114] Biological plausibility may be based on the "analogy" argument that the agent at issue causes a similar disease, or that a similar chemical causes the same disease.[115] Such a plausibility argument, however, is not adequate to

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110. Green et al., *supra* note 64, at 377–78 (citation omitted); *see also* SILVA, *supra* note 93, at 296 ("If similar results have been found in different populations using different study designs, the association is more likely to be causal, since it is unlikely that all studies were subject to the same type of bias and/or confounding.").

111. Adami & Trichopoulos, *supra* note 10, at 105.

112. *Id.* at 107.

113. *Compare* Cadarian v. Merrell Dow Pharms., Inc., 745 F. Supp. 409, 412 (E.D. Mich. 1989) (holding a single Bendectin study insufficient to support an expert's opinion because the study's authors concluded that the results could not be interpreted without independent confirmatory evidence), *with* Kehm v. Proctor & Gamble Co., 580 F. Supp. 890, 901 (N.D. Iowa 1982) (noting the persuasive power of multiple independent studies, each of which reached the same finding of an association between toxic shock syndrome and tampon use), *aff'd*, 724 F.2d 613 (8th Cir. 1983).

114. *See, e.g.*, Hollander v. Sandoz Pharms. Corp., 95 F. Supp. 2d 1230, 1236 (W.D. Okla. 2000) (excluding expert's theory that drug caused plaintiff's stroke in part because expert's theory of mechanism by which drug caused injury "was still only a hypothesis, as opposed to scientific knowledge").

115. *See, e.g.*, Ruff v. Ensign-Bickford Indus., 168 F. Supp. 2d 1271, 1281 (D. Utah 2001) (finding admissible plaintiffs' causation expert's theory that 1,1-dimethylhydrazine and 1,2-dimethylhydrazine are capable of causing non-Hodgkin's lymphoma in humans based in part on a mouse study showing that a related compound, benzoylhydrazine, produced a significant increase in lymphomas). For another type of analogy argument, see Maher v. Quest Diagnostics, 847 A.2d 978 (Conn. 2004) (rejecting the lower court's opinion that the

establish admissibility of causation testimony.[116] Likewise, while animal studies may provide evidence for the biological plausibility that an agent can cause a disease in humans, animal studies alone are generally insufficient evidence of causation in toxic tort cases.[117]

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doubling time for the growth of breast cancer is a reliable indicator of the doubling time for the growth of cervical cancer).

116. Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 603–09 (D.N.J. 2002) (holding medical expert's opinions inadmissible because he failed to explain why he accorded weight to studies involving chemicals other than the chemical at issue, and studies involving types of cancer other than plaintiff's type); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981, 1004 (C.D. Cal. 1996) (stating that "plausibility" does not equal "reliability," and the fact that aldehydes are skin irritants does not show that they can cause respiratory diseases). *But see* Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314, 328 (Ill. 2002) (affirming admission of plaintiffs' experts' causation opinion based on a method of "extrapolation" by which plaintiffs' causation experts concluded that subject agent likely caused plaintiffs' rare form of cancer, even though science had not established a link between the agent and plaintiffs' cancer type, stating that "extrapolation offers those with a rare disease the opportunity to seek a remedy for the wrong they have suffered").

117. *See, e.g.*, Allison v. McGhan Med. Corp., 184 F.3d 1300, 1314 (11th Cir. 1999) (finding inadequate the results of animal studies linking plaintiff's disease with breast implants where more than twenty epidemiological studies failed to find a link); Conde v. Velsicol Chem. Corp., 24 F.3d 809, 814 (6th Cir. 1994) (finding animal studies inadequate for showing causation of diseases in humans); Turpin v. Merrell Dow Pharms., Inc., 959 F.2d 1349, 1358–61 (6th Cir. 1992) (holding animal studies insufficient to allow a jury to find that a drug caused birth defects); Brock v. Merrell Dow Pharms., Inc., 874 F.2d 307, 313 (5th Cir. 1989) (questioning the applicability of animal studies to humans); Int'l Union v. Pendergrass, 878 F.2d 389, 394 (D.C. Cir. 1989) ("Humans are not rats, and it is far from clear how readily one may generalize from one mammalian species to another."); Gulf S. Insulation v. U.S. Consumer Prod. Safety Comm'n, 701 F.2d 1137, 1147 n.19 (5th Cir. 1983) (questioning whether an effective dose in rats is the same in humans).

"[B]oth quantitative and qualitative differences in response to toxic substances may occur among different species." David L. Eaton & Curtis D. Klaassen, *Principles of Toxicology, in* CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS 11, 25 (Curtis D. Klaassen ed., 6th ed. 2001). "For example, the LD50 [,which is the statistically derived single dose of a substance that can be expected to cause death in fifty percent of the animals tested,] for the highly toxic dioxin (TCDD) 2,3,7,8-tetrachlorodibenzo-*p*-dioxin differs by more than 1000-fold between guinea pigs and hamsters." *Id.* "Identifying the mechanistic basis for species differences in response to chemicals is an important part of toxicology because only through a thorough understanding of these differences can the relevance of animal data to human response be verified." *Id.*

Another example demonstrating the uncertainty of extrapolating from animal experimentation to humans concerns the artificial sweetener saccharin. While saccharin is a weak bladder carcinogen in male rats, it is not shown to cause bladder cancers in female rats or in any other species. Samuel H. Cohen & Leon B. Ellwein, *Risk Assessment Based on High-Dose Animal Exposure Experiments*, 5 CHEMICAL RES. TOXICOLOGY 742 (1992); G.P. Schoenig et al., *Evaluation of the Dose-Response and in Utero Exposure to Saccharin in the Rat*, 23 FOOD & CHEMICAL TOXICOLOGY 475 (1985); S. Takayama et al., *Long-term Feeding of Sodium Saccharin to Nonhuman Primates: Implications for Urinary Tract Cancer*, 90 J. NAT'L CANCER INST. 19 (1998); John Whysner & Gary M. Williams, *Saccharin Mechanistic Data and Risk Assessment: Urine Composition, Enhanced Cell Proliferation, and Tumor Promotion*, 71 PHARMACOLOGY & THERAPEUTICS 225 (1996). Scientists have concluded that the bladder tumors seen in male rats are due to two proteins in the urine of male rats not found in humans or other species—these proteins react with high levels of saccharin to produce crystals that damage the bladders of male rats. Samuel H. Cohen et al., *A Proposed Role for Silicates and Protein in the Proliferative Effects of*

Animal experimentation can play a supporting role in the proof of a causal link, but the party offering animal studies as causation evidence must show that the animal data are relevant and that extrapolation from animal data to human experience is reasonable.[118]

5. Alternative Explanations—One must always evaluate whether factors other than the agent at issue are responsible for the finding of an association, including study errors, biases, confounders and random chance.[119] Consideration of alternative explanations applies not only to the issue of general causation, but also to the issue of specific causation. Failure to weigh alternative explanations for a plaintiff's injury is proper grounds for excluding proffered specific causation testimony.[120]

6. Specificity—It makes little sense to lump different diseases into a single category for causation analysis. "Specificity" requires that the specific disease ostensibly associated with a particular agent must be a distinct disease entity for causation analysis purposes. For example, in *Allen v. Pennsylvania Engineering Corp.*, the decedent's widow blamed her husband's brain cancer on his occupational exposures to ethylene oxide (EtO), a known carcinogen.[121] Pursuant to the FRE Rules 702 and 703, and *Daubert*, the trial court barred the plaintiff's causation expert's opinion testimony linking

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Saccharin on the Male Rat Urothelium, 12 CARCINOGENESIS 1551 (1991); Michael J. Olson et al., *A Comparison of Male Rat and Human Urinary Proteins: Implications for Human Resistance to Hyaline Droplet Nephropathy*, 102 TOXICOLOGY & APPLIED PHARMACOLOGY 524 (1990); Joanne Zurlo & Robert A. Squire, *Is Saccharin Safe? Animal Testing Revisited*, 90 J. NAT'L CANCER INST. 2 (1998). Given this mechanistic theory and the inability of saccharin to produce bladder cancers in female rats and other species, the male rat studies would be an unreliable foundation for an opinion that saccharin consumption caused a claimant's bladder cancer.

118. *See, e.g., In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 743 (3d Cir. 1994) ("[I]n order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans, just as the methodology of the studies must constitute good grounds to reach conclusions about the animals themselves."); *Hollander*, 95 F. Supp. 2d at 1238–39 ("Although animal studies can contribute to an expert's scientific conclusions as to causation, the court finds that the animal studies on which the plaintiffs' experts rely are too dissimilar to the facts presented in this litigation to be reliable."); Marder v. G.D. Searle & Co., 630 F. Supp. 1087, 1094 (D. Md. 1986) ("There is a range of scientific methods for investigating questions of causation—for example, toxicology and animal studies, clinical research, and epidemiology—which all have distinct advantages and disadvantages."), *aff'd sub nom.* Wheelahan v. G.D. Searle & Co., 814 F.2d 655 (4th Cir. 1987).

119. Green et al., *supra* note 64, at 354, 374.

120. See *infra* Part VIII.D.3.f (discussing the importance of alternative causation and Bayesian analysis in the context of a *Daubert* challenge to proffered expert specific causation testimony).

121. 102 F.3d 194, 195 (5th Cir. 1996).

the exposure to the disease.[122] The appellate court affirmed because, among other reasons, there was no evidence that EtO causes brain cancer.[123] "Evidence has been found that suggests a connection between EtO exposure and human lymphatic and hematopoietic cancers, but this is not probative on the causation of brain cancer."[124]

The benzene-leukemia link provides an important example of the need for specificity in causation analysis. It is now evident that the disease known as "leukemia" is in fact several distinct malignancies.[125] To say "benzene causes leukemia" is not much more meaningful than to say "benzene causes cancer." In fact, there is evidence that benzene exposures increase the risk of one type of leukemia (acute myeloid leukemia [AML]) but not other cell specific types of leukemia.[126] Most courts recognize that the different

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122. *Id.*

123. *Id.* at 197.

124. *Id.*; *see also* Burleson v. Glass, 268 F. Supp. 2d 699, 707 (W.D. Tex. 2003) (granting defendant's motion to exclude expert's causation testimony in part because the relied-on epidemiological literature found an association between the subject exposure and liver, spleen, and bone cancers, but not the type of cancers—lung and throat—from which plaintiff suffered); Wills v. Amerada Hess Corp., 379 F.3d 32 (S.D.N.Y. 2002) (excluding expert's opinion that decedent's occupational exposures caused his squamous cell carcinoma because none of the published studies on which the expert relied linked the alleged exposures with decedent's type of cancer); Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1352 (N.D. Ga. 2001) ("There is no 'fit' where there is 'simply too great [an] analytical gap between the data and the opinion offered,' as when an expert offers animal studies showing one type of cancer in laboratory mice to support causation of another type of cancer in humans." (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997))). *But see* Roberti v. Andy's Termite & Pest Control, Inc., 6 Cal. Rptr. 3d 827, 828 & n.2 (Cal. Ct. App. 2003) ("For purposes of this opinion, we conclude it makes no difference whether plaintiff suffers from autism as opposed to brain damage, etc. Our conclusion would be the same regardless of the precise label applied to his condition.").

125. Martha S. Linet & Raymond A. Cartwright, *The Leukemias*, *in* CANCER EPIDEMIOLOGY AND PREVENTION 841, 841 (David Schottenfeld & Joseph F. Fraumeni, Jr. eds., 2d ed. 1996); John N. Lukens, *Classification and Differentiation of the Acute Leukemias*, *in* 2 WINTROBE'S CLINICAL HEMATOLOGY 1873, 1873 (G. Richard Lee et al. eds., 9th ed. 1993); Eleni Petridou & Dimitrios Trichopoulos, *Leukemias*, *in* TEXTBOOK OF CANCER EPIDEMIOLOGY 556, 556–57 (Hans-Olov Adami et al. eds., 2002).

126. L. Brandt et al., *Occupational Exposure to Petroleum Products in Men with Acute Non-Lymphocytic Leukaemia*, 1 BRIT. J. MED. 555 (1978); Richard D. Irons et al., *Synergistic Action of the Benzene Metabolite, Hydroquinone, On Myelopoietic Stimulation Activity of Granulocyte Macrophage Colony Stimulation Factor in Vitro*, 89 PROC. NAT'L ACAD. SCI. 3691 (1992); M.S. Linet et al., *Comparison of Methods for Determining Occupational Exposure in a Case-Control Interview Study of Chronic Lymphocytic Leukaemia*, 29 J. OCCUPATIONAL MED. 136 (1987); K.E. Malone et al., *Chronic Lymphocytic Leukaemia in Relation to Chemical Exposure*, 130 AM. J. EPIDEMIOLOGY 1152 (1989); P.A. McKinney et al., *Chronic Myeloid Leukaemia in Yorkshire: A Case-Control Study*, 83 ACTA HAEMATOLOGICA 35 (1990); Otto Wong & G.K. Raabe, *Cell-Type-Specific Leukemia Analyses in a Combined Cohort of More Than 208,000 Petroleum Workers in the United States and the United Kingdom, 1937–1989*, 21 REG. TOXICOLOGY & PHARMACOLOGY 307 (1995); Otto Wong et al., *Health Effects of Gasoline Exposure. II Mortality Patterns of Distribution Workers in the United States*, 101 ENVTL. HEALTH PERSP. 63 (Supp. 6 1993).

types of leukemia are distinct diseases.[127] Lumping the leukemias together for causation analysis may mask or underestimate the increased risk of AML due to benzene exposure, or may lead to the erroneous conclusion that benzene exposure increases the risk of all leukemias when, in fact, it increases only the risk of AML (and perhaps other distinct types). Specificity prevents these analytical errors.

7. *Dose-Response Relationship*—A dose-response relationship demonstrates a direct relationship between the level of exposure and the risk of disease. This criterion recognizes a basic premise of toxicology: the resultant injury depends on the dose of the agent received.[128] In epidemiologic terms, this means that for a causal relationship, the Odds Ratio (OR) or Relative Risk (RR) of an injury must increase with increasing exposure.[129] Associations that demonstrate dose-response gradients are powerful indicators of causal relationships. In contrast, so-called "ecological studies," which collect data about a group as a whole (e.g., "railroad workers") without regard to varying exposures among the group members, are regarded as "weak indicators of general causation."[130]

Related to the concept of a dose-response relationship is the concept of a "threshold dose." The "threshold" or "no effect level" is the level of exposure below which the toxic substance does not

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127. *See, e.g.*, Austin v. Kerr-McGee Ref. Corp., 25 S.W.3d 280, 288–92 (Tex. App. 2000) (upholding exclusion of plaintiff's expert's testimony that benzene caused decedent's chronic myelogenous leukemia because expert lacked evidence that benzene causes CML); *see also* Mitchell v. Gencorp Inc., 165 F.3d 778 (10th Cir. 1999); Chambers v. Exxon Corp., 81 F. Supp. 2d 661 (M.D. La. 2000).

128. The dose-response relationship "is the most fundamental and pervasive concept in toxicology." Eaton & Klaassen, *supra* note 117, at 18; *see also* Newman v. Motorola Inc., No. 02-2424, 2003 WL 22407265 (4th Cir. Oct. 22, 2003) (affirming trial court's exclusion of expert's opinion that cellular phone use caused plaintiff's brain cancer because, among other things, the expert's evidence "failed to demonstrate a dose-response relationship; that is, it failed to show that with a greater use of cellular phones, a person faces a greater risk of developing a tumor").

129. There are two types of dose-response relationships: that which applies to the responses of an *individual* to varying doses of a toxin, and that which applies to the distribution of responses to varying doses of a toxin administered to a *population* of individuals. Eaton & Klaassen, *supra* note 117, at 18. Since epidemiology addresses the issue of general causation, it is the *population* dose-response relationship that is of interest at this point. In contrast, the *individual* dose-response relationship is of interest in the context of specific causation.

130. Green et al., *supra* note 64, at 344; *see also* SILVA, *supra* note 93, at 250 ("Ecological studies are frequently used as a first step in investigating a possible exposure-outcome relationship, because they can be performed quickly and inexpensively by using readily available information."); *id.* at 299 ("Ecological studies per se can show associations, but because of their great potential for confounding they can never be used to establish causation at an individual level.").

exhibit a toxic effect, or at least does not exert a clinical effect. Courts require the plaintiffs' experts to demonstrate that the plaintiff was exposed at a level greater than the threshold dose.[131] For example, in *Cartwright v. Home Depot U.S.A., Inc.*, the plaintiff's expert toxicologist opined that the defendant's paints caused the plaintiff's asthma.[132] While the toxicologist identified several components of the paints that were known respiratory irritants, he provided no information as to how much of the particular components the plaintiff was exposed. Likewise, he failed to "provide any quantification to substantiate in scientific terms what level of exposure would have been sufficient to cause asthma in the plaintiff or anyone else."[133] The court granted the defendant's motion to exclude the plaintiff's toxicology evidence, stating:

> Plaintiffs cite no authority for the propositions that irritating chemicals in latex paints become bioavailable in relevant amounts, that actual exposure levels from any particular uses of latex paint are high enough to cause any reaction, that prolonged, unspecified low level exposure to irritants can cause asthma, or that latex paints generally (or these paints in particular) cause asthma.[134]

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131. To be precise, "dose" and "exposure" are related, but not identical. Dose is the amount of the agent that enters the body from the external environment. Eaton & Klaassen, *supra* note 117, at 13. In contrast, exposure considers both: 1) the level or concentration of the agent in environmental media (for example, the concentration of a chemical in air or water) with which the body comes in contact (via inhalation, skin contact, or ingestion); and 2) the duration of contact with the agent in the environment. *Id.* at 14. The dose received by the body depends to a great degree on the exposure. *Id.* In epidemiologic studies, rarely, if ever, are the actual doses known, so epidemiologists use exposures as a surrogate for doses. *See* Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 169 (E.D.N.Y. 2001) ("[I]t is accepted practice in epidemiology and toxicology to measure dose in terms of ambient concentration in cases . . . where the study subjects' actual body burdens of the chemical in question have not or cannot be measured at the time of exposure." (citing ENVIRONMENTAL & OCCUPATIONAL MEDICINE 40 (William N. Rom ed., 3d ed. 1998) ("In most cases, doses and dose rates cannot be measured directly, and surrogate measures must be developed from data on exposures observed in the environment external to the worker. Exposure concentration or intensity is used as a surrogate for dose rate . . . ."))), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

132. 936 F. Supp. 900, 902 (M.D. Fla. 1996).

133. *Id.* at 904.

134. *Id.* at 905; *see also* Downs v. Perstorp Components, Inc., No. 00-5507, 2002 WL 22000 (6th Cir. Jan. 4, 2002) (excluding proffered causation testimony by plaintiff's expert because he failed to ascertain the plaintiff's exposure level and failed to determine the level of exposure necessary to cause harm); Mitchell v. Gencorp Inc., 165 F.3d 778, 781 (10th Cir. 1999) ("In order to carry [her] burden, a plaintiff must demonstrate 'the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover.'" (quoting Wright v. Willamette Indus., Inc., 91 F.3d 1105, 1106 (8th Cir. 1996))); Allen v. Pa. Eng'g Corp., 102

8. Cessation of Exposure—Data demonstrating that elimination of exposure reduces the incidence of disease are strong evidence of a causal association.[135] For many exposure-disease investigations, however, intervening to remove the exposure is impossible.[136]

F.3d 194, 199 (5th Cir. 1996) ("Scientific knowledge of the harmful level of exposure to a chemical, plus knowledge that the plaintiff was exposed to such quantities, are minimal facts necessary to sustain the plaintiffs' burden in a toxic tort case." (citing *Wright*, 91 F.3d at 1107)); *Wright*, 91 F.3d at 1107–08 (citing Abuan v. Gen. Elec. Co., 3 F.3d 329, 332–34 (9th Cir. 1993)) (requiring plaintiff in a toxic tort case to prove levels of exposure that are hazardous to human beings generally, as well as plaintiff's actual exposure); *Abuan*, 3 F.3d at 333 ("In cases claiming personal injury from exposures to toxic substances, it is essential that the plaintiff demonstrate that she was, in fact, *exposed to harmful levels* of such substances." (quoting Maddy v. Vulcan Materials Co., 737 F. Supp. 1528, 1533 (D. Kan. 1990) (emphasis added by the court))); Christophersen v. Allied-Signal Corp., 939 F.2d 1106, 1114–15 (5th Cir. 1991) (excluding expert's opinion that was based on insufficient data regarding level and duration of exposure to harmful agent); Wills v. Amerada Hess Corp., No. 98 CIV. 7126(RPP), 2002 WL 140542 (S.D.N.Y. Jan. 31, 2002) (holding that without information relating to decedent's occupational exposures to toxins, plaintiff's causation expert could not form a scientifically reliable opinion); Current v. Atochem N. Am., Inc., No. W-00-CV-332, 2001 WL 1875950 (W.D. Tex. Dec. 17, 2001) (affirming summary judgment for defendant because, among other reasons, plaintiff's medical expert lacked reliable evidence of the plaintiff's level of exposure to arsenic); Aldridge v. Goodyear Tire & Rubber Co., 34 F. Supp. 2d 1010, 1023–24 (D. Md. 1999) (citing Cavallo v. Star Enter., 892 F. Supp. 756, 760–61 (E.D. Va. 1995)) (finding it critical that a causation expert testify as to the threshold level required to cause particular effect), *aff'd in relevant part*, 100 F.3d 1150 (4th Cir. 1996); Stasior v. Nat'l R.R. Passenger Corp., 19 F. Supp. 2d 835 (N.D. Ill. 1998) (holding inadmissible an ergonomist's testimony due in part to the fact that he did not determine a safe level of wrist flexion or repetition relative to carpal tunnel injury); Schmaltz v. Norfolk & W. Ry. Co., 878 F. Supp. 1119, 1122 (N.D. Ill. 1995) (granting defendant's motion for summary judgment where expert was unaware of plaintiff's exposure levels); Chikovsky v. Ortho Pharm. Corp., 832 F. Supp. 341, 345–46 (S.D. Fla. 1993) (barring causation testimony because expert did not know at what dosage Vitamin A is unsafe for pregnant women, and did not know mother's dose); O'Conner v. Commonwealth Edison Co., 807 F. Supp. 1376, 1396 (C.D. Ill. 1992) (excluding causation testimony of plaintiff's treating physician who failed to take plaintiff's radiation dose into account), *aff'd*, 13 F.3d 1090 (7th Cir. 1994); Mateer v. U.S. Aluminum, No. Civ. A 88-2147, 1989 WL 60442, at *8 (E.D. Pa. June 6, 1989) (granting summary judgment in defendants' favor because plaintiffs' experts failed to describe the plaintiffs' dosages and the level of exposure hazardous to humans); Cerna v. S. Fla. Bioavailability Clinic, Inc., 815 So. 2d 652 (Fla. Dist. Ct. App. 2002) ("Extrapolating from such [in vitro] studies in order to opine on [the drug] erythromycin's effects on humans at normal dosages and normal pH conditions is not methodologically sound or accepted."); Christian v. Gray, 65 P.3d 591, 607 (Okla. 2003) ("[An expert's testimony] should reveal a reliable method for determining the quantity of the toxin necessary to cause injuries of the type experienced by plaintiff (general causation), unless plaintiff can show that the circumstances are such that general causation should not be necessary.").

The proffered exposure estimates need not be scientifically exacting, only reliable using accepted methods. *See* discussion *infra* note 370; *see also* Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584 (D.N.J. 2002) (holding that industrial hygienist's use of "odor threshold test" to estimate plaintiff's exposures to solvent is not the most reliable method, but it is a generally accepted method to determine air levels of contaminants in absence of air sampling data).

135. Green et al., *supra* note 64, at 378.

136. SILVA, *supra* note 93, at 298.

9. Consistency with Other Knowledge—This final criterion, sometimes termed "coherence,"[137] directs the researcher to step back and consider whether other evidence exists to support or undermine a finding of a causal association. For example, the finding in national statistics that lung cancer rates increased after an increase in tobacco consumption buttresses the view that cigarette smoking causes lung cancer.[138] By contrast, a decline in the number of smokers in recent years, and improvements in air quality in the United States over the last three decades, undermines the view that smoking or air pollution is responsible for either the nationwide increase in numbers of asthematics or for an increase in aggravation of asthmatic symptoms.[139]

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137. *See* Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001) (noting that coherence criterion asks: "Is the association consistent with what is known of the natural history and biology of the disease?"), *aff'd*, 303 F.3d 256 (2d Cir. 2002). This concept of coherence can also apply to specific causation analysis. *E.g.*, Medalen v. Tiger Drylac, 269 F. Supp. 2d 1118 (D. Minn. 2003). In *Medalen*, the court found incoherence in the alleged association between the plaintiff's skin cancer and her occupational exposure to powdered coatings. *Id.* at 1132. The plaintiff's causation expert failed to explain why the plaintiff's cancer appeared on her nose, which was covered and unexposed to the powder, and not on exposed skin, such as her hands. *Id.* At bottom, coherence is applied common sense.

138. Green et al., *supra* note 64, at 378–79. Similarly, the spread of HIV infections may help explain the extraordinary increase in the rates of non-Hodgkin's lymphoma (NHL). In 1950, the United States mortality rate for NHL was 2.9 deaths per 100,000 population; by 1990, the rate more than doubled to 6.3 deaths per 100,000 population. Paul A. Scherr & Nancy E. Mueller, *Non-Hodgkin's Lymphomas*, *in* CANCER EPIDEMIOLOGY AND PREVENTION, *supra* note 125, at 920, 922. NHL is prevalent among immunosuppressed persons. *Id.* at 925–26. "NHL[s] are the most frequent opportunistic malignancies seen in HIV-I-infected persons." *Id.* at 927. These data support the inference of a causal association between HIV infection and NHL.

139. Between 1980 and 1995, the overall rate of asthma increased seventy-five percent in the United States. Centers for Disease Control and Prevention, *Surveillance for Asthma—United States, 1960–1995*, 47 MORBIDITY & MORTALITY WKLY. REP. 1 (1998). In comparison, over the same period the adult smoking rate decreased from 33.2% to 24.7%, a 25% drop. CENTERS FOR DISEASE CONTROL AND PREVENTION, PERCENTAGE OF ADULTS WHO WERE CURRENT, FORMER, OR NEVER SMOKERS: NATIONAL HEALTH INTERVIEW SURVEYS, SELECTED YEARS—UNITED STATES, 1965–2000, http://www.cdc.gov/tobacco/research_data/adults_prev/adstat1.htm (last visited Mar. 16, 2005). Moreover, air quality has improved in recent years. The Environmental Protection Agency reports that particulates like soot and dust have decreased 22% between 1988 and 1995 and that sulfur dioxide concentrations have dropped by 60% since 1970. Ronald Bailey, *Asthma Attack: The Unexpected Cause of a New Epidemic*, REASON ONLINE, Jan. 3, 2001, http://www.reason.com/rb/rb010301.shtml. As one researcher stated: "Like most people, I assumed tobacco smoke and pollution were the problem—this was the politically correct way to think. But these factors turned out not to play a major role. In high-pollution areas, in low-pollution areas, among all ethnic groups, there was asthma. Clearly, something else was involved." Ellen Ruppel Shell, *Does Civilization Cause Asthma*, ATLANTIC MONTHLY, May 2000, at 94 (quoting Fernando Martinez). Thus, the theory that smoking or air pollution causes asthma currently lacks coherence.

B. Attributable Risk

The "attributable risk" (AR) is the proportion of disease in a population theoretically caused by exposure to a certain agent. One scholar notes:

> A frequently used measurement of risk is the attributable risk (AR). The attributable risk represents the amount of disease among exposed individuals that can be attributed to the exposure. It can also be expressed as the proportion of the disease among exposed individuals that is associated with the exposure (also called the "attributable proportion of risk," the "etiologic fraction" or "attributable risk percent"). The attributable risk reflects the maximum proportion of the disease that can be attributed to exposure to an agent and consequently the maximum proportion of disease that could be potentially prevented by blocking the effect of the exposure or by eliminating the exposure. In other words, if the association is causal, the attributable risk is the proportion of disease in an exposed population that might be caused by the agent and that might be prevented by eliminating exposure to that agent.

To determine the proportion of a disease that is attributable to an exposure, a researcher would need to know the incidence of the disease in the exposed group and the incidence of disease in the unexposed group. The attributable risk is:

$$AR = \frac{(\text{incidence in exposed persons}) - (\text{incidence in nonexposed persons})}{(\text{incidence in exposed persons})}$$ [140]

The AR is the proportion of disease cases induced by the agent in the total number of disease cases.[141] For example, suppose that the incidence of the subject disease among the exposed group is seven 7 out of 100 persons, while the incidence among the unexposed group is five 5 out of 100 persons. The AR is: $(7 - 5)/ 7 = 0.29$.[142]

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140. Green et al., *supra* note 64, at 351–52 (citations omitted).

141. This definition of AR assumes that the greater incidence of disease in the exposed group is a consequence of the exposure and not due to some (confounding) characteristic that differentiates "exposed" and "unexposed" populations, aside from the exposure itself.

142. Alternatively, one can calculate the AR by using the RR or OR found in an epidemiology study rather than the raw numbers of diseased persons in the exposed and

This means that, in theory, 29% of those exposed incurred the disease because of the exposure to the subject agent, and 71% of those exposed incurred the disease for other reasons.

C. Epidemiology of Cancer

The quantitative knowledge available concerning exposure to various agents and cancer is quite good in some cases, while in other cases it is not.[143] In their seminal work addressing the causes of cancer in America, Doll and Peto made their best estimate, based on epidemiologic evidence, of the proportion of cancers caused by various factors. The following table, a modification of Table 20 in Doll and Peto's book,[144] summarizes their findings.

PERCENT OF CANCER DEATHS ATTRIBUTABLE TO VARIOUS DIFFERENT FACTORS

PERCENT OF ALL CANCER DEATHS		
FACTOR OF CLASS OF FACTOR	BEST ESTIMATE	RANGE OF ACCEPTABLE ESTIMATES
Tobacco	30	25–40
Alcohol	3	2–4
Diet	35	10–70
Food Additives	<1	-5–2

unexposed groups. The proportion of risk of disease (RR) or death (OR) in the exposed population due to the exposure is:

$$AR = (RR - 1) / RR; \text{ or } AR = (OR - 1) / OR.$$

Green et al., *supra* note 64, at 351–52.

143. RICHARD DOLL & RICHARD PETO, THE CAUSES OF CANCER, at Preface (1981).

144. *Id.* at 1256. Prior to the publication of Doll and Peto's work, other respected cancer scientists allocated cancer incidences among various causes as best they could. Their estimates are surprisingly consistent with those of Doll and Peto's. *See* John Higginson & Calum S. Muir, *Environmental Carcinogenesis: Misconceptions and Limitations to Cancer Control*, 63 J. NAT'L CANCER INST. 1291 (1979); Ernest L. Wynder & Gio B. Gori, *Contributions of the Environment to Cancer Incidence: An Epidemiologic Exercise*, 58 J. NAT'L CANCER INST. 825 (1977); *see also* ROBERT LICHTER & STANLEY ROTHMAN, ENVIRONMENTAL CANCER—A POLITICAL DISEASE? 61–63 (1999) (summarizing and comparing the estimates of Doll & Peto, Wynder & Gori, and Higginson & Muir).

PERCENT OF ALL CANCER DEATHS		
FACTOR OF CLASS OF FACTOR	BEST ESTIMATE	RANGE OF ACCEPTABLE ESTIMATES
Reproductive and Sexual Behavior	7	1–13
Occupational	4	2–8
Pollution	2	<1–5
Industrial Products	<1	<1–2
Medicines and Medical Procedures	1	0.5–3
Geophysical Factors	3	2–4
Infection	10(?)	1–?
Unknown	?	?

More recently, researchers have recognized that cancer is an unavoidable risk. Common elements such as background radioactivity, errors in DNA synthesis, free radicals produced in metabolism, and normal hormones all contribute to cancer risk.[145] For the U.S. population, the baseline risk of developing cancer sometime during life is almost one in two (proportion of cancer incidence in males is 0.43; in females, it is 0.38). The DNA damage that inevitably accumulates over a lifetime is the probable cause of the vast majority of human cancers. In fact, the risk factor for cancer that overwhelms all other risk factors is age.[146] Still, Doll and Peto's estimates remain a fair base on which to ground cancer causation analysis.

For the purposes of this Article, we have chosen to focus on cancers associated with occupational exposures, often the subject of toxic tort claims. As seen in the table above, Doll and Peto estimate that occupational exposures cause four percent of all cancers.[147]

145. Brian E. Henderson et al., *Toward the Primary Prevention of Cancer*, 254 SCIENCE 1131 (1991).

146. L.A.G. RIES ET AL., NAT'L INST. OF HEALTH, PUB. NO. 99-2789, SURVEILLANCE EPIDEMIOLOGY AND END RESULTS: SEER CANCER STATISTICS REVIEW, 1973–1996, at 39, 63–66 (1999).

147. Now, more than two decades after Peto and Doll published their comprehensive study, their estimate that four percent of cancers are attributable to occupational exposures is probably high. Henry C. Pitot III & Yvonne P. Dragan, *Chemical Carcinogenesis*, *in* CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, *supra* note 117, at 241, 284 ("In regard to the general causative relationship between exposure to chemicals in the workplace and the development of human cancer, Doll and Peto (1981) have presented a compelling argument that only about 4 percent of all cancer deaths in the United States can be attributed to occupational circumstances. With strict government regulation of actual and

Based on this estimate, and without further information, a claim that occupational exposures caused a person's cancer would have to be supported by causation testimony with sufficient specificity to identify more than 96% of all cancers that are not caused by occupational exposures; that is, where $x = 0.04$. Applying the formula derived in Section IV:

$$\text{Required Specificity} = (1 - 2x) / (1 - x) = 0.92 / 0.96 \cong 0.96.$$

There is always, however, additional information. Most conspicuous is the particular type of cancer at issue. In a toxic tort case involving cancer, the plaintiff will claim that a particular agent or group of agents caused the particular type of cancer at issue. Some types of cancer are more closely associated with occupational exposures than other types. Indeed, Doll and Peto estimated the percentage of certain cancers ascribable to occupational exposures:[148]

ESTIMATED PERCENTAGE OF CERTAIN CANCERS ASCRIBABLE TO OCCUPATION

TYPE OF CANCER	NO. DEATHS IN 1978		CANCER DEATHS ASCRIBED TO OCCUPATIONAL HAZARDS IN 1978 UNITED STATES			
	MALE	FEMALE	MALE DEATHS ASCRIBED	% ASCRIBED	FEMALE DEATHS ASCRIBED	% ASCRIBED
Mesentery and peritoneum	652	697	98	15	35	5
Liver and Intrahepatic bile ducts	1,812	984	72	4	10	1
Larynx	2,909	550	58	2	6	1
Lung	71,006	24,080	10,651	15	1,204	5
Pleura, nasal sinuses, and remaining respiratory sites	857	496	214	25	25	5
Bone	997	740	40	4	7	1
Skin other than melanoma	1,061	753	106	. 10	15	2
Prostate	21,674	—	217	1	—	—

potential industrial health hazards during the last two decades, it is likely that this figure will decrease even further in the future.").

148. DOLL & PETO, *supra* note 143, at 1244 tbl.19.

TYPE OF CANCER	NO. DEATHS IN 1978		CANCER DEATHS ASCRIBED TO OCCUPATIONAL HAZARDS IN 1978 UNITED STATES			
	MALE	FEMALE	MALE DEATHS ASCRIBED	% ASCRIBED	FEMALE DEATHS ASCRIBED	% ASCRIBED
Bladder	6,771	3,078	677	10	154	5
Leukemia	8,683	6,708	868	10	335	5
Other & Unspecified	15,445	14,821	1,045	6.8	185	1.2

Doll and Peto estimated that the total effect of occupational factors (U.S., 1978) was for males, 14,777 / 218,337 = 6.77%; and for females, 2,292 / 183,618 = 1.25%.[149] More recent estimates of cancer risks indicate that occupational exposures may cause 5% of all cancers in the U.S.[150]

VI. APPLICATION OF EPIDEMIOLOGIC DATA AND BAYES' LAW IN TOXIC TORT CASES

As stated, epidemiology addresses the issue of general causation—that is, whether the agent at issue is capable of causing disease.[151] It follows that epidemiologic studies are relevant evidence of causation in toxic tort cases in which general causation is at issue.[152] But the use of epidemiologic studies in legal cases often goes beyond establishing general causation. In some circumstances, the calculated Attributable Risk (AR) as determined in epidemiologic studies can provide a measure of the likelihood that

149. *Id.*; *see also* ROGER W. FINDLEY & DANIEL A. FARBER, ENVIRONMENTAL LAW CASES AND MATERIALS 378–79 (2d ed. 1985) (reporting that man-made carcinogens may cause less than eight percent of cancer deaths in the United States); Peter Huber, *Safety and the Second Best: The Hazards of Public Risk Management in the Courts*, 85 COLUM. L. REV. 277, 295–97 (1985) (citing a study concluding that, except for tobacco-induced cancers, the risk of cancer in the United States is holding steady despite an influx of chemical and industrial hazards).

150. Harvard Center for Cancer Prevention, Harvard School of Public Health, *Harvard Report on Cancer Prevention: Vol I: Causes of Human Cancer*, 7 CANCER CAUSES & CONTROL S3, S55–S58 (Supp. 1996).

151. *See* Brennan, *supra* note 6, at 512 ("Epidemiology makes statements only about the group, not the individual. Individual attribution involves uncertainty, because the epidemiological data produce only summary statistics applicable to the sample or to the population the sample represents.").

152. Hall & Silbergeld, *supra* note 66, at 445–46 ("Although the epidemiological study by itself does not conclusively show that an individual plaintiff's injury was caused by exposure to a particular chemical, it is at least relevant circumstantial evidence, showing the probability of a relationship between the chemical in question and the injury." (citing Grinnell v. Pfizer & Co., 79 Cal. Rptr. 369, 375 (Cal. Ct. App. 1969))).

the exposures at issue caused the particular plaintiff's injury (specific causation).

Suppose that a male claimant sought workers' compensation for his lung cancer, which he claims resulted from his on-the-job exposure to diesel exhaust. Doll and Peto's estimated base rate (designated "percent ascribed" in the table above) for occupational lung cancer among males with lung cancer is 15%. Given this base rate, the claimant's medical expert would have to demonstrate that the causation analysis has sufficient specificity to identify eighty-two percent of nonoccupational lung cancers,[153] absent more detailed information concerning exposure levels and attendant ARs among persons so exposed.[154] There often is additional information available, however, allowing experts to refine the AR for those exposed to the subject agent.

Arguably, benzene is the most thoroughly studied of all potential occupational carcinogens.[155] One extensively studied and quantified exposure-effect relationship is the benzene-leukemia link and,

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153. Required Specificity = $(1 - 2x) / (1 - x) = 0.7 / 0.85 \cong 0.82$. For a discussion and derivation of the formula used to determine the required specificity, see *supra* Part IV.

154. Doll and Peto suspect that their estimate of occupational lung cancer risk may be "a little high." DOLL & PETO, *supra* note 143, at 1244.

155. Benzene has received intense scrutiny because it is an economically important chemical that is associated with a dreadful human health effect: leukemia. Assessment of the leukemogenic risk of benzene became particularly important following *Industrial Union Department, AFL-CIO v. American Petroleum Institute*, in which the United States Supreme Court overturned the 1978 Occupational Safety and Health Administration (OSHA) revised benzene standard on the ground that OSHA had not demonstrated that benzene exposure in compliance with the previous benzene standard presented a significant risk of leukemia. 448 U.S. 607 (1980). That decision spawned extensive research on the quantitative assessment of benzene exposure risk. *See, e.g.*, KENNY S. CRUMP & BRUCE C. ALLEN, OCCUPATIONAL SAFETY & HEALTH ADMIN., DOCKET H-059B, QUANTITATIVE ESTIMATES OF RISK OF LEUKEMIA FROM OCCUPATIONAL EXPOSURE TO BENZENE Exhibit 152 (1984); D. GILBERT, U.S. ENVTL. PROT. AGENCY, CONTRACT 68-01-5949, AN EXPOSURE AND RISK ASSESSMENT FOR BENZENE (1982); Harland Austin et al., *Benzene and Leukemia: A Review of the Literature and a Risk Assessment*, 127 AM. J. EPIDEMIOLOGY 419 (1988); Susan M. Brett et al., *Review and Update of Leukemia Risk Potentially Associated with Occupational Exposure to Benzene*, 82 ENVTL. HEALTH PERSP. 267 (1989); Daniel M. Byrd & Elizabeth T. Barfield, *Empirical Degree-Of-Belief Methods for Risk Assessments Based on Epidemiology Data: Application of a Procedure for Combinational Analysis of Risk-Related Components to a Series of Occupational Studies of Leukemia Incidence Associated with Benzene Exposure at Several Rubber Hydrochloride Plants in Ohio*, *in* RISK ASSESSMENT AND RISK MANAGEMENT OF INDUSTRIAL AND ENVIRONMENTAL CHEMICALS 209 (C. Richard Cothern et al. eds., 1988); Robert A. Rinsky et al., *Benzene and Leukemia: An Epidemiologic Risk Assessment*, 316 NEW ENG. J. MED. 1044 (1987) [hereinafter Rinsky et al., *Risk Assessment*]; Robert A. Rinsky et al., *Leukemia in Benzene Workers*, 2 AM. J. INDUS. MED. 217 (1981); Mary C. White et al., *A Quantitative Estimate of Leukemia Mortality Associated with Occupational Exposure to Benzene*, 2 RISK ANALYSIS 195 (1982). Quantitative risk assessment since has become the standard method used by regulatory agencies to estimate the risk of cancer presented by environmental or industrial exposures to the regulated agent. Steven H. Lamm et al., *Consistencies and Inconsistencies Underlying the Quantitative Assessment of Leukemia Risk from Benzene Exposure*, 82 ENVTL. HEALTH PERSP. 289, 289 (1989).

more particularly, acute myeloid leukemia (AML).[156] We can use the benzene-AML association in an example analysis to demonstrate the impact of Bayes' Law on the reliability of causation analyses.

In one epidemiologic study ("Rinsky Study"),[157] the authors attempted to reconstruct the cohort's benzene exposures and, based on these calculated exposures, estimate the risk of contracting leukemia per unit cumulative exposure of benzene as measured in parts per million•years (ppm•yrs). The authors derived the following formula for determining the Odds Ratio (OR) of contracting leukemia:

$$OR = e^{(0.0126 \times ppm\bullet yrs)}.$$

Based on the formula in the Rinsky Study, one can calculate the Odds Ratio for any given cumulative benzene exposure. Then, having derived the Odds Ratio for contracting leukemia at the given exposure level, one can determine the level of specificity required for a causation analysis to achieve a 50% predictive value.

For example, assume that the plaintiff alleges that occupational exposure to benzene caused his AML. Assume further that the best estimate of the plaintiff's daily occupational exposure to benzene is 1 ppm, 8-hour time-weighted average, which equals the current permissible exposure limit (PEL) for benzene established by the Occupational Safety and Health Administration (OSHA).[158] Finally, assume that the plaintiff was so exposed during his 20-year career, resulting in an estimated cumulative benzene exposure of 20 ppm•yrs. According to the Rinsky Study, the Odds Ratio for those in the plaintiff's exposure class is:

$$OR = e^{(0.0126 \times 20)} = 1.29.$$

An Odds Ratio of 1.29 means that the proportion of the leukemias in persons so exposed attributable to benzene exposure (that is, the Attributable Risk, or AR) is:

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156. *See id.* at 290 ("Clinical and epidemiologic evidence consistently indicate that acute myeloid leukemia (AML) and its variants (alternatively called acute nonlymphocytic leukemias, or ANLL) can be caused by benzene exposure. While some studies have implicated other types of leukemia or even lymphomas, only AML and its variants have consistently been seen in excess in groups of workers with excess benzene exposure.").

157. Rinsky et al., *Risk Assessment*, *supra* note 155.

158. 29 C.F.R. § 1910.1028 (2004).

$$AR = (1.29 - 1) / 1.29 = 0.22, \text{ or } 22\%.$$

Since 22% of the persons with leukemia who are exposed to a cumulative exposure of 20 ppm•yrs are (in theory) attributable to the benzene exposure, the causation analysis must have the following specificity to achieve a predictive value of 0.5:

$$\text{Required Specificity} = 1 - 2(0.22) / (1 - 0.22) = 0.72.$$

In this hypothetical, the plaintiff's causation experts must demonstrate that their methods have sufficient specificity to identify in this exposure population more than 72% of AMLs in the benzene-exposed population that are not benzene-induced (that is, less than 28% "false negatives") to achieve reliability greater than 50%. Since the exposure itself does not establish causation within a reasonable degree of medical certainty (that is, more likely than not), the plaintiff's causation expert must be able to establish causation by considering factors other than exposure. Failure to evaluate alternative explanations for the plaintiff's leukemia weakens the specificity of the plaintiff's proffered causation analysis by increasing the probability of "false positives."

VII. SEQUENTIAL UNCERTAINTIES

As in other negligence cases, a toxic tort plaintiff bears the burden to prove "an unbroken causal connection between the alleged negligent act and the injuries suffered."[159] There are several links in the causal chain leading from an alleged exposure to the alleged injury:

1. Whether the person in fact has the alleged injury;
2. Whether the agent is capable of causing the injury;
3. Whether the person was exposed to the agent at a sufficient level to cause the injury;
4. Whether the injury arose after the person received an etiologically significant dose of the agent; and
5. Whether the causation analysis attained the specificity required to identify the agent as the probable cause of the injury.

159. 65A C.J.S. *Negligence* § 715 (2000) (citing Wu v. Town of Fairfield, 528 A.2d 364 (Conn. 1987)).

The uncertainties attending each of these steps decrease the overall probability that the exposure in fact caused the person's injury. To the extent that these factors are independent, the likelihood that all factors are true equals the product of the probabilities of each factor.[160] This "product rule" is sometimes called sequential uncertainties.

The product rule is a special case of conditional probabilities that give rise to Bayes' Law. Recall the definition of Predictive Value discussed in Section II. In the context of a medical test used to indicate the presence of a disease, the predictive value is the proportion of positive test results that are true positives:

$$\text{Predictive Value} = \frac{\text{true positive test result}}{\text{total number of positive test results}}$$

In terms of conditional probabilities, this equation is:

$$P(H|E) = P(H\&E) \,/\, P(E),$$

where P(H|E) is the predictive value, or probability that the hypothesis is true (that is, the person has the disease), given the evidence of a positive test; P(H&E) is the probability that the individual has the disease and the test is positive (that is, the probability of a true positive); and P(E) is the probability of a positive test, given P(H) as the probability that an untested individual has the disease (in Bayesian terms, the "prior" probability).[161] Rearranging the terms, the probability of finding both the disease and a

160. The product rule states that the probability of the joint occurrence of two (or more) independent events is the product of their individual probabilities. *E.g.*, Koehler & Shaviro, *supra* note 19, at 254 (citing RICHARD A. WEHMHOEFER, STATISTICS IN LITIGATION 41 (1985), & Alan D. Cullison, *Probability Analysis of Judicial Fact-Finding: A Preliminary Outline of the Subjective Approach*, 1 U. TOL. L. REV. 538, 541–42 (1969)). "Two Events, *A* and *B*, are independent if the probability of *A* equals the probability of *A* given that *B* has occurred, and the probability of *B* equals the probability of *B* given that *A* has occurred (that is, P(A) = P(A|B) and P(B) = P(B|A))." *Id.* at 254 n.24. In other words, "[i]f the occurrence of event *B* is in no way affected by the occurrence of event *A*, then the two events, *A* and *B*, are said to be independent." KNAPP & MILLER, *supra* note 23, at 21. The statistical formula for the product rule is: P(A&B) = P(A)P(B). *Id.* The typical example of this principle is a coin toss. Each flip of a coin is independent of all other flips of the coin. Thus, the probability of tossing a coin twice and getting two heads is: $0.5 \times 0.5 = 0.25$, or one out of four.

161. *See supra* note 42 and accompanying text. Note that the probability of both the presence of disease and a positive test result equals the prevalence of the disease multiplied by the sensitivity of the test. In probabilistic terms, the relationship is: P(H&E) = P(H)P(E|H).

positive result ("true positive") is expressed in the following formula:

$$P(H\&E) = P(H|E)P(E).$$

This is the general multiplication rule in terms of conditional probabilities.[162] The product rule, also called sequential uncertainties, is the general multiplication rule applied to instances of independent events. If the occurrence of event B is in no way influenced by the occurrence of event A, then $P(A|B) = P(A)$, and the general multiplication rule simplifies to:

$$P(A\&B) = P(A)P(B)$$

in cases of independent events.[163]

In Harber & Shusterman, *Medical Causation Analysis Heuristics*,[164] the authors provide the following example of sequential uncertainties in the context of an alleged occupational asthma. "[I]f it is 80% certain that an employee has asthma, 80% certain that the employee was exposed to moderate levels of chlorine, 80% certain that such repetitive exposures are capable of inducing asthma, and 80% certain that the employee did not have preexisting asthma, then according to the multiplicative approach, the likelihood of work-relatedness is much less than 50% ($.80 \times .80 \times .80 \times .80$)."[165]

The product rule dictates that, to prove causation, each independent step of the plaintiff's expert's causation analysis must *substantially* exceed 0.5 probability. Otherwise, the product rule dooms the ultimate conclusion that the exposure actually caused the injury to "less likely than not" status. For example, if the probability of the expert's specific causation testimony achieves 70% probability of truth *independent of general causation*, the plaintiff's claim must nevertheless fail if the independent probability of general causation is 70% or less (that is, $0.7 \times 0.7 = 0.49$). A logical corollary of the product rule is that "the probability of the entire chain (or the last link) being true is *always and without exception less*

162. KNAPP & MILLER, *supra* note 23, at 21.

163. *Id.* As an example of independency in the context of testing for diseases, suppose that the testers apply the wrong assay for a particular disease. In that case, a positive result would be independent of disease presence. If the incidence of the disease in the population [P(H)] is 0.1, and the probability of a positive test result in this population [P(E)] is 0.5, then the probability of having both a positive test result and presence of the disease [P(H&E)] is determined by the product rule: P(H&E) = (0.1) (0.5) = 0.05, or 5%, assuming that the test result is not influenced by the presence of the disease.

164. 38 J. OCCUPATIONAL & ENVTL. MED. 577 (1996).

165. *Id.* at 580.

probable than the probability of the least probable link in the chain."[166] Thus, if general causation, or any other independent link in the causal chain, is less than fifty percent probable, then the probability of the entire chain of causation is inevitably less likely than not. Similarly, if the product of the probabilities of any two or more independent links in the causative chain is less than 0.5, then, again, the probability of the entire causal chain being true is less likely than not. In either case, if the truth of the entire causal chain is improbable, the ultimate link in the causal chain (that is, the subject agent caused the plaintiff's injury) is likewise improbable.

It is essential for proper use of the product rule that each factor is independent, just as each flip of a coin is independent of all the flips that have gone before. *People v. Collins* is a case in which the trial court misunderstood this independence requirement for proper application of the product rule.[167] At trial, the prosecutor offered evidence concerning the probability of the joint occurrence of several unusual traits displayed by the two defendants.[168] The prosecutor applied the product rule, assuming each trait was independent.[169] This assumption was incorrect, as the California Supreme Court found.[170] "If traits are not independent, but rather tend to occur together, then the multiplication of the individual

166. PIATTELLI-PALMARINI, *supra* note 18, at 136. According to this corollary, the probability of the *ultimate link* being true is less than the probability of the least probable link. This statement does not mean that the probability of the truth of the ultimate link *determined independently* must be less than the weakest link. Rather, it means that the ultimate link must be weaker than the weakest link when the probability of each preceding link is considered as a factor in the probability of the ultimate link being true. For example, in the context of a toxic tort case, one could determine that the probability of the ultimate link of specific causation being true is 0.9, *assuming that all previous links are true.* This independent probability may actually be greater than any previous link. But, if the probabilities of all the preceding links are factored into the probability of the ultimate link, then the corollary of the product rule is logically inevitable. Thus, in a toxic tort case, if the probability that the agent is capable of causing the alleged injury is only 0.6, then the probability of the ultimate link being true, that is, that the agent in fact caused the plaintiff's injury, must be less than 0.6. In the context of a toxic tort case, one can state this corollary as: general causation is the *sine qua non* of specific causation. *See* Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1413 (D. Or. 1996) (holding that testimony regarding specific causation is irrelevant unless general causation is established).

167. 438 P.2d 33 (Cal. 1968); *see also* Michael O. Finkelstein & William B. Fairly, *A Bayesian Approach to Identification Evidence*, 83 HARV. L. REV. 489, 490–91 (1970) ("[T]he prosecution called an instructor of mathematics at a state college in an attempt to establish that, assuming the robbery was committed by a Caucasian blond with a ponytail who left the scene in a yellow car accompanied by a Negro with a beard and a mustache, the probability was overwhelming that the accused were guilty because they answered to this unusual description.").

168. *Collins*, 438 P.2d at 36–37.

169. *Id.*

170. *Id.* at 38–42.

probabilities of each factor usually yields a composite probability that is far too small, even if the individual probabilities are accurate."[171]

In Section IV, we derived this formula for determining the required specificity to achieve a predictive value of 0.5 at a base rate of x:

$$\text{Required Specificity} = (1 - 2x) / (1 - x).$$

As demonstrated in this Section, due to sequential uncertainties the plaintiffs' causation experts may sometimes need predictive values greater than 0.5 for their causation opinions. We need a general formula for specificity that yields the predictive values necessary in the face of sequential uncertainties.

Recall that the predictive value is equal to the rate of "true positives" divided by the rate of disease in the population ("true positives" plus "false negatives"). Using the 2×2 grid:

$$\text{Predictive Value} = A / (A + C).$$

Recall that, if we assume 100% sensitivity, the rate of "true positives", A, is the same as the rate of the disease in the population, x. So:

$$\text{Predictive Value} = x / (x + C).$$

Rather than setting the predictive value equal to 0.5 as we did in Section IV, we now set it equal to the variable "y":

$$\text{Predictive Value} = x / (x + C) = y.$$

Recall that specificity is the rate of "true negatives" (that is, those free of the disease who test negative) divided by the total number tested who are disease-free (that is , "true negatives" plus "false positives"). Using the 2×2 grid, specificity is D / (D + C). As shown

171. Finkelstein & Fairly, *supra* note 167, at 491–92. In the *Collins* case, the prosecutor listed separately the characteristics "Man with mustache" and "Negro man with beard." *Id.* If the assumed probabilities for these two characteristics (0.25 and 0.1, respectively) are multiplied, the probability of randomly selecting a Negro man with a beard and a mustache is 0.025, or approximately one out of forty. These characteristics, however, are not likely independent. "[I]f every Negro man with a beard also had a mustache then the chance of a Negro man with a beard and a mustache is one-tenth, not one fortieth as indicated by the product rule." *Id.* at 492.

in Section IV, assuming 100 percent sensitivity, D = 1 – (A + C). The formula for specificity becomes:

$$D / (D + C) = (1 - A - C) / (1 - A).$$

Since A equals x, the specificity formula becomes:

$$\text{Specificity} = (1 - x - C) / (1 - x).$$

Since the predictive value is $x / (x + C) = y$, then $C = (x / y) - x$. Replacing "C" in the specificity formula:

$$\text{Specificity} = 1 - x - [(x / y) - x] / (1 - x);$$

Simplifying,

$$\text{Specificity Required for Predictive Value of } y = [1 - (x / y)] / (1 - x).$$

As an example of the use of this general formula for required specificity, suppose that the plaintiff claims that her employer, a railroad, negligently exposed her on the job to diesel exhaust, which caused her lung cancer. Further, suppose that the court assigns a probability of general causation of 0.75 because diesel exhaust is a "likely" lung carcinogen.[172] Sequential uncertainties dictate that the required predictive value is:

$$0.5 / 0.75 = 0.67.$$

An epidemiologic study of railroad workers ("Garshick Study")[173] found a relative risk (RR) of 1.45 (CI = 1.11, 1.89) for lung cancer among a group of railroad workers with the longest possible duration of diesel exhaust exposure.[174] Among this group of exposed

172. *See* NAT'L CTR. FOR ENVTL. ASSESSMENT, U.S. ENVTL. PROT. AGENCY, EPA/600/8-90/057F, HEALTH ASSESSMENT DOCUMENT FOR DIESEL ENGINE EXHAUST 9–24 (2002) [hereinafter HEALTH ASSESSMENT FOR DIESEL EXHAUST] (classifying diesel exhaust as "likely to be carcinogenic in humans by inhaling").

173. Eric Garshick et al., *A Retrospective Cohort Study of Lung Cancer and Diesel Exhaust Exposure in Railroad Workers*, 137 AM. REV. RESPIRATORY DISEASES 820 (1988) [hereinafter Garshick *Study*].

174. The EPA considers the Garshick *Study*, *supra* note 173, "to have the best available exposure data for possible use in establishing exposure-response relationships and deriving a cancer unit risk." HEALTH ASSESSMENT FOR DIESEL EXHAUST, *supra* note 172, at 9–22. A reanalysis of the data used in the Garshick *Study*, *supra* note 173, however, uncovered "some concerns and potential shortcomings" of this cohort study. Kenny S. Crump, *Lung Cancer Mortality and Diesel Exhaust: Reanalysis of a Retrospective Cohort Study of U.S. Railroad Workers*, 11

railroad workers, the base rate of cases attributable to diesel exhaust exposure (the "Attributable Risk," or AR) based on this RR is $(1.45 - 1) / 1.45 = 0.31$, or 31%.

Given that diesel exhaust is not a known human carcinogen, but is classified by the EPA as a likely one, and assuming that the plaintiff was exposed to levels of diesel exhaust comparable to the railroad workers in the Garshick Study cohort, what specificity must the plaintiff's medical expert's causation analysis achieve to exceed, at a minimum, a predictive value of 0.67? Using the general formula derived above to determine the minimum specificity required:

$$(1 - (0.31 / 0.67)) / (1 - 0.31) = 0.78.$$

In this hypothetical, the plaintiff's medical expert must demonstrate that the causation analysis has sufficient specificity to detect and identify more than three out of four lung cancers not induced by diesel exhaust among similarly diesel exhaust-exposed persons. Failing to explain how the causation analysis excludes the endemic cases of lung cancer, the expert's opinion is unreliable.

VIII. BAYES' LAW, SEQUENTIAL UNCERTAINTIES, AND *DAUBERT*

A. The Court as Gatekeeper

Rules of evidence address the admissibility and inadmissibility of proffered evidence. Generally, courts exclude irrelevant evidence, unfairly prejudicial evidence, and unreliable evidence, such as

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INHALATION TOXICOLOGY 1, 12 (1999). This reanalysis showed that the highest rates of lung cancer were not among the workers with the highest exposures, thereby failing the "exposure gradient" causation criteria discussed above. The elevated lung cancer rates among trainmen—those who ride in trains, including engineers, brakemen, and conductors—were more likely due to lifestyle factors, such as dietary and smoking habits, rather than diesel exhaust exposure. *Id.* at 11. The workers with the highest potential diesel exhaust exposures, who were exposed also to asbestos and welding fumes, experienced lung cancer mortality rates no different from the lowest exposure group, a fact that "argues against a causal effect of diesel exposure in this cohort." *Id.* at 14. The Health Effects Institute (HEI) convened an expert panel to evaluate strengths and limitations of epidemiologic studies for diesel exhaust quantitative risk estimation. HEALTH EFFECTS INSTITUTE, DIESEL EMISSIONS AND LUNG CANCER: EPIDEMIOLOGY AND QUANTITATIVE RISK ASSESSMENT: A SPECIAL REPORT OF THE INSTITUTE'S DIESEL EPIDEMIOLOGY EXPERT PANEL 33 (1999). The expert panel concluded: "the lack of a positive exposure-response association in the railroad worker cohort date substantially weakens that study's potential to provide a reliable quantitative estimate of risk of exposure to diesel engine emissions." *Id.*

hearsay.[175] One can argue that courts should not act as gatekeepers excluding such evidence because aggressive cross-examination of witnesses will reveal weaknesses. Courts nevertheless disallow the introduction of such evidence to the jury. "[M]uch of the law of evidence consists of excluding evidence because we are afraid the lawyers will *not* do a good enough job of persuading the jury of the defects in the evidence—or at least that the jury will not satisfactorily perceive those defects."[176] Courts are particularly wary of opinion evidence offered by experts.[177]

Prior to the adoption of the Federal Rules of Evidence, all federal and most state courts followed the test set forth in *Frye v. United States* to determine the admissibility of scientific evidence.[178] Under the *Frye* test, scientific evidence was admissible only if such evidence was based on a principle that was "sufficiently established to have gained general acceptance in the particular field in which it belongs."[179] In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,[180] the United States Supreme Court held that the Federal Rules of Evidence, in particular FRE 702,[181] superseded the *Frye* test.[182] In *Daubert*, the Court held that the Federal Rules of Evidence did not

175. *See* FED. R. EVID. 402 (excluding irrelevant evidence); FED. R. EVID. 403 (excluding unfairly prejudicial evidence); FED. R. EVID. 802 (excluding hearsay evidence, with exceptions).

176. Ronald J. Allen et al., *Probability and Proof in* State v. Skipper*: An Internet Exchange*, 35 JURIMETRICS J. 277, 294 (1995) (quoting E-mail from Richard Friedman, Professor of Law, University of Michigan Law School, to bayesian-evidence@massey.ac.nz (Aug. 8, 1994)).

177. *See, e.g.*, Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 318 (7th Cir. 1996) (holding that courts must determine whether an expert's opinion "is genuinely scientific [or] unscientific speculation offered by a genuine scientist"); United States v. Addison, 498 F.2d 741, 744 (D.C. Cir. 1974) ("Scientific proof may in some instances assume a posture of mystic infallibility in the eyes of a jury of laymen."); Huntingdon v. Crowley, 414 P.2d 382, 390 (Cal. 1966) (acknowledging the existence of a "misleading aura of certainty which often envelops a new scientific process, obscuring its currently experimental nature"). *But see* MCCORMICK ON EVIDENCE 491 (Edward W. Oleary et al. eds., 2d ed. 1972) ("Any relevant conclusions which are supported by a qualified expert witness should be received unless there are other reasons for exclusion.").

178. 293 F. 1013 (D.C. Cir. 1923).

179. *Id.* at 1014; *see also* Paul C. Giannelli, *The Admissibility of Novel Scientific Evidence:* Frye v. United States*, A Half-Century Later*, 80 COLUM. L. REV. 1197, 1207 (1980) (citing People v. Barbara, 255 N.W.2d 171, 194 (Mich. 1977) ("It therefore is best to adhere to a standard which in effect permits the experts who know the most about a procedure to experiment and to study it. In effect, they form a kind of technical jury, which must first pass on the scientific status of a procedure before the lay jury utilizes it in making its findings of fact.")) ("[The *Frye* test] assures that those most qualified to assess the general validity of a scientific method will have the determinative voice." (quoting *Addison*, 498 F.2d at 743–44)).

180. 509 U.S. 579 (1993).

181. FED. R. EVID. 702; *see also supra* note 11 (setting forth FRE 702).

182. *Daubert*, 509 U.S. at 589.

incorporate the *Frye* standard.[183] To the contrary, the issue in a court's determination whether to admit scientific opinion testimony is whether the expert used reliable methods.[184]

Daubert introduced a "new era" in the scrutiny of expert testimony.[185] Prior to *Daubert*, the *Frye* "general acceptance" test stood in as a surrogate for reliability; after *Daubert*, the trial judge must directly assess reliability.[186] The Supreme Court recognized that expert testimony could be "both powerful and quite misleading because of the difficulty in evaluating it."[187] Faced with a proffer of expert scientific evidence, the trial court is now charged with the role of "gatekeeper," and must initially determine pursuant to FRE 104(a)[188] whether the expert is proposing to testify to scientific knowledge that will assist the trier of fact to understand or determine a fact in issue.[189] If so, the court must consider whether the

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183. *Id.*

184. *Id.* at 597.

185. Rice v. Cincinnati, New Orleans & Pac. Ry. Co., 920 F. Supp. 732, 736 (E.D. Ky. 1996). In at least some federal circuits, it is now necessary that, when faced with a *Daubert* challenge to proffered testimony, the trial court "must adequately demonstrate by specific findings on the record that it has performed its duty as gatekeeper." Goebel v. Denver & Rio Grande W. R.R., 215 F.3d 1083, 1088 (10th Cir. 2000). In other circuits, however, if no party raises an objection to proffered testimony, trial courts are not required to make "explicit on-the-record rulings. . . . [Appellate courts will] assume that the district court performs such analysis *sub silentio* throughout the trial with respect to all expert testimony." Hoult v. Hoult, 57 F.3d 1, 5 (1st Cir. 1995).

186. Daniel J. Capra, *The* Daubert *Puzzle*, 32 GA. L. REV. 699, 703 (1998); *see also* Lee Epstein & Gary King, *The Rules of Inference*, 69 U. CHI. L. REV. 1, 12 (2002) ("[After *Daubert*, judges] can no longer exclusively rely on a consensus in the scientific community to evaluate the quality of research presented by experts in their courtrooms. They are now also required to judge the research *themselves*, to evaluate its credibility, to assess its methods, and to appraise its design."). Professor Capra argues, persuasively, that although the "general acceptance" test may exclude novel, yet reliable, scientific evidence, this surrogate for reliability is nevertheless superior to direct reliability assessments by judges. Capra, *supra*, at 703 ("With all due respect to federal judges, the scientists in the field are probably in a better position to assess the reliability of complex scientific testimony. For this reason, some surrogate test or touchstone for admissibility must still be found—it is simply not enough to tell trial judges that they must determine whether expert testimony is 'reliable.'"). That said, general acceptance remains an important criterion within the *Daubert* inquiry. *Id.* at 705 ("In many cases . . . the acceptance factor may well be decisive, or nearly so. Thus, we expect that a technique that satisfies the *Frye* test usually will be found to be reliable as well. On the other hand, a known technique which has been able to attract only minimal support within the community is likely to be found unreliable." (quoting United States v. Downing, 753 F.2d 1224, 1238 (3d Cir. 1985))).

187. *Daubert*, 509 U.S. at 595 (quoting Judge Jack B. Weinstein, *Rule 702 of the Federal Rules of Evidence is Sound; It Should not be Amended*, 138 F.R.D. 631 (1991)).

188. "Preliminary questions concerning the qualifications of a person to be a witness . . . or the admissibility of evidence shall be determined by the court. . . . In making its determination it is not bound by the rules of evidence except those with respect to privileges." FED. R. EVID. 104(a).

189. *Daubert*, 509 U.S. at 592; *see also* Goebel v. Denver & Rio Grande W. R.R., 215 F.3d 1083, 1088 (10th Cir. 2000) ("[A] district court, when faced with a party's objection, must

proffered testimony meets the reliability and relevancy tests of FRE 702. The proponent of the proffered expert testimony bears the burden of establishing its admissibility by a preponderance of proof.[190] The focus of the *Daubert* inquiry is the expert's testimony, not the expert's credentials.[191] The Ninth Circuit recognized that "something doesn't become 'scientific knowledge' just because it's uttered by a scientist."[192]

FRE 702 contains two requirements. First, the evidence must be reliable, or in other words, trustworthy.[193] Trustworthiness guarantees that scientific methods and procedures support the information.[194] Second, the evidence must be relevant.[195] Courts have described the relevance criterion as one of "fit."[196] To satisfy this requirement, the proffered testimony or evidence must relate to the facts of the case in such a way that it will help the jury resolve

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adequately demonstrate by specific findings on the record that it has performed its duty as gatekeeper.").

190. *Daubert*, 509 U.S. at 592 n.10 (citing Bourjaily v. United States, 483 U.S. 171, 175–76 (1987)); Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1316 (9th Cir. 1995); Schmaltz v. Norfolk & W. Ry. Co., 878 F. Supp. 1119, 1120 (N.D. Ill. 1995); *see also* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1306, 1312 (11th Cir. 1999) ("[T]he proponent of the testimony does not have the burden of proving that it is scientifically correct, but that by a preponderance of the evidence, it is reliable."); Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001) ("[B]urden is on Plaintiffs to show that well-conducted epidemiology studies do show a statistically significant relationship [between disease and alleged agent]. It is not Defendant's burden to show the lack of such relationship.").

191. *See* FED. R. EVID. 702 advisory committee's note (2000) ("The trial court's gatekeeping function requires more than simply 'taking the expert's word for it.'"); *Goebel*, 215 F.3d at 1088 (citing DePaepe v. Gen. Motors Corp., 141 F.3d 715, 720 (7th Cir. 1998)) ("It is axiomatic that an expert, no matter how good his credentials, is not permitted to speculate."); Nat'l Bank of Commerce v. Assoc. Milk Producers, Inc., 22 F. Supp. 2d 942, 983 (E.D. Ark. 1998) (noting that "plaintiff's experts are highly credentialed in their fields," but nevertheless excluding their proffered opinions); Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 711 (Tex. 1997) (noting that the central issue in a *Daubert* challenge is scientific reliability of the proffered opinions, not the experts' credentials). *Contra* Ferebee v. Chevron Chem. Co., 736 F.2d 1529, 1534 (D.C. Cir. 1984) (stating, pre-*Daubert*, that "[o]n questions such as these, which stand at the frontier of current medical and epidemiological inquiry, if experts are willing to testify that such a link exists, it is for the jury to decide whether to credit such testimony").

192. *Daubert II*, 43 F.3d at 1315–16.

193. *Daubert*, 509 U.S. at 590 n.9; *see also* FED. R. EVID. 702 ("[A]n expert . . . may testify . . . if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case."); FED. R. EVID. 702 advisory committee's note (2000) (providing examples of several factors the courts have used to assess the reliability of proffered opinion testimony after *Daubert*).

194. *Daubert*, 509 U.S. at 590.

195. *Id.* at 591.

196. *Id.* (citation omitted).

a factual dispute.[197] "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility."[198]

In *Daubert* the Supreme Court provided four nonexclusive (and nondispositive) factors that trial courts should consider in making this determination under Rule 702. First, the court must evaluate whether the theory or technique can be, and has been, tested.[199] Second, the court must determine whether the theory or technique has been subjected to peer review and publication.[200] Third, the court must consider the known or potential rate of error.[201] Finally, as required under the superseded *Frye* test, the court must evaluate the general acceptance of the theory in the scientific community.[202] Upon remand of *Daubert*, the Ninth Circuit also con-

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197. *Id.*; *see also* Robinson v. G.D. Searle & Co., 286 F. Supp. 2d 1216, 1221 (N.D. Cal. 2003) (excluding causation expert's opinion that prescription drug caused plaintiff's rebound insomnia because expert was not privy to the fact that plaintiff experienced rebound insomnia prior to her first drug dose); Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 163 (E.D.N.Y. 2001) (holding that if expert testimony shows that toxic agent causes one type of disease, but plaintiff has another type of disease, testimony, though reliable, does not "fit" and is inadmissible), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

198. *Daubert*, 509 U.S. at 591–92; *see also* Lockheed Litig. Cases, 10 Cal. Rptr. 3d 34, 37 (Cal. Ct. App. 2004) (rejecting plaintiffs' argument that an epidemiologic study is the type of data experts rely on, and a causation expert's testimony based on one is, therefore, per se reasonable and admissible).

199. *Daubert*, 509 U.S. at 593; *see also* Brumley v. Pfizer, Inc., 200 F.R.D. 596, 602 (S.D. Tex. 2001) (citing FOSTER & HUBER, *supra* note 21, at 37–68) ("The 'testability' requirement is a threshold requirement aimed at excluding pseudoscience from the courtroom. A theory that is untestable is unfalsifiable and of no practical value in the courtroom. . . . But to stop the analysis at testability would allow in any theory, even one universally recognized as wrong, merely because it is falsifiable.").

200. *Daubert*, 509 U.S. at 593; *see also* Burleson v. Glass, 268 F. Supp. 2d 699, 705 (W.D. Tex. 2003) (excluding plaintiff's causation expert in part because his theory that exposure to thoriated tungsten welding rods could cause lung or throat cancer "has never been tested and never been submitted for peer review").

201. *Daubert*, 509 U.S. at 594; *see, e.g.*, *Burleson*, 268 F. Supp. 2d at 707 ("Defendants argue that the two-year period from alleged exposure to tumor onset supports their position that the potential for error with respect to [plaintiff's causation expert's] theory is high. The Court agrees.").

202. *Daubert*, 509 U.S. at 594. As one court noted, "[t]he decision in *Daubert* kills *Frye* and then resurrects its ghost." *In re* Joint E. & S. Dist. Asbestos Litig., 827 F. Supp. 1014, 1033 (S.D.N.Y. 1993). The *Daubert* rule requires the court to determine where the mainstream of scientific consensus lies. The novelty of a scientific opinion weighs against admissibility because "the courtroom is not the place for scientific guesswork even of the inspired sort. Law lags science; it does not lead it." Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996). As noted by the Superior Court of Arizona:

> The "general acceptance" issue can be addressed by permitting scientists to speak to the courts through their published writings and scholarly treatises and journals and that courts view such writings as "evidence" not of the actual reliability of the new scientific technique, but of its acceptance in the scientific community.

Lofgren v. Motorola, No. CV 93-05521, 1998 WL 299925, at *8 (Ariz. Super. Ct. June 1, 1998). The burden is on the proponent of the new theory to show a scientific consensus supporting its use. *Id.* Judicial review of scientific publications helps to distinguish the mainstream views from the fringe. "Even a person who knows nothing about hydrology can distinguish the mainstream of the Mississippi from stagnant pools near its banks." PETER W. HUBER, GALILEO'S REVENGE: JUNK SCIENCE IN THE COURTROOM 200 (1991).

Standing the "general acceptance" factor on its head, some courts in toxic tort cases have expressed the view that the law cannot wait for science to establish the requisite causal link between the subject agent and injury. For arguably the most egregious example of this flip, see Bonner v. ISP Techs., Inc., 259 F.3d 924 (8th Cir. 2001). In *Bonner*, a worker alleged that two occupational exposures several months apart caused her to suffer acute symptoms—nausea, headache, tiredness, respiratory problems, trembling, and skin irritation—and permanent brain damage and psychological problems. *Id.* at 927–30. A jury returned a verdict of $2.2 million for the plaintiff. *Id.* at 928. The defendant appealed on the ground that the trial court should have excluded the plaintiff's causation experts' opinions. Among other shortcomings, the defendant complained that the expert who testified as to the plaintiff's permanent brain damage, a neuropsychologist, lacked any established scientific support for his opinion that the chemical could cause the plaintiff's alleged permanent injuries. *Id.* at 931–32. Affirming the judgment, the Eighth Circuit did not refute the defendant's contention that the expert lacked established scientific support for his general causation opinions. Instead, the court deferred to the district court's finding of scientific validity. *Id.* at 932, and stated a relaxed evidentiary standard. *Id.* at 928. "[T]he first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed." *Id.* (quoting Turner v. Iowa Fire Equip. Co., 229 F.3d 1202, 1208–09 (8th Cir. 2000)). Thus, the Eighth Circuit believes that law leads science and that it can establish the plaintiff's causal link by judicial ukase. Not resting on its tortured tautology, the Eighth Circuit went on to state that the plaintiff's causation expert's novel conclusion was admissible in part because the defendant failed to prove the impossible, that is, that the subject agent "is incapable of causing permanent injury." *Id.* at 932. The Eighth Circuit thereby improperly shifted to the party challenging the proffered causation testimony the burden of proving the inadmissibility of the testimony, contrary to *Daubert*. *See supra* note 190 and accompanying text.

The Eighth Circuit justifies this burden shifting in the context of toxic tort cases with the emotional argument that the court cannot wait for the epidemiologic body counting. This view, too, is contrary to *Daubert*.

> We recognize that in practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will prevent the jury from learning of authentic insights and innovations. That, nevertheless, is the balance that is struck by the Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes.

Daubert, 509 U.S. at 597. Since future discovery of a heretofore unknown causal association is always possible, the Eighth Circuit's "law leads science" test will never exclude proffered opinion testimony on the ground that general causation evidence is lacking. *See* Chlorine Chemistry Council v. EPA, 206 F.3d 1286, 1290–91 (D.C. Cir. 2000) ("EPA cannot reject the 'best available' evidence simply because of the possibility of contradiction in the future by evidence unavailable at the time of action—a possibility that will *always* be present."). No one can know whether future research will show the alleged connection between the subject agent and the injury, contrary to the Eighth Circuit's presumption. Contrary to *Bonner*, and consistent with fairness, justice, logic, and *Daubert*, the Fifth Circuit averred: "We must resolve cases in our courts on the basis of scientific knowledge that is currently available."

sidered whether the expert's proffered testimony grew "naturally and directly" from research conducted independent of litigation and was thereby trustworthy, or whether the expert formed his opinion in the context of litigation, rendering the testimony suspect.[203]

Moore v. Ashland Chem. Inc., 151 F.3d 269, 276 (5th Cir. 1998), *rev'd en banc*, 151 F.3d 269 (5th Cir. 1998).

The injustice of the *Bonner* rationale is on display in the case law. Consider the numerous cases spanning the decades from the 1940s to the 1960s in which courts awarded plaintiffs damages grounded on the now disproved "traumatic cancer theory," which maintained that simple trauma could cause cancer. *See* HUBER, *supra*, at 39–56 (reviewing history of the trauma-induced cancer cases). These cases seem humorous today, yet the injustice visited upon numerous defendants in these cases who were in fact not responsible for the plaintiffs' cancers was a consequence of the same "law leads science" theory advanced by the *Bonner* court. Indeed, the *Bonner* court's reasoning echoes a trauma-cancer case in which the New Mexico Supreme Court proclaimed that it would not wait for medical evidence to establish an indisputable causal connection between the trauma and the cancer. White v. Valley Land Co., 322 P.2d 707, 711 (N.M. 1957). These decisions belie the view that "[b]ecause of the problems of identifying chemically induced disease, fewer people will be compensated than are actually harmed." Hall & Silbergeld, *supra* note 66, at 444. To the contrary, admitting opinions based on the mere possibility of general causation, such as in *Bonner* and the trauma-cancer cases, results in compensation to many plaintiffs not harmed by the agent at issue. Alchemists were right after all: one *can* create gold through pseudoscience, at least in some courtrooms.

203. Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1317 (9th Cir. 1995). The Ninth Circuit powerfully explained this important criterion for determining the reliability of the expert's testimony:

> That an expert testifies based on research he has conducted independent of the litigation provides important, objective proof that the research comports with the dictates of good science. *See* PETER W. HUBER, GALILEO'S REVENGE: JUNK SCIENCE IN THE COURTROOM 206–09 (1991) (describing how the prevalent practice of expert-shopping leads to bad science). For one thing, experts whose findings flow from existing research are less likely to have been biased toward a particular conclusion by the promise of remuneration; when an expert prepares reports and findings before being hired as a witness, that record will limit the degree to which he can tailor his testimony to serve a party's interests. Then, too, independent research carries its own indicia of reliability, as it is conducted, so to speak, in the usual course of business and must normally satisfy a variety of standards to attract funding and institutional support. Finally, there is usually a limited number of scientists actively conducting research on the very subject that is germane to a particular case, which provides a natural constraint on parties' ability to shop for experts who will come to the desired conclusion. *That the testimony proffered by an expert is based directly on legitimate, preexisting research unrelated to the litigation provides the most persuasive basis for concluding that the opinions he expresses were "derived by the scientific method."*

Daubert II, 43 F.3d at 1317 (emphasis added); *see also* Braun v. Lorillard Inc., 84 F.3d 230, 235 (7th Cir. 1996) ("[*Daubert* prevents] the hiring of reputable scientists, impressively credentialed, to testify for a fee to propositions that they have not arrived at through the methods that they use when they are doing their regular professional work rather than being paid to give an opinion helpful to one side in a lawsuit."); *Rosen*, 78 F.3d at 318 (commenting that a court's duty under *Daubert* is to weed out courtroom science from real science).

The U.S. Supreme Court clarified that:

> [N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* [bare authority] of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.[204]

It is now clear that the experts' conclusions, as well as their methodologies, are subject to the courts' scrutiny and excludable under *Daubert*.[205] "When a scientist claims to rely on a method practiced by most scientists, yet presents conclusions that are shared by no other scientist, the district court should be wary that the method has not been faithfully applied."[206] Some courts recognize that in a toxic tort case, the court's gatekeeping duty is "especially

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204. Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997); *see also* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1314 (11th Cir. 1999) ("[*Daubert* decisions] warn against leaping from an accepted scientific premise to an unsupported one."); Brumley v. Pfizer, Inc., 200 F.R.D. 596, 602 (S.D. Tex. 2001) (holding that an expert cannot rely on a study to support a conclusion that the study itself does not make).

205. *Joiner* modified *Daubert*, allowing trial judges to evaluate data offered to support the experts' bottom-line opinions to determine whether that data provide adequate support. *Joiner*, 522 U.S. at 146; *see also* Metabolife Int'l, Inc. v. Wornick, 264 F.3d 832, 845 (9th Cir. 2001) (allowing the district court, on remand, "to plumb the depths of the precise relationship between the materials cited and the conclusions drawn"); Ruiz-Troche v. Pepsi Cola of P.R. Bottling Co., 161 F.3d 77, 81 (1st Cir. 1998) ("[D]istrict courts must be careful not to 'don the amateur scientist's cap in ruling on scientific validity.' But, trial judges remain free to determine as a threshold question whether an expert is in fact predicating her conclusions on the scientific theory, procedure, or principle on which she purports to rely." (quoting Summers v. Mo. Pac. R.R. Sys., 132 F.3d 599, 604 (10th Cir. 1997))); Hall & Silbergeld, *supra* note 66, at 448 ("Courts should . . . scrutinize epidemiological evidence for reliability.") (citation omitted). *But see* Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314, 324 (Ill. 2002) (applying the *Frye* "general acceptance" standard as interpreted by Illinois courts, affirming trial court's admission of plaintiffs' causation expert's conclusion that exposure caused plaintiffs' cancers even though expert admitted that no scientific consensus supported her causation conclusion) ("'[G]eneral acceptance' does not concern the ultimate conclusion. Rather, the proper focus of the general acceptance test is on the underlying methodology used to generate the conclusion."). For an expression of the pre-*Joiner* "methods v. conclusions" dichotomy, compare Ferebee v. Chevron Chem. Co., 736 F.2d 1529, 1534 (D.C. Cir. 1984) ("Judges, both trial and appellate, have no special competence to resolve the complex and refractory causal issues raised by the attempt to link low-level exposure to toxic chemicals with human disease. On questions such as these, which stand at the frontier of current medical epidemiological inquiry, if experts are willing to testify that such a link exists, it is for the jury to decide whether to credit such testimony."), with Wilson v. Petroleum Wholesale, Inc., 904 F. Supp. 1188, 1191 (D. Colo. 1995) (refusing, pre-*Joiner*, to examine the analytical gap between the doctor's general causation opinion and the absence of scientific support).

206. Lust v. Merrell Dow Pharms., Inc., 89 F.3d 594, 598 (9th Cir. 1996).

sensitive" because a "jury may blindly accept an expert's opinion that conforms with their underlying fears of toxic substances without carefully understanding or examining the basis for that opinion."[207]

The ideal view is that "the primary goal of an expert witness is to convey knowledge to the court in a truthful and accurate manner."[208] As the gatekeeper of opinion testimony, however, the courts must take a more suspect view of proffered opinion testimony.[209]

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207. Whiting v. Boston Edison Co., 891 F. Supp. 12, 24 (D. Mass. 1995) (quoting O'Conner v. Commonwealth Edison Co., 807 F. Supp. 1376, 1391 (C.D. Ill. 1992)).

208. Andrew A. Marino & Lawrence E. Marino, *The Scientific Basis of Causality in Toxic Tort Cases*, 21 DAYTON L. REV. 2, 19 (1995).

209. *See, e.g.*, Newton v. Roche Labs., 243 F. Supp. 2d 672, 679 (W.D. Tex. 2002) ("[An expert of dubious qualifications] more closely fits the profile of an 'expert for hire' whose opinions are more likely to be biased."); Trigon Ins. Co. v. United States, 204 F.R.D. 277, 289 (E.D. Va. 2001) ("[Some experts] are of dubious assistance to the trier of fact . . . [and are] often less then [sic] helpful and sometimes misleading . . . ."). In a candid statement, two physicians who often appear in toxic tort cases as expert witnesses for plaintiffs stated that "[s]cientific testimony in court is offered on behalf of one side or another, and it does not represent consensus, but rather the opinion of the expert or experts involved." Daniel T. Teitelbaum & Nachman Brautbar, *Benzene and Multiple Myeloma: Appraisal of the Scientific Evidence*, 95 BLOOD 2995, 2996 (2000). Although unintended, this statement encapsulates the necessity for *Daubert* scrutiny of proffered opinion testimony. *Daubert* commands that, in court, science must do the speaking, not merely the scientist. Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1315–16 (9th Cir. 1995); *see also* Turpin v. Merrell Dow Pharms., Inc., 959 F.2d 1349, 1360 (6th Cir. 1992) (excluding plaintiff's expert's opinion because "personal opinion, not science, is testifying here"); Chambers v. Exxon Corp., 81 F. Supp. 2d 661, 665 (M.D. La. 2000) (stating that "[p]ersonal opinions" do not suffice as scientific evidence); Johnston v. United States, 597 F. Supp. 374 (D. Kan. 1984) (observing that when an expert becomes an advocate for a cause, the expert departs from the ranks of objective scientists). Assuming these experts practice what they publish, courts are well advised to carefully scrutinize their proffered testimony. Given their approach to opinion testimony, it is unsurprisingly that these physicians have been the targets of successful *Daubert* challenges. *See, e.g.*, *Joiner*, 522 U.S. 136 (excluding Dr. Teitelbaum's testimony that polychlorinated biphenyls (PCBs) caused plaintiff's lung cancer); Cabrera v. Cordis Corp., 134 F.3d 1418, 1422 (9th Cir. 1998) (excluding Dr. Brautbar's proffered testimony that plaintiff developed "autoimmune disease with atrophy" caused by silicone contained in a surgically implanted brain shunt); *Chambers*, 81 F. Supp. 2d 661 (excluding Dr. Brautbar's proffered testimony that plaintiff's occupational exposures to benzene caused plaintiff's chronic myelogenous leukemia); *In re* Ingram Barge Co., 187 F.R.D. 262 (M.D. La. 1999) (excluding Dr. Brautbar's proffered testimony that plaintiffs' occupational exposures to various solvents increased their risks of developing cancer); Nat'l Bank of Commerce v. Associated Milk Producers, Inc., 22 F. Supp. 2d 942 (E.D. Ark. 1998) (excluding Dr. Teitelbaum's proffered testimony that aflatoxins caused plaintiff's laryngeal cancer), *aff'd*, 191 F.3d 858 (8th Cir. 1999); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981, 986 (C.D. Cal. 1996) (excluding Dr. Brautbar's proffered testimony that plaintiff's occupational exposures to fragrances caused her to develop "multiple chemical sensitivity"); Leija v. Marathon Oil, No. 96-617531 (Mich. Cir. Ct. Feb. 15, 2000) (excluding Dr. Teitelbaum's proffered testimony based on a novel skin absorption model used to estimate the plaintiff's benzene dose); Austin v. Kerr-McGee Ref. Corp., 25 S.W.3d 280 (Tenn. Ct. App. 2000) (excluding Dr. Teitelbaum's proffered testimony that plaintiff's occupational exposures to benzene caused his chronic myelogenous leukemia).

Both truthfulness and accuracy are necessary for reliable scientific testimony. While in some circumstances the sincerity of expert witnesses may be an issue,[210] this Article addresses the reliability of honestly held opinions. Honest opinions held by competent expert witnesses may nevertheless be unreliable.[211] In toxic tort cases, failure to address the base-rate problem will lead to unreliable causation judgments. Such judgments may at times be correct, but they are not reliable because they fail to consider the crucial base-rate factor.[212] A causation analysis that ignores the base-rate problem is frequently inaccurate and always unreliable.[213]

In *Allen v. Pennsylvania Engineering Corp.*, the plaintiff's expert was as blunt as Drs. Brautbar and Teitelbaum when asked about his work in the case: "This is not a scientific study. This is a legal opinion." 102 F.3d 194, 198 (5th Cir. 1996). The *Allen* court responded:

> [T]he goal of *Daubert* and this court's previous cases has been to bring more rigorous scientific study into the expression of legal opinions offered in court by scientific and medical professionals. In the absence of scientifically valid reasoning, methodology and evidence supporting these experts' opinions, the district court properly excluded them.

Id.

210. *E.g.*, Claar v. Burlington N. R.R., 29 F.3d 499, 503 (9th Cir. 1994) ("[S]cientists whose conviction[s] about the ultimate conclusion of their research is so firm that they are willing to aver under oath that it is correct prior to performing the necessary validating tests [may] properly be viewed by the district court as lacking the objectivity that is the hallmark of the scientific method."); *see also Lust*, 89 F.3d at 597 (concluding that doctor's testimony "was influenced by a litigation-driven financial incentive"); Wills v. Amerada Hess Corp., No. 98 CIV.7126(RPP), 2002 WL 140542, at *10 (S.D.N.Y. Jan. 31, 2002) ("The paucity of support for his opinion in his First Report demonstrates that Dr. Bidanset was ready to form a conclusion first, without any basis, and then try to justify it."); Baxter Int'l, Inc. v. McGaw, Inc., No. 95 C 2723, 1996 WL 145778, at *4 (N.D. Ill. Mar. 27, 1996) (disregarding expert's report because expert did not prepare it), *aff'd in part and rev'd in part on other grounds*, 149 F.3d 1321 (Fed. Cir. 1998); Marbled Murrelet v. Pac. Lumber Co., 880 F. Supp. 1343, 1365 (N.D. Cal. 1995) (finding expert's testimony lacked objectivity and credibility because it was crafted by attorneys), *aff'd*, 83 F.3d 1060 (9th Cir. 1996); Occulto v. Adamar of N.J., Inc., 125 F.R.D. 611, 616 (D.N.J. 1989) (noting that expert cannot simply be alter ego of trial attorney). *Cf. Turpin*, 959 F.2d at 1351 (commenting on repeated appearances by the same causation experts in numerous Bendectin suits).

211. *See* PIATTELLI-PALMARINI, *supra* note 18, at 84 ("[A] witness can easily give false testimony in perfectly good faith. Between good faith and reliable testimony lie the heuristics and the blind spots we have been discussing[, such as ignoring the base rate].").

212. "The cognitive illusions shown up by this blind spot [of ignoring the base rate] are so universal and so pertinacious that we would be wise enough (and lucky enough) to remain in good health and never find ourselves wrongly accused of a crime we did not commit." *Id.* at 215–16. To that observation, one should add the corollary that one should be wise enough and lucky enough not to find oneself as a defendant in a toxic tort case wrongly alleged to have negligently exposed a sick person, or a dead person, to a toxic agent.

213. Admittedly, under *Daubert* courts may at times bar opinions that are in fact correct. Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 597 (1993) ("We recognize that, in practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will

B. Bayes' Law as a Component of Daubert *Scrutiny in Toxic Tort Cases*

It is crucial that judges (or their special masters) undertaking a *Daubert* inquiry in toxic tort cases understand Bayes' Law and apply it to the proffered testimony to determine its reliability. As the philosopher Philip Kitcher said: "If you ignore the base rate and follow some non-Bayesian process of reasoning you will almost certainly arrive at erroneous conclusions about your risk. Granting that people do not *naturally* perform the Bayesian computation, the significant points are that that computation improves their decision making and that they can be taught to do it."[214] All evidence is probabilistic.[215] "Overtly probabilistic evidence [such as base rates], however, makes the risk of error explicit."[216] Indeed, the known or potential error rate is one of the four express reliability factors set forth in *Daubert*.[217]

It is arguable that the rules of evidence *require* a judge to apply Bayesian analysis to determine the reliability of testimony. The Federal Rules of Evidence states:

> "Relevant evidence" means evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence.[218]

As stated by a National Research Council panel:

> From this rule one might infer that the court wishes and expects to have its judgments about facts at issue to be expressed in terms of probabilities. Such a situation is tailor-made for the application of Bayes' Theorem and the Bayesian form of

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prevent the jury from learning of authentic insights and innovations. That, nevertheless, is the balance that is struck by the Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes."); *see also* PIATTELLI-PALMARINI, *supra* note 18, at 21 (saying that judgments that are true may nevertheless be unreliable).

214. KITCHER, *supra* note 52, at 186 n.14; *see also* Koehler & Shaviro, *supra* note 19, at 267–68 (explaining that Bayes' theorem can be made intuitively plausible through examples and proved based on intuitively plausible principles).

215. *See id.*

216. *Id.* at 252; *see also* STATISTICAL EVIDENCE, *supra* note 18, at 4 ("[S]ince courts deal with uncertainty in reaching decisions, ... formal statistical theory can provide a proper framework for improving judicial decision making.").

217. 509 U.S. at 594.

218. FED. R. EVID. 401.

> statistical inference in connection with evidence. Thus some have characterized the Bayesian approach as *what the Court needs and often thinks it gets.*[219]

A Bayesian approach to evaluating proffered epidemiologic evidence would help avoid a frequent judicial misapprehension of the legal significance of Odds Ratios (OR) and Relative Risks (RR).[220] Some courts have held that epidemiologic studies must have an OR or RR of 2.0 or greater to support the plaintiff's contention that the exposure more likely than not caused the injury.[221] The reasoning is simple. The standard of proof on the issue of causation is by a preponderance of the evidence, that is, that the defendant's conduct "more likely than not" caused the plaintiff's injury.[222] In epidemiologic terms, this standard of proof requires an RR or OR of greater than 2.0. As explained in *Hall v. Baxter Healthcare Corp.*:

> The threshold for concluding that an agent was more likely the cause of a disease than not is relative risk greater than 2.0. Recall that a relative risk of 1.0 means that that agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other background causes. Thus, a relative risk of 2.0 implies a 50% likelihood that an exposed individual's disease was caused by the agent.[223]

From this viewpoint, only if the OR or RR exceeds 2.0 does the Attributable Risk exceed 50%, and only then may one conclude that a given injury among the study subjects is more likely than not a result of the exposure. Conversely, if the OR or RR is less than

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219. STATISTICAL EVIDENCE, *supra* note 18, at 193.

220. *See supra* Part V.A.1 (discussing Odds Ratio and Relative Risk).

221. *Id.*; *see also* ROBERT P. CHARROW & DAVID E. BERNSTEIN, SCIENTIFIC EVIDENCE IN THE COURTROOM: ADMISSIBILITY AND STATISTICAL SIGNIFICANCE AFTER *Daubert* 28–34 (1994) (contending that a relative risk of slightly more than 2.0 will rarely, if ever, satisfy the legal causation standard); Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 NW. U. L. REV. 643, 691 (1992) (concluding that in the absence of other information, a doubling of the risk found in epidemiology studies is inadequate to support a plaintiff's verdict, though lower risks may suffice if other risk factors can be eliminated).

222. *See supra* note 2.

223. 947 F. Supp. 1387, 1403 (D. Or. 1996); *see also* Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 717 (Tex. 1997) (holding that to be considered reliable scientific evidence of general causation, epidemiologic studies must, at a minimum, result in an RR of more than 2.0 and a statistically significant association).

2.0, any given case in the study population is less likely than not caused by the exposure.[224]

Other courts disagree. In a case where the plaintiff is able to eliminate most or all known or suspect risk factors other than the exposure at issue, the plaintiff could argue that an RR or OR of less than 2.0 is nevertheless admissible evidence that the agent caused the injury. As explained in the *Reference Guide on Epidemiology*:

> For example, genetics might be known to be responsible for 50% of the incidence of a disease independent of exposure to the agent. If genetics can be ruled out in an individual's case, then a relative risk greater than 1.5 might be sufficient to

224. An OR or RR greater than 2.0 in an epidemiology study does not mean that there is a greater than 50% chance that the plaintiff's disease was caused by the exposure. It means only that, among the study subjects, the risk of developing the disease exceeds the "base" or "background" risk. *See* James Robins & Sander Greenland, *The Probability of Causation Under a Stochastic Model for Individual Risk*, 45 BIOMETRICS 1125, 1126 (1989). The RR or OR of an epidemiology study does not apply to a plaintiff whose exposure circumstances are different than the subject of the epidemiology study. "Epidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?) rather than that of specific causation (i.e., did it cause disease in a particular individual?)." Green et al., *supra* note 64, at 336. As one commentator illustrated:

> Epidemiological studies can predict the risk of death from riding bicycles on roadways. But can the value of the risk be applied with confidence to an individual cyclist in a particular situation? The answer is certainly no. Such a value merely averages risk and does not take into account potentially pertinent factors such as the number of hours ridden per week, safety equipment worn, level of training, or type of roadway.

Melissa Moore Thompson, Comment, *Causal Inference in Epidemiology: Implications for Toxic Tort Litigation*, 71 N.C. L. REV. 247, 254 (1992); *see also* Heckman v. Fed. Press Co., 587 F.2d 612, 617 (3d Cir. 1977) ("[S]tatistical data about a group do not establish concrete facts about an individual."); David E. Bernstein, *The Admissibility of Scientific Evidence After* Daubert v. Merrell Dow Pharmaceuticals, Inc., 15 CARDOZO L. REV. 2139, 2165 (1994) ("In a case where a plaintiff alleges personal injury from exposure to a substance, the issue at hand is not whether the agent can potentially cause that injury. Rather, the issue is whether the agent caused the particular plaintiff's injury."), *quoted in Hall*, 947 F. Supp. at 1400. "External validity" concerns the appropriateness of applying epidemiological findings to persons outside the study. Sven Hernberg, *Validity Aspects of Epidemiological Studies*, *in* EPIDEMIOLOGY OF OCCUPATIONAL HEALTH 269, 269–73 (M. Karvonen & M.I. Mikheev eds., 1986). Since it is unlikely that the plaintiff was a subject of the epidemiology study, external validity requires an examination to determine whether it is appropriate to apply the results of an epidemiology study to the plaintiff. *See In re* Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124, 1131 (2d Cir. 1995) (observing that causation in toxic tort cases is usually subject to a two-step inquiry: (1) Does epidemiology evidence establish a causal link between agent and disease? and (2) Is plaintiff within class of persons to which inferences from general causation should be applied?); *Havner*, 953 S.W.2d at 720 (requiring plaintiffs to show that their circumstances were similar to those in relied-on epidemiology study).

> support an inference that the agent was more likely than not responsible for the plaintiff's disease.[225]

In *Grassis v. Johns-Manville Corp.*, the New Jersey court expressed this view:

> The physician or other such qualified expert may view the epidemiological studies and factor out other known risk factors such as family history, diet, alcohol consumption, smoking . . . or other factors which might enhance the remaining recognized risks, even though the risk in the study fell short of the 2.0 correlation.[226]

Similarly, the Second Circuit in *In re Joint Eastern & Southern District Asbestos Litigation* declined to adopt a threshold for a RR.[227] The court held that the trial court would instruct the jury on statistical significance, letting the jury decide whether a number of studies with RR's between 1.0 and 2.0 have significance in the aggregate.[228]

Our analysis shows that a plaintiff's causation expert can rely on epidemiology studies with ORs or RRs less than 2.0 so long as the expert's methods have sufficient specificity and are otherwise reliable. As a preliminary matter, it is important to note that the

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225. Green et al., *supra* note 64, at 386 (citations omitted); *see also* Carl F. Cranor et al., *Judicial Boundary Drawing and the Need for Context-Sensitive Science in Toxic Torts After* Daubert v. Merrell Dow Pharmaceuticals, Inc., 16 VA. ENVTL. L.J. 1, 37–40 (1996) (arguing that courts should not exclude epidemiologic evidence simply because the relative risk is less than 2.0, unless there is no other supporting evidence).

226. 591 A.2d 671, 675 (N.J. Super. Ct. App. Div. 1991).

227. 52 F.3d at 1134.

228. *Id.*; *see also* Allen v. United States, 588 F. Supp. 247, 418–19 (D. Utah 1984) (rejecting the fifty percent standard of causation in connection with statistical evidence); Oxendine v. Merrell Dow Pharms., Inc., 506 A.2d 1100 (D.C. 1986) (holding that an epidemiology study with a risk ratio between 1.3 and 1.8 with other supporting data was sufficient to get to the jury on the issue of causation); Landrigan v. Celotex Corp., 605 A.2d 1079, 1087 (N.J. 1992) ("[A] relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence, among others, for the court to consider determining whether the expert has employed a sound methodology in reaching his or her conclusion."). Some commentators have suggested that courts adjust the recoveries allowed toxic tort plaintiffs based on the RR found in the relied-upon epidemiology studies. *See* 2 AM. LAW INST., ENTERPRISE RESPONSIBILITY FOR PERSONAL INJURY 369–75 (1991) (suggesting proportionate compensation to all with a particular disease based on the attributable fractions of causation); Gold, *supra* note 5, at 397–401 (suggesting a compensation scheme that discounts recoveries to reflect uncertainty); Robins & Greenland, *supra* note 224, at 1131 (1989) (concluding that proportional liability schemes cannot be based on epidemiologic data alone). *But see* Daniel A. Farber, *Toxic Causation*, 71 MINN. L. REV. 1219, 1237–51 (1987) (suggesting, pre-*Daubert*, a "most likely victim" theory of recovery whereby plaintiffs whose injuries were most likely caused by defendants' conduct recover full compensation, while those whose claims are most speculative recover nothing).

Attributable Risk (AR, derived from the OR or RR of an epidemiology study) is a group statistic measuring the strength of association between an agent and a disease. The AR is not a measure of a particular person's odds of contracting a disease as a result of exposure to the agent.[229] In brief, the AR addresses *general* causation as opposed to *specific* causation. An RR or OR of less than 2.0 (resulting in an AR of less than 50%) indicates a weak association[230] and, thus, indicates that the putative association is less likely to be a real, causal association. Nevertheless, "strength of association," which RRs and ORs measure, is but one of the Bradford Hill criteria[231] and is not dispositive on the issue of general causation. Epidemiology studies consistently showing a positive, though weak, association between the agent and the disease can be persuasive evidence that the agent is capable of causing the disease in exposed persons. For example, a weak carcinogen that yields a low AR is nevertheless a real carcinogen. From a general causation viewpoint, an RR or OR less than 2.0 is not dispositive.

As seen in cases such as *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*,[232] and *Sanderson v. International Flavors & Fragrances, Inc.*,[233] courts use Relative Risks and Odds Ratios (and by implication the resulting ARs) derived in epidemiology studies as measures of specific causation—that is, as a measure of the odds that the subject exposures caused the plaintiffs' injuries in a particular case. Although not the true meaning of ARs, this use has some merit. We do not object to this use of ARs per se,[234] so long as the court recognizes that the plaintiff must first provide reliable evidence of general causation.

Assuming that the plaintiff has sufficient evidence of general causation, the court can then turn to the AR calculated from the relied-upon epidemiology studies to determine whether the plaintiff has reliable evidence of specific causation. At this step, we disagree that an OR or RR of at least 2.0 (that is, an AR of more than 50%) is a threshold for proof of specific causation. As argued in Part VIII.C.3.d, the proper Bayesian approach is to allow the plaintiff's expert to demonstrate that his or her causation analysis

229. *See supra* Part VI (discussing the application of epidemiologic group statistics to particular cases).

230. *See supra* note 96 (discussing "weak" and "strong" associations).

231. *See supra* Part V.A (discussing the Bradford Hill criteria).

232. 911 F.2d 941, 958–59 (3d Cir. 1990).

233. 950 F. Supp. 981, 1000 (C.D. Cal. 1996).

234. Scientists agree that ARs may be useful in this regard. *See* Hall & Silbergeld, *supra* note 66, at 445–46 (observing that epidemiologic studies carry inferences for specific causation analyses).

has sufficient reliability to reach the jury. To determine whether the proffered testimony is reliable, the court must consider the base rate of the agent-induced disease in the reference population—that is, the AR derived from the RR or OR found in the relied-on epidemiology study. Given that base rate and its relevance in the case, the expert must show that the causation analysis employed has sufficient specificity to detect those in the reference population who have the disease, but not as a result of exposure to the agent ("false positives"). If the rate of the agent-induced disease in the reference population drops below 50% (that is, if the OR or RR drops below 2.0), the opinion that the plaintiff's injury was more likely than not caused by the exposure becomes more difficult to support. Nevertheless, the opinion can be reliable if the expert's causation analysis is sufficiently and demonstrably specific. A blanket rule barring epidemiologic studies with ARs of 50% or less deprives causation experts the chance to show that their causation-determining methods are specific enough to limit "false positives" and achieve legally sufficient proof. Courts should allow—indeed, require—causation experts to show that their methods are sufficiently specific to overcome the base-rate problem.

This conflict among the courts may be more apparent than real. Many of the courts that apply an RR or OR threshold of 2.0 qualify this view, recognizing that plaintiffs may be able to eliminate certain alternative causative agents in their particular cases, thereby raising the odds that their injuries were induced by the subject agents. As explained in *Daubert II*, a case applying the 2.0 threshold:

> A statistical study showing a relative risk of less than two could be combined with other evidence to show it is more likely than not that the accused cause is responsible for a particular plaintiff's injury. For example, a statistical study may show that a particular type of birth defect is associated with some unknown causes, as well as two known potential causes—e.g., smoking and drinking. If a study shows that the relative risk of injury for those who smoke is 1.5 as compared to the general population, while it is 1.8 for those who drink, a plaintiff who does not drink might be able to reanalyze the data to show that the study of smoking did not account for the effect of drinking on the incidence of birth defects in the general population. By making the appropriate comparison—between

non-drinkers who smoke and non-drinkers who do not smoke—the teetotaller plaintiff might be able to show that the relative risk of smoking for her is greater than two.[235]

C. Sequential Uncertainties as a Component of Daubert *Scrutiny*

Under the *Daubert* holding, "*any* step that renders the analysis unreliable . . . renders the expert's testimony inadmissible. *This is true whether the step completely changes a reliable methodology or merely misapplies that methodology.*"[236] This logical point is an implicit recognition of the "sequential uncertainty" principle discussed in Part VII. Applied in a toxic tort case, this principle means that any unreliable or misapplied methodologic step in the expert's causation analysis renders the expert's ultimate opinion concerning specific causation unreliable and inadmissible pursuant to *Daubert*. Stated differently, the sequential uncertainty principle dictates that the probability of the ultimate link in a chain of events (in a toxic tort case, specific causation) is always less than the probability of the weakest link in the plaintiff's causation chain.[237] By necessity, if any link in the causal chain is unreliable, the plaintiff will be unable to bear the burden of proof.

An example of a case in which the court ignored this principle is *Hallahan v. Ashland Chemical Co.*[238] In *Hallahan*, the defendant chemical companies moved for summary judgment on the ground that there was no admissible evidence of an association between the plaintiff's disease, chronic myelogenous leukemia (CML), and human exposures to benzene.[239] The appellate court disagreed and affirmed the lower court's denial of the defendants' motion. The court reviewed the plaintiff's scientific evidence, which found a "suggestive increase in CML" reported among a series of benzene-exposed cases.[240] The plaintiff presented a recent epidemiology

235. Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1321 n.16 (9th Cir. 1995); *see also* Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1404 (D. Or. 1996) (applying an RR threshold of 2.0, but favorably citing *Daubert II* for the proposition that epidemiologic studies with an RR of less than 2.0 may be relevant under some circumstances).

236. FED. R. EVID. 702 advisory committee's note (2000) (quoting *In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 745 (3d Cir. 1994)); *see also* Heller v. Shaw Indus., Inc., 167 F.3d 146, 155 (3d Cir. 1999) (requiring that each stage of the expert's testimony be reliable).

237. *See supra* Part VII.

238. 699 N.Y.S.2d 612 (N.Y. App. Div. 1999).

239. *Id.* at 613.

240. *Id.* (quoting Song-Nian Yin et al., *A Cohort Study of Cancer Among Benzene-Exposed Workers In China: Overall Results*, 29 AM. J. INDUS. MED. 227, 232–33 (1996)).

study out of China that concluded: "[T]his study of benzene-exposed workers in China provides further support for the association of benzene exposure with an increased risk for myelogenous leukemia. The risk was strongest for AML [acute myelogenous leukemia], but an [statistically nonsignificant] excess of CML was also noted."[241] The Court concluded that the plaintiff's theory that his benzene exposure caused his CML "transcended 'the realm of mere speculation' . . . and was sufficient to raise a genuine factual issue as to the cause of plaintiff's disease."[242] In *Hallahan*, evidence that general causation is a mere possibility, somewhat more than speculation, sufficed for the plaintiff's case to reach the jury.

The plaintiff's evidence of general causation in *Hallahan* is facially unreliable.[243] A mere *possibility* that benzene can cause CML compels the conclusion that proof of specific causation (in this case, that the plaintiff's benzene exposure caused his CML) *must* fall short of the "more likely than not" standard of proof. As the principle of sequential uncertainties dictates, if the probability of the independent causal link of general causation (or any other independent causal link, for that matter) is less than 0.5, then the ultimate conclusion that the exposure caused the plaintiff's disease will be less than 0.5 even if the plaintiff establishes the remaining independent causal links with certainty (P = 1.0). In other words, the product of multiplying a probability of 0.5 or less by any other probabilities, even certainty (P = 1.0), will be at most 0.5. Finding a mere possibility of general causation, something a little better than

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241. *Id.*

242. *Id.* (citations omitted).

243. The proffered causation testimony is *facially* unreliable, because the *Hallahan* court apparently accepted the view that the plaintiff's evidence raised the mere possibility of general causation, that is, something less than probable. Thus, the court in effect allowed a jury to vote on the issue of specific causation based on evidence that the alleged causal association was less likely than not. In most toxic tort cases in which the parties present epidemiological evidence, the parties dispute the significance of the studies, the plaintiff arguing that the studies demonstrate a likely causal association between the agent and the disease, and the defendant arguing that the association is merely possible or unlikely. *See, e.g.*, Gen. Elec. Co. v. Joiner, 522 U.S. 136 (1997) (affirming district court's summary judgment in favor of defendant in part because epidemiologic studies offered in support of causation merely suggested the possibility that PCB exposure is associated with lung cancer). In essence, the *Hallahan* court accepted the typical defense view that the evidence raised a mere possibility of a causal association, but nevertheless held that a mere possibility of general causation was good enough to allow a jury to vote on specific causation. *See* Marino & Marino, *supra* note 208, at 8 & n.20 (opining that imposing on defendant the burden to show that the agent "can't cause" the injury is nearly impossible to bear). The *Hallahan* decision carries the implication that a defendant in a toxic tort case in which general causation is at issue faces, at the *Daubert* stage, the daunting task of proving the impossibility of general causation.

speculation, the *Hallahan* court should have dismissed the plaintiff's claim.

The mere possibility that benzene can cause CML passed admissibility muster in *Hallahan*, but not in *Austin v. Kerr-McGee Refining Corp.*,[244] or in *Chambers v. Exxon Corp.*[245] In *Austin*, the Texas Supreme Court affirmed the trial court's dismissal of the plaintiff's claim because her causation expert's opinions were unreliable pursuant to *Daubert* and its progeny.[246] The *Austin* court considered the same study central to the *Hallahan* court's holding, but judged it inadequate as evidence of general causation. The Texas Supreme Court noted that the study showed a statistically significant increased risk of leukemia generally, and AML specifically, among benzene-exposed workers. "The study showed, however, that the increase in . . . CML was not statistically significant."[247] The *Austin* court recognized what the *Hallahan* court missed: there were no studies cited by the plaintiff's causation expert that "recognized or posited that exposure to benzene causes CML specifically."[248] The scintilla of general causation evidence provided by the "China study" that there is a *possible association* between benzene and CML is facially unreliable specific causation evidence that there is a *probable causal association* between the decedent's CML and the decedent's benzene exposures.

Likewise, in *Chambers*, the federal district court noted that several studies mention the possibility that benzene exposure may cause CML, "but each one concludes that there was no statistically significant association between CML and exposure to benzene."[249] The "personal opinions" of plaintiff's experts "do not suffice as evidence" because "theories of toxic causation 'unconfirmed by epidemiological proof cannot form the basis for causation in a court of law.' "[250] Consequently, the court granted the defendant's motion in limine to exclude the opinion testimony of the plaintiff's causation experts.[251] The *Chambers* court recognized that the proffered testimony of the plaintiff's experts was pure *ipse dixit*. The underlying epidemiologic data suggested a mere possibility that benzene could cause CML, but the plaintiff's experts leapt across

244. 25 S.W.3d 280, 293 (Tex. App. 2000).
245. 81 F. Supp. 2d 661, 664 (M.D. La. 2000).
246. *Austin*, 25 S.W.3d at 293.
247. *Id.* at 290.
248. *Id.*
249. *Chambers*, 81 F. Supp. 2d at 664.
250. *Id.* at 665 (quoting Brock v. Merrell Dow Pharms., Inc., 874 F.2d 307, 315 (5th Cir. 1989)).
251. *Id.* at 666.

an analytical gap and concluded that benzene probably causes CML.[252]

D. Putting It Together: The Daubert *Test in Toxic Tort Cases*

Courts "must address the recurring issue of what is the quantity and quality of scientific evidence that a plaintiff must present on the issue of medical causation in a world of imperfect scientific knowledge."[253] That issue will continue to recur as courts judge the intrinsic reliability of proffered scientific and medical evidence supporting or refuting a causal link between a toxic agent and an injury. Courts will apply the reliability factors stated in *Daubert* and its progeny—testability, general acceptance, peer-reviewed publication, litigation independence, error rate, etc. Aside from the intrinsic reliability of the proffered evidence in toxic tort cases, however, there is an additional question: To pass the gatekeeper, what must intrinsically reliable scientific evidence show to substantiate the causation experts' opinions concerning the probability that the alleged exposures caused the plaintiff's injury? In other words, does the intrinsically reliable evidence show what the experts say it shows? Judging the *extrinsic* reliability of proffered evidence tests whether there is substantiation for the experts' opinions, or whether the opinions are unreliable *ipse dixit.* Put yet another way, is the proffered evidence reliable for the purpose given? The remainder of this Article addresses this issue of extrinsic reliability. This is the point of a *Daubert* inquiry where quantitative considerations such as Bayes' Law and sequential uncertainties come into play.

As a preliminary matter, it is important to stress that, at the *Daubert* phase, courts should not require the plaintiffs' causation experts to prove that the exposures more likely than not caused the plaintiffs' injuries. That is the standard of proof for the trier of fact to decide the ultimate question of specific causation. To the contrary, at the *Daubert* stage, the proponent of a causation opinion has the burden to prove a lesser assertion: that the proffered

252. *See* Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1360 (N.D. Ga. 2001) ("Mere possibility does not establish medical causation. Although an adverse case report is not required to 'rule out' every other possibility to have some reliability, it should do more than just fail to rule out the alleged cause.").

253. *Id.* at 1348.

causation opinion has reliable substantiation.[254] Reliability, not truth, is the extant issue. The *Daubert* focus, then, is on the data underlying the expert's opinions and the expert's extrapolations from the relied-on data. With this focus in mind, the question is what must the causation experts' evidence show, and what should be the standard for determining the admissibility of proffered expert causation opinions in a toxic tort case?

We present our proposed test for determining the extrinsic reliability of causation experts' opinions in toxic tort cases. After the court has applied the relevant qualitative *Daubert* factors to determine whether the underlying causation data are intrinsically reliable, the court should then determine whether the data are extrinsically reliable. The inquiry at this stage is whether the causation expert has reliable scientific evidence in support of an opinion that the truth of each independent link in the causal chain (diagnosis, general causation, and temporality) is highly probable, that is, "clear and convincing." Alternatively, if two of the three independent causal links are undisputed or otherwise shown to be true beyond a reasonable doubt, the experts' causation evidence passes scrutiny if the third independent causal link is shown to be true to a mere probability.

Then, if the experts' opinions survive this inquiry into the independent causal links, the court must judge the evidence offered in support of the "dependent" links of the specific causation analysis. The expert must have reliable evidence addressing: 1) the dose or exposure experienced by the plaintiff; 2) whether the plaintiff's dose or exposure exceeded the level generally hazardous to humans and capable of causing the subject injury; and 3) alternative causes and the predominance of the subject agent as the most likely cause of the injury based on quantitative causation analysis. The court must require the experts to produce reliable evidence addressing each one of these dependent links. The experts' specific causation opinions must be rational inferences drawn from the presented evidence.[255]

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254. "[P]rovability is a weaker notion than truth." DOUGLAS R. HOFSTADTER, GÖDEL, ESCHER, BACH: AN ETERNAL GOLDEN BRAID 19 (1979). In turn, reliability is a weaker notion than provability. *See* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1312 (11th Cir. 1999) ("[T]he proponent of the testimony does not have the burden of proving that it is scientifically correct, but that by a preponderance of the evidence, it is reliable.").

255. An authoritative textbook of cancer epidemiology suggests the following criteria for proof of causation that roughly parallel the criteria for evidence of causation suggested in this Article:

> Causality can be conclusively established between a particular exposure as an entity and a particular disease as an entity. In contrast, it is not possible to establish such a

To make clear, the causation expert need not show at the *Daubert* phase the truth of each of these factors with clear and convincing evidence.[256] Rather, the expert's burden at the *Daubert* phase is to show: 1) that there are reliable scientific data supporting the opinion that each independent causal link is true to a high probability; and 2) that the experts' specific causation conclusion rationally flows from the evidence presented. The court fulfills its gatekeeping duty by reviewing the scientific evidence presented by the expert witness to determine its reliability, considering the reliability factors and principles set forth in *Daubert* and its progeny. The expert's failure to produce reliable scientific evidence supporting the opinion that any one of the independent causal links is true to a high probability,[257] or failure to produce reliable scientific evidence that the agent most likely caused the plaintiff's injuries, would render the expert's opinions unreliable and inadmissible.

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link conclusively between an individual exposure and a particular disease of a given individual, for example, smoking in a patient with lung cancer. It is possible, however, to infer deductively that the specific individual's illness was *more likely than not* caused by the specified exposure. For this conclusion to be drawn, all of the following criteria must be met . . . : (1) The exposure under consideration, as an entity, must be an established cause of the disease under consideration as an entity . . . . (2) The relevant exposure of the particular individual must have properties comparable (in terms of intensity, duration, associated latency, etc.) to those that have been shown to cause the disease under consideration. (3) The disease of the specified person must be identical to, or within the symptomatologic spectrum of the disease that, as an entity, has been etiologically linked to the exposure. (4) The patient must not have been exposed to another established or likely cause of this disease. If the patient has been exposed to both the factor under consideration (for example, smoking) *and* another causal factor (for example, asbestos), individual attribution becomes a function of several relative risks, all versus the completely unexposed: (a) relative risk of those who only had the exposure under consideration, (b) relative risk of those who had only been exposed to the other causal factor(s), and, (c) relative risk of those who had a combination of these exposures. (5) The relative risks allow inferences about probabilities in individuals, provided that the association has been documented as unbiased, unconfounded, precise, and causal. This is because a relative risk has a baseline component equal to 1 that characterizes the unexposed and another component that applies only to the exposed.

Adami & Trichopoulos, *supra* note 10, at 108 (citing BRIAN MACMAHON & DIMITRIUS TRICHOPOULOS, EPIDEMIOLOGY: PRINCIPLES AND METHODS (1996)).

256. *See In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 744 (3d Cir. 1994) (observing that the proponent of opinions need not prove that the opinions are correct, but that they are reliable) ("The evidentiary requirement of reliability is lower than the merits standard of correctness.").

257. *See infra* Part VIII.D.2 (discussing a qualification of this proposed standard of proof).

Note that this standard of admissibility addresses the causation expert's extrapolation from "reliable" scientific evidence.[258] Before reaching this point of *Daubert* scrutiny, the court must weed out the intrinsically unreliable scientific data by application of the four express *Daubert* factors and other reliability factors developed by the courts following *Daubert*.[259] In many cases, the expert's proffered opinions may involve such unreliable methodologies as to render the opinions inadmissible before the court turns to the expert's extrapolations from the data (the extrinsic reliability).[260]

In the remainder of this Section, this Article will explain in more detail the proposed standard for admission of expert causation testimony in toxic tort cases. A discussion of each of the independent

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258. The *Joiner* Court made clear that an examination of the expert's extrapolations, as well as the expert's methods, is within the scope of a court's *Daubert* scrutiny. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit [bare authority] of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."); *see also* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1314 (11th Cir. 1999) ("[*Daubert* decisions] warn against leaping from an accepted scientific premise to an unsupported one."). *But see* Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314, 326–27 (2002) (citing pre-*Joiner* and pre-*Daubert* cases to hold, under Illinois law, that experts' conclusions, no matter how novel, are admissible so long as experts' methods are generally accepted).

259. *See supra* Part VIII.A (discussing the reliability factors considered by the *Daubert* Court and its progeny); *see also* Castellow v. Chevron USA, 97 F. Supp. 2d 780, 793 (S.D. Tex. 2000) (recognizing that expert's recalculations and changes of opinion during litigation "call into question the validity of his opinions and undermine the value of those calculations to a factfinder"); Downs v. Perstorp Components, Inc., 126 F. Supp. 2d 1090 (E.D. Tenn. 1999) (recognizing several "red flags" raised by plaintiff's causation expert's opinions, including the fact that the expert reached his conclusions before completing his research); 2 STEPHEN A. SALTZBURG ET AL., FEDERAL RULES OF EVIDENCE MANUAL, 702-23 to 702-38 (8th ed. 2001) (describing the seven "red flags" that insinuate unreliability of proffered expert opinions).

260. The "extrinsic reliability" criterion as applied to specific causation testimony suggested in this Article is analogous to the "fit" criterion established in *Daubert* and applied by subsequent courts. *See, e.g.*, Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1315–16 (9th Cir. 1995) (explaining that, post-*Daubert*, courts must determine not only whether the proffered testimony is "good science"—intrinsically reliable—but also "ensure that the proposed expert testimony is 'relevant to the task at hand,' i.e., that it logically advances a material aspect of the proposing party's case") (citation omitted). The Supreme Court referred to this second prong of the analysis as the "fit" requirement. *Id.* at 1321 n.17 (citing Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 591 (1993)). Whichever label, the issue is: Does the evidence actually support what the expert says? More particularly, does the expert have data supporting the opinion that the agent most likely caused the plaintiff's injury? Evidence that does not fit, that is, evidence that is extrinsically unreliable, is irrelevant and inadmissible even if intrinsically reliable. For example, a high-quality, large-scale epidemiology study that detects a statistically significant elevated risk of acute myelogenous leukemia (AML) in workers exposed to relatively high levels of benzene for twenty or more years may have intrinsic reliability, but lacks extrinsic reliability to support a claim that low-level, short-term occupational exposure to benzene probably caused a plaintiff's chronic myelogenous leukemia (CML).

links of the causal chain—diagnosis, general causation, and temporality—and the dependent links of specific causation—dose/exposure, threshold, and alternative causation follows. Then, the Article will discuss each of these causal links in the context of *Daubert* case law.

1. The Independent Links and Sequential Uncertainties—The independent links of the causation chain are diagnosis, general causation, and temporality. These links are independent in the sense that experts can reach conclusions concerning each one of them without reference to any other causal link. For example, a physician can reach a diagnosis of a disease without knowing when the patient was exposed to the agent or whether the agent is capable of causing the diagnosed disease. Similarly, an epidemiologist can determine whether the agent at issue is capable of causing a particular disease without knowledge of the physician's diagnosis in a particular case.

A valid analysis requires the court to separately consider these three independent causal links. As explained above, proper use of the sequential uncertainties principle, also known as the product rule, requires independence for each link in the causal chain, just as each flip of a coin is independent of all prior flips.[261] In counterpoint, the product rule does not apply to dependent links in a causal chain, such as the "exposure/dose" link and the related "threshold" link. These links are dependent because the latter link, addressing whether the exposure/dose in a particular case was sufficient to cause the injury, is dependent on the exposure/dose at issue.

It is the principle of sequential uncertainties that compels the standard of proof suggested above. To reiterate, this Article suggests that the court should require causation experts to produce reliable scientific evidence in support of an opinion that the truth of each independent link in the causal chain is highly probable, that is, "clear and convincing." Alternatively, if two of the three independent causal links are undisputed or otherwise shown to be true beyond a reasonable doubt, the experts' causation evidence passes scrutiny if the third independent causal link is shown to be true to a mere probability. Pursuant to sequential uncertainties, if each independent link is merely probable (say $P = 0.7$), then the probability of all three independent links being true would be less likely than fifty percent ($0.7 \times 0.7 \times 0.7$). On the other hand, if two

261. *See supra* Part VII (explaining "independent" events and the importance of the concept of independence in statistical analysis).

of the three independent links are uncontested (P = 1.0) or otherwise shown to be beyond reasonable doubt (say, P = 0.9), then the experts' causation chain remains intact so long as the third independent link is probable (P > 0.5).

In this analysis, the Article addresses various standards of proof, namely, "more likely than not," "probable," "clear and convincing," "highly probable," and "beyond reasonable doubt." These standards of proof require some explanation. Here, the Article takes a small detour to discuss them.

2. *Standards of Proof*—As discussed at the beginning of this Article, a toxic tort plaintiff must establish that exposures to the toxic agent probably caused the injury. The term "probable" is easy enough to understand, with a consistent definition in the disciplines involved in toxic tort cases: statistics, toxicology, medicine, and the law. In statistics, the term "probable" is designated as P > 0.5.[262] Toxicologic and epidemiologic researchers apply this statistical concept in their work. In essence, the meaning of the term "probable" in law is the same, stated in such phrases as "preponderance of the evidence," "more probable than not," or a "balance of probabilities."[263]

"[P]hrases such as 'clear and convincing,' 'clear, cogent, and convincing,' and 'clear, unequivocal, and convincing' have all been used to require a plaintiff to prove his case to a higher probability than is required by the preponderance-of-the-evidence standard."[264] On the other end of the proof scale, the "clear and convincing" standard does not rise so far as the "beyond a reasonable doubt" standard.[265] The "clear and convincing" standard is "an intermediate standard of proof."[266] In *Colorado v. New Mexico*, the United

262. *See, e.g.*, Knapp & Miller, *supra* note 23, at 17 (probability lies between 0 and 1; 0 means the event cannot occur; 1 means the event definitely will occur; 0.5 means that the event is equally probable to occur or not to occur).

263. "The first term[, preponderance of the evidence,] is the most common phrase used in the United States, while the latter ones are more common in England and Australia." Statistical Evidence, *supra* note 18, at 200. "Indeed, terms and phrases such as 'beyond a reasonable doubt,' 'preponderance of the evidence,' 'more likely than not,' and 'substantial probability of cause' are arguably subject to statistical representation and analysis." *Id.* at 4. Nevertheless, "[w]hile the use of statistics has burgeoned in court cases, this use has almost never extended to quantifying and analyzing the uncertainty reflected in legal terms." *Id.*

264. California *ex rel.* Cooper v. Mitchell Bros. Santa Ana Theatre, 454 U.S. 90, 93 n.6 (1981) (citation omitted).

265. Santosky v. Kramer, 455 U.S. 745, 756 (1982).

266. *Id.*; *see also* Cruzan v. Dir. of Mo. Dep't of Health, 497 U.S. 261, 282 (1990) (characterizing "clear and convincing" as an "intermediate standard of proof"); BLACK'S LAW DICTIONARY 577 (7th ed. 1999) ("[A clear and convincing evidence standard] indicat[es] that the thing to be proved is highly probable or reasonably certain. This is a greater burden

States Supreme Court stated that the clear and convincing evidence standard "place[s] in the ultimate factfinder an abiding conviction that the truth of [the] factual contentions are highly probable."[267] This standard of proof, applied to causation testimony as suggested in this Article, requires the plaintiffs' causation experts to produce reliable scientific evidence showing that each of the three independent causal links (diagnosis, general causation, and temporality) is highly probable.

Why do we suggest a "clear and convincing" level of evidentiary proof of each causal link at the *Daubert* stage? This suggestion is a consequence of sequential uncertainties. If any one of these links was merely probable, it would be impossible for the plaintiff to prove specific causation by a preponderance of the evidence (except as discussed in the next paragraph). For example, suppose that a causation expert has sufficient scientific data to demonstrate that it is merely probable, but not clear and convincing, that the subject agent is capable of causing the injury (that is, general causation). Let us set the probability of general causation in this hypothetical at 60%, that is, P = 0.6. Even if the remaining two independent causal links (temporality and diagnosis) are each assigned a very high probability of 90%, that is, P = 0.9, the overall probability drops below 0.5:

$$0.6 \times 0.9 \times 0.9 = 0.49,$$

meaning that the scientific evidence does not support the plaintiff's claim.

Admittedly, if scientific data show that two of the causal factors are true beyond a reasonable doubt, meaning each is true to a certainty of more than 95% ($P > 0.95$), the plaintiff's case can get past the *Daubert* stage if the evidence in support of the remaining factor's truth supports a conclusion of mere probability. Likewise, if the defendant does not challenge the admissibility of two of the causal links, the court may assume that the probability of the truth of the unchallenged links is 100%, and the causal chain passes *Daubert* scrutiny so long as the expert has evidence that the remaining causal link is probably true.

Based on this logic, we propose a standard for determining the extrinsic reliability of proffered causation testimony. As stated

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than preponderance of the evidence, . . . but less than evidence beyond a reasonable doubt . . . .").

267. 467 U.S. 310, 316 (1984).

above, and repeated here, courts exercising their gatekeeping function should require causation experts to produce *reliable scientific evidence demonstrating that the truth of each independent causal link (diagnosis, general causation, and temporality) is clear and convincing; or, if reliable scientific evidence demonstrates that the truth of two of the three independent causal links is uncontested or otherwise beyond a reasonable doubt, then the causation expert's opinion is admissible if reliable scientific evidence supports the truth of the remaining independent causal link to a mere probability.*

Even if the expert's testimony passes this scrutiny, the plaintiff may nevertheless be unable to prove that the subject agent probably caused his injury. That ultimate issue is for the trier of fact. But the testimony should not reach the trier unless the expert possesses reliable scientific evidence that the plaintiff's ultimate claim that the agent caused the injury is "reasonably possible."[268] Under the principle of sequential uncertainties, toxic tort plaintiffs establish a reasonable possibility that the subject agents caused their injuries only with reliable evidence that the causal links pass the *Daubert* inquiry suggested above.

3. The Causal Links—The following subsections discuss each of the links in the causation expert's chain of causation.

a. The Independent Link of Diagnosis—In most cases, the "diagnosis" link in the plaintiff's causation chain is among the strongest links, most easily demonstrated to be reliable.[269] In many toxic tort cases, the defendants do not challenge the medical doctors' diagnoses,[270] particularly when the diagnoses are formed independent

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268. In Marino & Marino, *supra* note 208, at 27, the authors suggest that the court's gatekeeping function is to determine whether the expert's testimony is "reasonably possible," and therefore reliable. Defining their terms, the authors state: " 'Possible' means only that the causal relationship is not impossible. In science, 'possible' can be applied to *any* asserted causal relation because none are impossible. The term 'reasonably possible' refers to causal statements whose probability of truth is greater than the naked minimum (anything greater than zero)." *Id.* at 23 (footnote omitted). "Any standard of truth greater than 'reasonably possible' would usurp the function of the trier of fact." *Id.* at 27. Marino and Marino's "reasonably" does not qualify "possible" in any meaningful way because the phrase still applies to anything that is at all possible, which—according to Marino and Marino—means it applies to any asserted causal relation. For this Article, the authors adopt a different and, we think, more useful definition of "reasonably possible." That is, the truth of the plaintiff's assertion that the exposure caused the injury is "reasonably possible" only if reliable scientific evidence demonstrates that each link in the causal chain is most probable.

269. *See In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 758 (3d Cir. 1994) ("[D]ifferential diagnosis generally is a technique that has widespread acceptance in the medical community, has been subject to peer review, and does not frequently lead to incorrect results.").

270. *See, e.g.*, Westberry v. Gislaved Gummi AB, 178 F.3d 257 (4th Cir. 1999) (involving plaintiff with severe sinus problems that required surgery); Zuchowicz v. United States, 140 F.3d 381, 383 (2d Cir. 1998) ("There is no doubt in the case before us either as to the injury or as to the defendant's wrong; both are conceded."); Ambrosini v. Labarraque, 101 F.3d 129 (D.C.

of the litigation. In such cases, the accuracy and reliability of the medical diagnosis are not at issue. The court may accept the diagnosis as proven, with a probability of 100% (P = 1.0).

Courts are highly deferential to physicians' conclusions based on differential diagnoses.[271] This deference is misplaced, given that a treating physician's testimony "is subject to the same standards of scientific reliability that govern the expert opinions of physicians hired for purposes of litigation."[272] In addition, a court should never defer to the plaintiffs' experts no matter what their qualifications are. In effect, such deference imposes on the defendant the burden of demonstrating the unreliability of the plaintiff's proffered medical causation testimony, contrary to the law.[273] Most important,

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Cir. 1996) (involving plaintiff with birth defects); McCullock v. H.B. Fuller Co., 61 F.3d 1038 (2d Cir. 1995) (involving plaintiff with throat polyps); Wilson v. Petroleum Wholesale, Inc., 904 F. Supp. 1188 (D. Colo. 1995) (involving plaintiff with hearing loss and tinnitus). The defendants in these cases conceded that the medical experts' differential diagnoses were reliable. The major issue in these cases was general causation: Could the alleged exposure have caused the plaintiff's disease? Thus, the physicians' differential diagnoses were not at issue.

271. *See, e.g.*, Hardyman v. Norfolk & W. Ry. Co., 243 F.3d 255, 260–61 (6th Cir. 2001) (reversing trial court's exclusion of doctor's causation testimony that plaintiff's carpal tunnel syndrome was occupationally induced) ("[D]ifferential diagnosis is an acceptable method of determining causation . . . ."); *Westberry*, 178 F.3d at 262–63 (finding that differential diagnosis is a tested methodology, subjected to peer review and publication, infrequently leading to incorrect results, and generally accepted in the medical community); Boren v. Burlington N. & Santa Fe Ry. Co., 637 N.W.2d 910, 920 (Neb. Ct. App. 2002) (citing *Westberry*, 178 F.3d 257) ("The admission of an expert opinion on causation based on differential diagnosis has been upheld by the federal courts.").

272. Turner v. Iowa Fire Equip. Co., 229 F.3d 1202, 1207 (8th Cir. 2000). Medical diagnoses are prominent in the debate as to whether, pursuant to *Daubert*, courts should assess the reliability of "technical" evidence in the same fashion as they assess the reliability of "hard science." *Compare* Jean Macchiavoli Eggen, *Clinical Medical Evidence of Causation in Toxic Tort Cases: Into the Crucible of* Daubert, 38 HOUS. L. REV. 369, 390–94 (2001) (arguing that a physician's diagnostic methods are not "hard science" and thus the *Daubert* factors do not apply), *with* Capra, *supra* note 186, at 706 ("[C]ourts that scrutinize nonscientific testimony less rigorously than scientific testimony risk drawing a questionable line between the two and encourage experts to evade the stricter *Daubert* factors by claiming to be nonscientific."). Indeed, as argued in this section, many courts improperly have conflated a physicians "scientific" causation analysis with their "technical" differential diagnosis and, consequently, have deferentially treated the causation opinions of physicians, according to them a less rigorous reliability analysis than accorded other causation scientists such as epidemiologists and toxicologists. *See supra* note 271. In *Kumho Tire Co. v. Carmichael*, the United States Supreme Court addressed this issue, holding that the Federal Rules of Evidence require courts to assess the reliability of *all* proffered opinions based on scientific or technical principles. 526 U.S. 137, 147–49 (1999). The specific language of Rule 702 requires no less. *See supra* note 11. However, the Court allowed lower courts to not apply all of the *Daubert* reliability factors—testability, peer review and publication, error rate, and general acceptance—to "technical" opinions. *Id.* at 150–51.

273. *See supra* note 2 (discussing the plaintiff's burden of proof on the issue of causation).

the deference is undeserved; differential diagnoses are often wrong, arguably among the least reliable of opinions allowed in front of a jury.[274] The unreliability of differential diagnosis increases in the context of litigation, where physicians are assisting claimants pursuing money damages (or assisting defendants avoiding payment of damages) rather than patients seeking treatment.[275]

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274. *See* EDMOND A. MURPHY, THE LOGIC OF MEDICINE 201 (2d ed 1997) (stating that the process of exclusion to arrive at a diagnosis is often abused and rarely justified); B. Ermenc, *Comparison of The Clinical and Post Mortem Diagnoses of the Causes of Death*, 114 FORENSIC SCI. INT'L 117 (2000) (comparing post-mortem diagnoses with clinical diagnoses and finding total agreement in 49.30% of diagnoses and total disagreement in 9.87% of cases); Lician L. Leape, *Error in Medicine*, 272 JAMA 1851, 1851 (1994) ("Autopsy studies have shown high rates (35 percent to 40 percent) of missed diagnoses causing death. . . . [A] 1 percent failure rate is substantially higher than is tolerated in industry, particularly in hazardous fields such as aviation and nuclear power. As W.E. Deming points out (written communication, November 1987), even 99.9 percent may not be good enough: 'If we had to live with 99.9 percent, we would have: 2 unsafe plane landings per day at O'Hare, 16,000 pieces of lost mail every hour, 32,000 bank checks deducted from the wrong bank account every hour.'"). In one study, researchers found that autopsy disproved 27% of the main clinical diagnoses, and in another 12% of cases, autopsies demonstrated that the main clinical diagnoses were merely subsidiary in contributing to death. H.M. Cameron & E. McGoogan, *A Prospective Study of 1152 Hospital Autopsies: I. Inaccuracies in Death Certificates*, 133 J. PATHOLOGY 273 (1981). "Experience has shown many ways in which clinical judgments can go awry." Farber, *supra* note 228, at 1257 (citing R. APFEL & S. FISHER, TO DO NO HARM: DES AND THE DILEMMAS OF MODERN MEDICINE 142 (1984)); *see also* TO ERR IS HUMAN: BUILDING A BETTER HEALTH SYSTEM 1 (Linda T. Kohn et al. eds., 2000) (asserting that between 44,000 and 98,000 patients die in hospitals each year as a result of medical errors). Some courts tacitly have acknowledged the weaknesses of differential diagnoses in the context of litigation by stating, tautologically, that a *reliable* differential diagnosis "does not frequently lead to incorrect results." *In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 758 (3d Cir. 1994). "If a *reliable* differential diagnosis does not frequently lead to incorrect results, consider the likelihood of an invalid result when the ruling out process is not so reliable." Sheldon Margulies, *The Differential Diagnosis: Its Use and Misuse*, FOR THE DEFENSE, Aug. 2002, at 14, 56.

275. Courts recognize that expert opinions offered in the courtroom, including medical opinions, are less reliable than those offered in practice, in research, and for peer review. *See, e.g.*, Daubert v. Merrell Dow Pharms., Inc. (*Daubert II*), 43 F.3d 1311, 1317 (9th Cir. 1995) (stating that one reliability factor to consider is whether the expert reached his or her opinion for the purpose of testifying, and that courts "may not ignore the fact that a scientist's normal work place is the lab or field, not the courtroom or the lawyer's office"); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 527 (W.D. Pa. 2003) ("Expert opinions generated as the result of litigation have less credibility than opinions generated as the result of academic research or other forms of 'pure' research."); Newton v. Roche Labs., 243 F. Supp. 2d 672, 679 (W.D. Tex. 2002) (observing that an expert of dubious qualifications "more closely fits the profile of an 'expert for hire' whose opinions are more likely to be biased"); Trigon Ins. Co v. United States, 204 F.R.D. 277, 289 (E.D. Va. 2001) (observing that some experts "are of dubious assistance to the trier of fact" and are "often less then [sic] helpful and sometimes misleading"). As stated in *Stolson v. United States*, "there is not much difficulty in finding a medical expert witness to testify to virtually any theory of medical causation short of the fantastic." 708 F.2d 1217, 1222 (7th Cir. 1983). Justice William O. Douglas expressed a blunt view on this topic: "[A] doctor for a fee can easily discover something wrong with any patient . . . . [A doctor's or psychiatrist's] report may either overawe or confuse the jury and prevent a fair trial." Schlagenhauf v. Holder, 379 U.S. 104, 125 (1964) (Douglas, J.,

The respective parties' attorneys retain experts to testify as to a particular opinion. Cases in which the defendant challenges the plaintiff's medical expert's diagnosis present the courts with antagonistic medical opinions concerning diagnoses. Someone is wrong. The court should not tip the scales by deferring to either party's medical causation experts.

Indeed, the courts' *Daubert* analysis must include scrutiny of the plaintiff's medical expert's diagnosis if challenged by the defendant with competent medical evidence. Bayesian analysis bears on this issue. Physicians should, and do, take into account the base rate of the disease in the population when determining the most likely disease afflicting an individual based on the signs and symptoms presented.

> [P]hysicians frequently rely on the principles of Bayesian reasoning when deciding on a diagnosis. Doctors combine probabilities of disease (prevalence) with their knowledge of the frequency of signs and symptoms in a given disease and competing diseases to progressively modify and ultimately

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dissenting in part). A lawyer who wants to tell a story to the jury can always find an expert to help. As Bernard Goldberg put it in the context of biased journalism: "[H]ere's one of those dirty little secrets journalists are never supposed to reveal to the regular folks out there in the audience: a reporter can find an expert to say anything the reporter wants—*anything*!" BERNARD GOLDBERG, BIAS: A CBS INSIDER EXPOSES HOW THE MEDIA DISTORT THE NEWS 20 (2002). Lawyers can do the same.

For a stark example of judicial skepticism of a litigation-dependent "differential diagnosis," see Reiff v. Denver Publ'g Co., No. 98-Z-1658, 1999 WL 1442047 (D. Colo. Dec. 23, 1999). In *Reiff*, the plaintiff's retained medical expert conducted a "differential diagnosis" and determined that the plaintiff's short-term, occupational exposure to lacquer thinner caused certain acute symptoms. *Id.* at *5–6. The medical witness relied solely on the plaintiff's oral medical history presented to him in the context of litigation, years after the exposure incident. *Id.* at *6. The court observed that a medical history given independent of litigation is generally reliable, "based on the reasonable assumption that patients who are seeking diagnosis and treatment for a medical illness would not fabricate their symptoms." *Id.* The court, however, would not extend this assumption of reliability to the plaintiff's oral history underlying the medical expert's "differential diagnosis." Under the circumstances, the court concluded that the plaintiff did not appear in the doctor's office "for diagnosis and treatment of any illness or symptoms," but rather "for purposes of assisting in this lawsuit." *Id.* at *6–7. Thus, the court excluded the medical witness's opinions based on this "sham" consultation. *Id.*

For a clear example of judicial preference for litigation-independent diagnosis of the plaintiff's treating physicians as compared with the retained expert's diagnosis reached in the context of litigation, see *Sepulveda v. HHS*, No. 92-349V, 1995 WL 502887 (Fed. Cl. Aug. 10, 1995). "It is difficult to believe that the treating physicians, who worked so hard to determine a diagnosis for petitioner, and who specifically noted the particular cranial nerve involvement petitioner endured, simply missed the diagnosis of bulbar poplio [offered by petitioner's retained medical expert]." *Id.* at *3.

> arrive at their view of the likelihood of the disease under consideration."[276]

Courts should consider the specificity of the plaintiff's medical expert's observations and tests. Did the expert consider the prevalence of the diagnosed disease and the prevalence of other diseases manifesting the same signs and symptoms? How did the expert eliminate competing diseases as the most likely disease? These are the types of questions that toxic tort defendants should raise when challenging the plaintiff's medical diagnosis, and that the court should consider in its *Daubert* analysis.

The plaintiff's claim faces serious trouble if the defendant asserts a legitimate challenge to the medical expert's diagnosis. Such cases frequently result in summary judgment for the defendant because an unreliable diagnosis overlays other weak causal links. For example, in *Downs v. Perstorp Components Inc.*, a chemical splashed on the plaintiff's arms and face causing an immediate burning sensation.[277] Later, the plaintiff allegedly experienced neurological symptoms and sought treatment from Dr. Kaye Kilburn, who diagnosed chemical encephalopathy and opined that the chemical splash had caused the injury.[278] The magistrate judge excluded Dr. Kilburn's proffered causation opinion, finding that it failed to meet *Daubert*'s reliability test.[279] The appellate court affirmed summary judgment for the defendants, finding that Dr. Kilburn relied on unorthodox neurological and neuropsychological tests in reaching his diagnosis.[280] In addition, Dr. Kilburn could not cite a single scientific study suggesting that the chemical could cause toxic encephalopathy.[281] *Downs* exhibits a typical pattern: an

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276. Mary Sue Henifin et al., *Reference Guide on Medical Testimony*, *in* REFERENCE MANUAL, *supra* note 44, at 439, 467.

277. 26 F. App'x 472, 474 (6th Cir. 2002).

278. *Id.*

279. *Id.*

280. *Id.* at 475–76.

281. *Id.* at 476. Dr. Kilburn's dismal track record in *Daubert* and *Frye* challenges may well have played a part in the *Downs* court's rejection of his neurological opinions. Prior to *Downs*, numerous courts had held that Dr. Kilburn's proffered opinions were unreliable and inadmissible. *See, e.g.*, Nelson v. Tenn. Gas Pipeline Co., 243 F.3d 244 (6th Cir. 2001); Valentine v. Pioneer Chlor Alkali Co., 921 F. Supp. 666 (D. Nev. 1996); Thomas v. FAG Bearings Corp., Inc., 846 F. Supp. 1400 (W.D. Mo. 1994); Weaver v. Shoals Pest Control, No. CV-92-000287 (Ala. Cir. Ct. Aug. 25, 1999), *aff'd*, 787 So. 2d 722 (Ala. 2000); Lofgren v. Motorola, No. CV 93-095521, 1998 WL 299925 (Ariz. Super. Ct. June 1, 1998); Goeb v. Tharaldson, No. C3-92-602051 (Minn. Dist. Ct. Feb. 4, 1998), *aff'd*, No. CX-98-2275, 1999 WL 561956 (Minn. Ct. App. Aug. 3, 1999), *aff'd*, 615 N.W.2d 800 (Minn. 2000); Griffin v. Mont. Rail Link, Inc., No. DV-98-86150, 2000 Mont. Dist. LEXIS 1320 (Mont. Dist. Ct. Sept. 28, 2000); *see also* Georgine v. Amchem Prods., Inc., 157 F.R.D. 246, 271 (E.D. Pa. 1994) (rejecting Dr. Kilburn's opinion that a settlement agreement was unfair to asbestos-exposed workers, in part

unreliable general causation opinion often accompanies an unreliable diagnosis.[282]

As a general rule, only physicians can offer medical diagnoses in court.[283] Other scientists, however, can opine on other causal links,

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because Dr. Kilburn's "diatribe . . . appeared immoderate and contrary to the weight of the scientific evidence and therefore unpersuasive").

282. *See, e.g.*, Cabrera v. Cordis Corp., 134 F.3d 1418 (9th Cir. 1998) (excluding opinion that plaintiff developed "autoimmune disease with atrophy" caused by silicone contained in a surgically implanted brain shunt); Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147 (E.D.N.Y. 2001) (excluding questionable diagnosis of plaintiff's chronic neurological condition that lacked reliable scientific evidence that acute exposure to organic solvents could cause such conditions), *aff'd*, 303 F.3d 256 (2d Cir. 2002); Grant v. Bristol-Myers Squibb, 97 F. Supp. 2d 986, 992 (D. Ariz. 2000) (excluding causation opinion because experts were unable to specify criteria for diagnosing "atypical syndrome" caused by breast implants) ("[W]here experts propose that breast implants cause a disease but cannot specify the criteria for diagnosing the disease, it is incapable of epidemiological testing."); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981 (C.D. Cal. 1996) (excluding opinion that plaintiff's occupational exposures to fragrances caused her to develop "multiple chemical sensitivity").

283. *See, e.g.*, *In re* TMI Litig., 193 F.3d 613, 683 (3d Cir. 1999) (affirming the trial court's exclusion of plaintiff's retained expert on specific causation because the expert was not a medical doctor), *amended by*, 199 F.3d 158 (3d Cir. 2000); Newton v. Roche Labs., Inc., 243 F. Supp. 2d 672 (W.D. Tex. 2002) (excluding expert's testimony that acne drug caused psychiatric injury because, though he held himself out as a pharmacologist, expert had no degree in pharmacology and had conducted no clinical research); Plourde v. Gladstone, 190 F. Supp. 2d 708 (D. Vt. 2002) (holding toxicologist not competent to perform "differential diagnosis"), *aff'd*, No. 02-9136, 2003 WL 21511764 (2d Cir. June 27, 2003); Magdaleno v. Burlington N. R.R., 5 F. Supp. 2d 899 (D. Colo. 1998) (holding non-physician ergonomist unqualified to opine as to cause of plaintiff's carpal tunnel syndrome); Whiting v. Boston Edison Co., 891 F. Supp. 12, 19 & n.30 (D. Mass. 1995) (holding epidemiologist unqualified to testify as to specific cause of a person's disease).

In *In re TMI Litigation*, the expert, James Gunckel, Ph.D. and Distinguished Professor Emeritus at Rutgers University, had been Chairman of the Radiation Science Center, Chairman of the Department of Radiation and Environmental Health and Safety, and Chairman of the Health Safety Council. 193 F.3d at 678. He offered to testify that residents in the vicinity of the Three Mile Island nuclear reactor at the time of the accident were exposed to radiation doses sufficient to cause erythema. *Id.* at 679. Despite his expertise in the area of ionizing radiation, the Third Circuit affirmed the trial court's exclusion of Gunckel's specific causation testimony. *Id.* at 683.

> Although Gunckel is a respected scientist, he is neither a medical doctor nor a health physicist. So far as the record is concerned, his only knowledge of the health effects of radiation was obtained from literature he reviewed in connection with his retention as an expert in this litigation. He plainly does not meet Rule 702's "Qualifications" requirement and cannot, therefore, offer an expert opinion as to radiation-induced medical conditions.

Id. at 680 (citations omitted).

More precisely, only physicians can offer diagnostic opinions concerning *human* illnesses. *See* Bitler v. A.O. Smith Corp., 391 F.3d 1114, 1123 (10th Cir. 2004) (labeling engineers' causation analysis as "nonmedical differential diagnosis"); *cf.* Clausen v. M/V New Carissa, 339 F.3d 1049, 1052–53 (9th Cir. 2003) (affirming admission of "differential diagnoses"

particularly general causation. Consequently, it is important to distinguish "differential diagnoses" and "causation analyses," a distinction often missed by courts. In a differential diagnosis, a physician observes the symptoms and signs displayed by the patient and conducts appropriate examinations and tests to arrive at a diagnosis of the patient's disease.[284] In contrast, a causation analysis is an expert's method of determining by scientific means the most likely cause of the disease. For example, an oncologist as a matter of course conducts tests to determine the type of cancer causing the plaintiff's symptoms (differential diagnosis), but seldom engages in research to determine the cause of the tumor's occurrence in the patient (causation analysis).[285] Many courts confuse the concepts of differential diagnosis and causation analysis.[286]

In one case, the United States Court of Appeals for the Eighth Circuit distinguished between the treating doctor's differential diagnosis and his causation analysis:

> Dr. Hof acknowledged that the differential diagnosis he performed was for the purpose of identifying Delores Turner's *condition*, not its *cause*. He admitted that he made no attempt to consider all the possible causes, or to exclude each potential cause until only one remained, or to consider which of two or more non-excludable causes was the more likely to have caused the condition.

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performed by aquatic biologists offered by both parties, each of whom offered differing opinions concerning the cause of oyster deaths).

284. *See* Turner v. Iowa Fire Equip. Co., 229 F.3d 1202, 1208 (8th Cir. 2000) (citing STEDMAN'S MEDICAL DICTIONARY 474 (26th ed. 1995)) (defining differential diagnosis as a systematic comparison of symptoms to determine the patient's disease).

285. *See, e.g.*, Medalen v. Tiger Drylac U.S.A., Inc., 269 F. Supp. 2d 1118 (D. Minn. 2001). In *Medalen*, the plaintiff's medical witness answered the defense counsel's question as to whether he attempted to determine the etiology of the plaintiff's basal cell carcinoma with: "I didn't attempt to determine it, because it really wouldn't impact treatment." *Id.* at 1137.

286. *See, e.g.*, Hardyman v. Norfolk & W. Ry. Co., 243 F.3d 255, 260–61 (6th Cir. 2001) (referring to physician's causation analysis as "differential diagnosis"); Westberry v. Gislaved Gummi AB, 178 F.3d 257, 262 (4th Cir. 1999) (describing differential diagnosis as a technique that identifies causes of medical conditions by eliminating likely causes until the most likely cause remains); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 609 (D.N.J. 2002); Wilson v. Petroleum Wholesale, Inc., 904 F. Supp. 1188, 1190 (D. Cal. 1995); Boren v. Burlington N. & Santa Fe Ry. Co., 637 N.W.2d 910, 920 (Neb. Ct. App. 2002) (stating that causation testimony based on differential diagnosis "has been upheld by the federal courts" (citing *Westberry*, 178 F.3d at 257)); *see also* 2 SALTZBURG ET AL., *supra* note 259, at 702-32 (describing differential diagnosis as "excluding other causes, such as genetics or other toxins, for a certain disease").

> As a treating physician, Dr. Hof wanted to identify Delores Turners' [sic] condition so he could treat it. Dr. Hof's diagnosis was, we believe, one which the medical community more properly identifies as "differential," *see, e.g.*, Stedman's Medical Dictionary 474 (26th ed. 1995) (identifying differential diagnosis as a systematic comparison of symptoms to determine which of two or more *conditions* is the one from which a patient is suffering), rather than the type of *causal* diagnosis which the legal community calls "differential," *see, e.g.*, *Westberry*, 178 F.3d at 262 (identifying differential diagnosis as a technique that identifies the cause of a medical condition by eliminating the likely causes until the most probable cause is isolated).[287]

Boiled down to essentials, a real, *medical* differential diagnosis determines a patient's disease based on signs and symptoms,[288] while a

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287. *Turner*, 229 F.3d at 1208; *see also* Lawrence v. Synthes Inc., No. 1623 EDA 2003 (Pa. Super. Ct. Aug. 10, 2004) (rejecting plaintiff's contention that differential diagnosis can determine causation because differential diagnosis addresses what a condition is and how to treat it, while causal assessment determines how a condition arose).

288. For medical texts that define "differential diagnosis" consistently with the definition employed in this Article, see STEPHEN N. ADLER ET AL., A POCKET MANUAL OF DIFFERENTIAL DIAGNOSIS, at xv (3d ed. 1994) ("In the practice of clinical medicine, one encounters a variety of symptoms, signs, and laboratory tests. Each clinical finding and test result is associated with a differential diagnosis; that is, a list of conditions or disease entities that can produce the given finding or result."); BECOMING A CLINICIAN 40 (Shirley Neitch & Maurice Murson eds., 1998) ("A differential diagnosis is a list of possible disease processes which may explain the etiology of a patient's complaint."); CECIL TEXTBOOK OF MEDICINE 59 (J. B. Wyngaarden & L. H. Smith, Jr. eds., 17th ed. 1985) ("For each diagnosis considered, the physician weighs information favoring that possibility against information that makes the diagnosis unlikely. Consideration of alternative possibilities in the differential diagnosis is helpful in directing the physician to select diagnostic studies that confirm or exclude each possible diagnosis."); CLINICAL MEDICINE 13 (Harry L. Greene et al. eds., 2d ed. 1996) ("A full diagnosis should answer the following questions: Is the identified disease(s) the explanation of the patient's signs and symptoms?"); R. DOUGLAS COLLINS, DYNAMIC DIFFERENTIAL DIAGNOSIS, at xiii (1981) ("The basic premise of teaching differential diagnosis is that the causes of each symptom can be analyzed by one or more of the basic sciences of anatomy, histology, physiology, and biochemistry."); LEONARD V. CROWLEY, INTRODUCTION TO HUMAN DISEASE 6 (4th ed. 1997) ("In a *differential diagnosis*, the practitioner considers a number of diseases that are characterized by the patient's symptoms."); RICHARD L. DEGOWIN & DONALD D. BROWN, DEGOWIN'S DIAGNOSTIC EXAMINATION 2 (7th ed. 2000) ("The clues that are found suggest a list of problems from which is generated hypotheses to explain the cause of the problems in terms of diseases in a list called the *differential diagnosis*."); DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 369 (W.B. Saunders ed., 26th ed. 1981) (defining differential diagnosis as "the determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings"); FRENCH'S INDEX OF DIFFERENTIAL DIAGNOSIS, at Preface Page (I.A.D. Bouchier et al. eds., 13th ed. 1996) ("The guiding principle throughout has been to suppose that a particular symptom attracts special notice

so-called *legal* differential diagnosis is in fact a causation analysis, which is the determination of the most likely cause of a plaintiff's injury.

This confusion has consequences. It is important to distinguish these two procedures because, as is often held, only medical experts (usually physicians) are qualified to provide testimony concerning differential diagnoses.[289] On the other hand, causation analyses require input from other scientific health disciplines, such as toxicology and epidemiology.[290] The reliability of a physician's

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in a given case, and that the diagnosis has to be established by differentiating between the various diseases to which this symptom may be due."); MOSBY'S MEDICAL, NURSING, & ALLIED HEALTH DICTIONARY 522 (6th ed. 2002) (defining differential diagnosis as "the distinguishing between two or more diseases with similar symptoms by systematically comparing their signs and symptoms"); TABER'S CYCLOPEDIC MEDICAL DICTIONARY 581 (19th ed. 1997) (defining differential diagnosis as "identification of a disease by comparison of illnesses that share features of the presenting illness, but differ in some critical ways"); TEXTBOOK OF GENERAL MEDICINE 6 (Mahendr Kochar ed., 1983) ("The most common and important use of laboratory tests is diagnostic. Physicians use them as aids in selecting the most likely diagnosis from a list of several possibilities that may have been suggested by the history and physical examination, that is, in making the differential diagnosis."); THE PRINCIPLES AND PRACTICE OF MEDICINE 20 (A. McGehee Harvey et al. eds., 21st ed. 1984) ("Indications for further or more intensive examination may arise from consideration of the differential diagnosis. . . . It is common practice to select laboratory tests on the basis of the diagnostic possibilities under consideration.").

289. *See, e.g.*, Smelser v. Norfolk S. Ry. Co., 105 F.3d 299, 305 (6th Cir. 1997) (limiting biomechanics expert's testimony because, though he was qualified to determine injury-causing forces in general, he was not qualified to render medical opinions regarding the cause of plaintiff's injuries); Gates v. United States, 707 F.2d 1141, 1144–45 (10th Cir. 1983) (holding that a non-physician with a doctorate in immunology and professorship in pathology was not qualified to attribute the plaintiff's injury to swine flu vaccine); Niklaus v. Vivadent, Inc., U.S.A., 767 F. Supp. 94, 96 (M.D. Pa. 1991) (holding that a Ph.D. in visual science was not qualified to make a medical diagnosis of an eye condition). *But see* Martin v. Shell Oil Co., 180 F. Supp. 2d 313, 320 (D. Conn. 2002) (allowing plaintiffs' toxicology expert to opine that the subject chemical agent caused the plaintiffs' injuries).

290. At least two commentators have opined that physicians are *unqualified* to conduct causation analysis. *See* Marino & Marino, *supra* note 208, at 12–14, 14 n.33 (distinguishing between "scientific" methods and "medical" methods) ("Courts have rarely recognized the impropriety of physicians testifying to causal links that are determinable only by the methods of science rather than medicine."); *see also* Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1363 (N.D. Ga. 2001) ("With respect to general causation, the relevant scientific field is epidemiology or toxicology and not clinical medicine."); Mason v. Texaco, Inc., 741 F. Supp. 1472, 1497 (D. Kan. 1990) (finding that scientists are more qualified than physicians to testify as to causation), *rev'd on other grounds*, 948 F.2d 1546 (10th Cir. 1991); Ballentine v. The Terminex Int'l Co., No. 98C-836 (Tenn. Cir. Ct. June 25, 2004) (excluding causation opinions of physicians because they were not toxicologists); *cf.* Cloud v. Pfizer, Inc., 198 F. Supp. 2d 1118, 1134 (D. Ariz. 2001) ("[A] physician cannot rely on general experience to give reliable statistical evidence." (citing Erickson v. Baxter Healthcare, Inc., 131 F. Supp. 2d 995, 999 (N.D. Ill. 2001))); Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 159 (E.D.N.Y. 2001) (excluding industrial hygienist's causation testimony because he was not an epidemiologist), *aff'd*, 303 F.3d 256 (2d Cir. 2002). *But see* Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 611 (D.N.J. 2002) (rejecting plaintiff's argument that defendants' retained physicians could not testify on medical causation because they

differential diagnosis depends on the quality of the physician's clinical methods (medical/clinical history, examination, diagnostic tests, etc.). These clinical methods have little to do with causation analysis.[291] In contrast, a causation analysis considers such things as the "Relative Risk," "Odds Ratio," or "Attributable Risk," found in relevant epidemiology studies; confounders; dose-response relationship; statistical significance; interspecies extrapolation from relevant toxicology studies; chemical analogies; and the "Bradford Hill" criteria.[292] These are the tools of causation science, not clinical medicine.

Nevertheless, physicians often present their causation analyses in the context of differential diagnoses. In this way, physicians are able to bootstrap their causation opinions through the permissive admissibility sieve accorded physicians' clinical diagnoses. Courts, however, should apply the same close scrutiny to physicians' causation analyses as they apply to the causation opinions of scientists such as toxicologists and epidemiologists.[293] The deference accorded medical witnesses' causation opinions, supported with scant scientific evidence, permits lay juries to find causal links science has not found.[294] After all, it was causation analyses masquerading

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were not epidemiologists); Michael B. Kent, Jr., Daubert, *Doctors And Differential Diagnosis: Treating Medical Causation Testimony As Evidence*, 66 DEF. COUNS. J. 525, 532 (1999) (averring that physicians can testify on issues of general causation, but they must employ the tools of toxicology and epidemiology to do so).

291. *See* Henifin et al., *supra* note 276, at 472 ("[A]n expert's opinion on diagnosis and his or her opinion on external causation should generally be assessed separately, since the bases for such opinions are often quite different.").

292. *See generally* Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, *in* REFERENCE MANUAL, *supra* note 44, at 401, 401; Green et al., *supra* note 64, at 333.

293. *See* Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 551 (W.D. Pa. 2003) ("[T]he mere statement by an expert that he or she applied differential diagnosis in determining causation does not *ipso facto* make that application scientifically reliable or admissible.").

294. Long ago legal scholars recognized that:

> What is needed is a separation between the issue of cause and all the other issues, which are often meritorious in themselves but too frequently parade meretriciously in the guise of cause. Perhaps this would affect substantive results only a little, but it would contribute much to clarity of thought.

Fleming James, Jr. & Roger F. Perry, *Legal Cause*, 60 YALE L.J. 761, 811 (1951). To help separate a physician's causation analysis from his or her differential diagnosis, thereby clarifying thought, courts should bar evidence concerning a physician's differential diagnosis in cases in which the diagnosis itself is not at issue. If the diagnosis is unchallenged, the physician's clinical methods are irrelevant.

as the physicians' diagnoses that opened the courthouse doors to the ludicrous trauma-cancer cases.[295]

Here, it is important to reiterate the distinction between "general causation" and "specific causation." To establish causation in a toxic tort case, the plaintiff's experts must be able to testify that the dose of the toxic agent at issue is capable of causing the disease (that is, *general causation*).[296] Then, the plaintiff's experts must be able to testify that the alleged exposure in fact caused the plaintiff's injury (that is, *specific causation*).[297] General causation is the purview of the toxicologists and epidemiologists.[298] On the other hand, the issue of specific causation requires input from medicine and the scientific causation fields of toxicology and epidemiology. The determination of the cause of a patient's disease must be based in part on the medical history of the patient, which will provide clues as to the cause of the patient's disease. Only a medical expert is

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295. *See supra* note 202 (discussing numerous cases in which physicians testified that traumatic blows caused the plaintiffs' cancers even though science never identified traumatic blows as a cause of cancer).

296. *See, e.g.*, Wheat v. Sofamor, S.N.C., 46 F. Supp. 2d 1351, 1357 (N.D. Ga. 1999) ("General causation is the capacity of a product to cause injury . . . ."); Cartwright v. Home Depot U.S.A., Inc., 936 F. Supp. 900, 906 (M.D. Fla. 1996) ("[T]he question for causation purposes is: At what levels of exposure do what kinds of harm occur?"); Cavallo v. Star Enter., 892 F. Supp. 756, 764 (E.D. Va. 1995) ("[A]ll chemicals can cause health problems at some level or concentration of exposure, but they vary widely in the types of harm caused and in the levels of exposure required to trigger those harms. In addition, all chemicals have thresholds of exposure that must be exceeded before the harms will occur, and these thresholds may be identified through scientific studies and literature. The task of the toxicologist, therefore, is to identify a dose-response relationship for a particular chemical (or chemical mixture) and illness and analyze the results to determine whether the duration and concentration of exposure in a given instance could have caused the alleged harms."), *rev'd in part on other grounds*, 100 F.3d 1150 (4th Cir. 1996). *Compare* Wright v. Willamette Indus., Inc., 91 F.3d 1105 (8th Cir. 1996) (holding that plaintiffs failed to make a submissible case of formaldehyde poisoning because they failed to establish levels of formaldehyde exposure generally hazardous to humans and plaintiffs' actual exposures), *with* Bednar v. Bassett Furniture Mfg. Co., 147 F.3d 737 (8th Cir. 1998) (holding that plaintiffs made a submissible case of formaldehyde poisoning because they established levels of formaldehyde exposure generally hazardous to humans and that their infant daughter's actual exposures likely exceeded hazardous levels).

297. *See* Pick v. Am. Med. Sys., Inc., 958 F. Supp. 1151, 1164 (E.D. La. 1997) ("Proof of causation has two components, general and specific. General causation deals with whether the substance at issue . . . can cause diseases or disorders in people in general. Specific causation focuses upon whether the substance . . . was in fact the cause of the ailments or symptoms in the particular patient."); *see also* Cloud v. Pfizer, Inc., 198 F. Supp. 2d 1118, 1132 (D. Ariz. 2001) (classifying causation expert's testimony into general or specific causation "because in order to carry her burden of proof, Plaintiff must show both general and specific causation" (citing Raynor v. Merrell Pharms., Inc., 104 F.3d 1371, 1376 (D.C. Cir. 1997))).

298. *See* Polaino v. Bayer Corp., 122 F. Supp. 2d 63 (D. Mass. 2000) (questioning qualifications of a medical doctor with no training in toxicology or epidemiology to testify as to general causation).

qualified to review the person's medical history and weigh the potential causes of the disease.[299] A physician, however, can reliably opine as to the potential causes of a patient's disease only if the putative cause is among those agents epidemiologic or toxicologic science has demonstrated to have a probable causal association with the disease at issue.[300] In addition, the physician must also consider the patient's dose of the alleged causal agent, a factor of import in medicine, toxicology and epidemiology.[301]

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299. *But see* Martin v. Shell Oil Co., 180 F. Supp. 2d 313, 320 (D. Conn. 2002) (holding that the plaintiffs' toxicology expert could offer his specific causation opinion that methyl tertiary-butyl ether [MTBE] caused the plaintiffs' injuries). The *Martin* court compounded its error by holding that the toxicologist could offer his medical opinion that the plaintiffs would require future medical monitoring for cancer. *Id.*

300. Tragically, not all courts apply this logic. Lack of scientific causation evidence did not deter the trauma-cancer cases from reaching the factfinders, who then awarded damages to plaintiffs for injuries not caused by the traumatic blows. *See supra* note 202. In *Suleski v. United States*, the court relied on a physician's testimony that swine flu vaccination caused the plaintiff's Guillain-Barre syndrome (GBS) despite the lack of reliable scientific evidence that the vaccine could cause GBS more than six weeks after the injection. 545 F. Supp. 426, 430 (S.D. W. Va. 1982) ("[E]xpert epidemiological testimony is not determinative of the issue of causation in this case . . . ."). In *Ferebee v. Chevron Chemical Co.*, the court affirmed judgment for the family of a deceased agricultural worker who claimed that the decedent's dermal absorption of the pesticide paraquat caused him to develop pulmonary fibrosis, a claim unsupported by the science. 736 F.2d 1529, 1535–36 (D.C. Cir. 1984). In an oft-cited passage, the court explained that a cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. *Id.* As long as the basic methodology employed to reach such a conclusion is sound, such as use of tissue samples, standard tests, and patient examination, products liability law does not require precluding recovery until a "statistically significant" number of people have been injured or until science has had time and resources to complete sophisticated laboratory studies of the chemical. *Id.* Relying on *Ferebee*, the court in *Wells v. Ortho Pharmaceutical Corp.*, affirmed a multimillion-dollar verdict for a child born with birth defects. 788 F.2d 741, 745 (11th Cir. 1986). The plaintiff lacked evidence that in utero exposure to the spermacide used by her mother could cause such birth defects. *Id.* To the contrary, the epidemiologic evidence presented by the defendant indicated no such association. *Id.* The court, however, rejected the defendant's negative evidence, explaining that "it does not matter in terms of deciding the case that the medical community might require more research and evidence before conclusively resolving the question." *Id.* In *Bonner v. ISP Techs., Inc.*, the Eighth Circuit demonstrated that this "law leads science" reasoning somehow survives *Daubert* and *Joiner*. 259 F.3d 924, 928 (8th Cir. 2001). The *Bonner* court affirmed judgment for a plaintiff claiming permanent brain damage as a result of occupational exposures, a claim bereft of epidemiologic support. *Id.* The court explained: "The first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed." *Id.* (quoting Turner v. Iowa Fire Equip. Co., 229 F.3d 1202, 1208–09 (8th Cir. 2000)); *see also supra* note 202 (discussing *Bonner*).

301. *Benedi v. McNeil-P.P.C., Inc.* presents a model of admissible causation testimony. 66 F.3d 1378 (4th Cir. 1995). In *Benedi*, the plaintiff claimed that a toxic combination of Extra-Strength Tylenol and alcohol caused his liver damage. *Id.* at 1381. The plaintiff offered the testimony of two liver disease specialists to prove general causation—that the toxic combination of the drug and alcohol is capable of causing the type of liver damage incurred. *Id.* at

Another reason to distinguish between a physician's differential diagnosis and his or her causation analysis is that, as mentioned above, some courts are highly deferential to physicians' conclusions based on differential diagnoses.[302] Such deference, however,

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1382. These experts were able to cite scientific literature to support their opinions that the subject drug-alcohol combination was associated with an increased risk of liver injury. *Id.* Then, the plaintiff offered the testimony of his two treating physicians to prove specific causation—that the subject dose caused his liver damage. *Id.* These physicians examined the plaintiff's liver and found evidence of drug toxicity; they also considered and eliminated confounders, most prominently viral infections, as possible causes of the injury. *Id.* Finally, the physicians considered the dose in concluding that the drug-alcohol combination caused the plaintiff's injury. *Id.* at 1384.

302. *See infra* Part VIII.D.3.a (discussing the inappropriateness of deferring to a physician's diagnosis in litigation). Worse than mere deference, some courts have stated that clinical medicine is not a "hard" science and, hence, the *Daubert* factors are inapplicable. *E.g.*, Moore v. Ashland Chem., Inc., 126 F.3d 679 (5th Cir. 1997), *rev'd en banc*, 151 F.3d 269 (5th Cir. 1998).

In *Moore*, the plaintiff alleged that he was occupationally exposed to irritating vapors that caused him to develop Reactive Airway Disease (RAD), a diagnosis and causation supported by his medical expert. *Id.* at 683. A panel of the Fifth Circuit reversed a verdict for the defendant, holding that the trial court had abused its discretion by excluding the plaintiff's proffered medical causation testimony. *Id.* at 687–88. In the panel's view, the *Daubert* reliability factors applied to "hard" or "Newtonian" science, and clinical medicine "is not a hard science discipline." *Id.* at 682. As a result, "the '*Daubert* factors,' which are techniques derived from hard science methodology, are, as a general rule, inappropriate for use in making the reliability assessment of expert clinical medical testimony." *Id.* Applying these principles to the proffered causation testimony, the court held that the plaintiff's medical expert's opinions were grounded in the methodology of clinical medicine. *Id.* at 696. The expert had examined the plaintiff, conducted medical tests, eliminated alternative causes, reviewed occupational safety standards, considered relevant medical literature, and applied his experience in treating patients with respiratory diseases. *Id.* The court concluded that this methodology is well accepted within the field of clinical medicine, and thus the physician's failure to rely on epidemiologic evidence was not critical. *Id.*

A dissenting judge assailed the *Moore* majority's "remarkable premise" that clinical medicine is not a hard science. *Id.* at 711 (Davis, J., dissenting). The dissenter complained that the medical expert had no scientific support for his conclusion that exposure to any irritant at unknown levels can trigger RAD. *Id.* at 714. He observed: "The purpose of *Daubert* was to exclude such speculation, based primarily on a temporal connection, as lacking any scientific validity." *Id.*

The authors endorse Professor Capra's analysis of the *Moore* panel's holding:

> The *Moore* panel's analysis is flawed because it permits a party to evade the requirements of hard science simply by calling a clinical expert who can testify to causation without having to rely on epidemiological evidence, animal studies, or any other of the bases ordinarily used by scientists. The fact that clinical medicine and laboratory medicine have different goals does not mean that a clinical doctor should be able to testify to causation on the basis of information that a laboratory scientist would reject as insufficient. The *Moore* court ignored the fact that clinical experts treat patients—they do not conclude definitively on causation in toxic tort situations. The *Moore* decision allows the clinical expert to testify in court to a conclusion that the expert would not and could not reliably draw in his professional life.

Capra, *supra* note 186, at 750–51. Fortunately, the Fifth Circuit corrected its error en banc. Moore v. Ashland Chem., Inc., 151 F.3d 269 (5th Cir. 1998) (citing Gen. Elec. Co. v. Joiner, 522 U.S. 136 (1997)).

Nevertheless, some commentators cling to the view that causation opinions offered by clinicians should be excused the exigent inquiry applied to opinions based on "hard" sciences. *See, e.g.*,

should never extend to an expert's causation analysis merely because the expert is a physician, as in *McCullock v. H.B. Fuller Co.*[303] In that case, the appellate court affirmed the admission of the medical expert's testimony that occupational exposures to glue caused the plaintiff's throat polyps despite the fact that the expert could point to no studies identifying glue as a causative agent of that disease. Nevertheless, the proffered causation testimony passed the court's *Daubert* scrutiny because the doctor characterized his causation

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Jean M. Eggen, *Clinical Medical Evidence of Causation in Toxic Tort Cases: Into the Crucible of* Daubert, 38 HOUS. L. REV. 369, 391–92 (2001) (arguing that causation assessment is a routine component of differential diagnosis and, in effect, that a physician can reach a reliable causation conclusion based on "experience and training" unaided by the "hard" sciences of toxicology and epidemiology); Jack E. Karns, *Establishing the Standard for a Physician's Patient Diagnosis Using Scientific Evidence: Dealing with the Split of Authority Amongst the Circuit Courts of Appeal*, 15 BYU J. PUB. L. 1, 29 (2000) ("The idea that the trier of fact would be shielded from scientific evidence [based on a physician's differential diagnosis] simply because it is not vetted in a manner comparable to methodologies generally accepted in the legal community is not acceptable.").

As Professor Capra points out, this view creates "a perverse result: a party will have the incentive to argue that its expert should be heard by the jury *because* the expert is not a scientist! This would create a race to the bottom for experts, and that is a race that must be rejected." Capra, *supra* note 186, at 748–49. "A trial judge becomes a matador, not a gatekeeper, if she must admit nonscientific expert testimony simply because the expert has the requisite experience." *Id.* at 741. Regarding the role of *Daubert*, Professor Capra discusses that:

> Even if the specific *Daubert* factors are held inapplicable, the *Daubert* gatekeeping function is and must remain applicable to all expert testimony. Expert testimony of all stripes must be reliable or else it is not helpful within the meaning of Rule 702, and [pace Professor Karns' opinion to the contrary,] *Daubert* makes clear that it is up to the trial judge under Rule 104(a) to determine that question. . . . Put in a positive sense, an expert who is not a scientist should receive the same degree of scrutiny for reliability as an expert who purports to be a scientist.

Id. at 747.

In the authors' view, a physician's reliance on "experience" to reach a general causation conclusion is at bottom an unreliable ipse dixit: "It is so because I am an expert and I say it is so."

Baker v. Metro-North Railroad Co. exhibits the "race to the bottom" Professor Capra fears. No. 3:98CV1073(RNC), 2003 WL 22439730 (D. Conn. Oct. 23, 2003). The *Baker* court allowed a physician to testify that the plaintiff's repetitive motions at work caused the plaintiff to develop carpal tunnel syndrome even though the physician failed to quantify the plaintiff's on-the-job repetitive motion stresses. *Id.* at *2. The court believed that the physician's "differential diagnosis provides a sufficiently reliable foundation for his opinions." *Id.* In contrast, the court barred the specific causation opinions of the plaintiff's retained ergonomist due to the same failure to quantify the plaintiff's workplace stressors. *Id.* at *3. Even assuming that the ergonomist was qualified to offer "medical causation testimony," the court nevertheless barred her specific causation opinion because her non-quantitative analysis "appears to differ substantially from the rigorous analysis an expert in her field would employ in the course of his or her work. . . . Plaintiff offers no evidence that experts in ergonomics determine medical causation without quantifying the individual's exposure to known risk factors and taking account of rest periods." *Id.* Thus, the court found reliable the specific causation testimony of the nonscientist who used the same non-quantitative analysis the court found unreliable in the hands of the scientist. The lesson to plaintiffs' attorneys: Retain nonscientists to present quasi-science in court.

303. 61 F.3d 1038 (2d Cir. 1995).

testimony as a differential diagnosis.[304] The McCullock court failed to recognize that "an expert's opinion on diagnosis and his or her opinion on external causation should generally be assessed separately, since the bases for such opinions are often quite different."[305] A differential diagnosis, no matter how well performed, cannot establish general causation.[306]

Contrast *McCullock* with *Caraker v. Sandoz Pharmaceutical Corp.*, in which the court did not defer to the physician's causation analysis.[307] Although the *Caraker* court mislabeled the physician's causation analysis as a "differential diagnosis," in the end the error was harmless. The court recognized the impropriety of extending a deferential review to the physician's causation determination.

> The methodology [of differential diagnosis], in the abstract, has been considered sound, but when it is used in the practice of science (as opposed to its use by treating physicians in the practice of medicine out of necessity) it must *reliably* "rule in" a potential [sic] for the expert to reliably place the purported potential cause on the differential diagnosis [sic] in the first place as well as reliably "rule out" the other potential causes until the physician is left with the most likely one. Both of these steps must be based on sufficient and reliable data for the methodology as a whole to be reliable. Thus, if the "ruling in" step is bad or if an extrapolation from the existing data is particularly questionable or involves too great an analytical leap (or several such leaps), the whole opinion is questionable.[308]

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304. *Id.* at 1043; *see also* Lakie v. SmithKline Beecham, 965 F. Supp. 49, 55 (D.D.C. 1997) (admitting causation opinions ostensibly based on differential diagnosis even though the defendants did not dispute the diagnosis of the plaintiff's disease, and thus the medical experts' differential diagnosis was not at issue, only their causation analysis); Cutlip v. Norfolk S. Corp., No. 02-1051 (Ohio App. Apr. 11, 2003) (holding that a sound differential diagnosis obviates the need for dose-response evidence or threshold dose data in determining admissibility of general causation evidence).

305. Henifin et al., *supra* note 276, at 472; *see also* Moore v. Ashland Chem. Inc., 151 F.3d 269, 275 n.7 (5th Cir. 1998) ("In other words, determining the etiology of a disease—its cause—involves the same scientific exercise, whether the decision is made by a clinician, an epidemiologist, or other scientist.").

306. So-called signature diseases present an exception to this principle. *See infra* notes 315–318 and accompanying text.

307. 172 F. Supp. 2d 1046, 1048 (S.D. Ill. 2001).

308. *Id.* (citations omitted). The court then held that the physician's differential diagnosis was unreliable because the "ruling in" step—the determination that the drug at issue, Parlodel, is capable of causing intracerebral hemorrhage—involved unreliable and unsupported extrapolations, analytical leaps, and loose application of scientific causation standards. *Id.* at 1048–53. Similarly, in *National Bank of Commerce v. Dow Chemical Co.*, the court mislabeled an expert's causation assessment as a differential diagnosis, but reached the correct conclusion. 965 F. Supp. 1490,

Similarly, in *Wynacht v. Beckman Instruments, Inc.*, the court grasped the distinction between differential diagnoses and causation analyses: "The ability to diagnose medical conditions is not remotely the same . . . as the ability to deduce, delineate, and describe, in a scientifically reliable manner, the causes of those medical conditions."[309]

To summarize, a reliable causation analysis depends on a proper diagnosis by a physician. Then, given the diagnosis, the causation expert must address the issue of general causation (that is, whether the subject agent is capable of causing the diagnosed disease) and specific causation (that is, whether the agent in fact caused the disease in the person diagnosed with the disease). In brief, a reliable differential diagnosis is necessary, though insufficient, evidence of causation. In *Hall v. Baxter Healthcare Corp.*, the court explained:

> Differential diagnosis is a patient-specific process of elimination that medical practitioners use to identify the "most likely" cause of a set of signs and symptoms from a list of possible causes. However, *differential diagnosis does not by itself prove the cause,* even for the particular patient. *Nor can the technique speak to the issue of general causation.* Indeed, differential diagnosis *assumes* that general causation has been proven for the list of possible causes it eliminates:
>
> "The process of differential diagnosis is undoubtedly important to the question of 'specific causation.' If other possible causes of an injury cannot be ruled out, or at least the possibility of their contribution to causation minimized, then the 'more likely than not' threshold for proving causation may not be met. *But, it is also important to recognize that a fundamental assumption underlying this method is that the final, suspected 'cause' remaining after this process of elimination must actually be capable of causing the injury. That is, the expert must 'rule in' the suspected cause as well as 'rule out' other possible causes.* And, of

1513 (E.D. Ark. 1996) (recognizing that colon cancer "has many risk factors: diet, obesity, exposure to environmental hazards, and genetics" that the plaintiff's causation expert failed to rule out, but mislabeling this ruling out process as differential diagnosis even though the expert's causation assessment was at issue, not the physician's diagnosis of colon cancer). Despite the misnomer, the *Caraker* and *National Bank of Commerce* courts reached the correct decision because they did not defer to the physicians' causation analyses.

309. 113 F. Supp. 2d 1205, 1209 (E.D. Tenn. 2000).

course, expert opinion on this issue of 'general causation' must be derived from scientifically valid methodology."[310]

If there is no scientific evidence linking the subject agent with the type of injury at issue, then a so-called differential diagnosis cannot supply it.[311] On the other hand, causation analysis must address the issue of general causation, the *sine qua non* of specific causation.[312]

Although differential diagnoses generally do not require physicians to form conclusions regarding causal agents,[313] there are rare

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310. 947 F. Supp. 1387, 1413 (D. Or. 1996) (first and second emphases added) (quoting Cavallo v. Star Enter., 892 F. Supp. 756, 771 (E.D. Va. 1995), *aff'd on this ground, rev'd on other grounds*, 100 F.3d 1150 (4th Cir. 1996)).

311. Moore v. Ashland Chem. Inc., 151 F.3d 269, 278 (5th Cir. 1998); *see also* Black v. Food Lion, Inc., 171 F.3d 308, 314 (5th Cir. 1999) (affirming trial court's exclusion of physician's causation opinion based on a differential diagnosis linking plaintiff's fall with her fibromyalgia because physician lacked evidence that trauma can cause that disease); Glastetter v. Novartis Pharms. Corp., 107 F. Supp. 2d 1015, 1027 (E.D. Mo. 2000) (citing *Hall*, 947 F. Supp. at 1413) (stating that differential diagnosis addresses specific causation, not general causation), *aff'd* 252 F.3d 986 (8th Cir. 2001); Lofgren v. Motorola, No. CV 93-05521, 1998 WL 299925, at *24 (Ariz. Super. Ct. June 1, 1998) (stating that differential diagnosis is "unequivocally rejected by the scientific community" as a means of determining causation); Valentine v. PPG Indus., No. 03CA17 (Ohio App. Aug. 20, 2004) (rejecting expert's differential diagnosis that chemical exposures caused plaintiff's glioblastoma multiforme because the only proven cause of the condition is ionizing radiation); Kent, *supra* note 290, at 532 ("Testimony based on differential diagnosis is never admissible with regard to whether a certain substance can generally cause the disease in question because it fails to satisfy both the reliability and relevance requirements of *Daubert*."). *But see* Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 807–09 (3d Cir. 1997) (reversing trial court's exclusion of physician's causation opinion based on a differential diagnosis even though physician produced no scientific literature evidencing an association between the agent and plaintiff's cognitive problems).

312. *See* Fabrizi v. Rexall Sundown, Inc., No. 01-289, 2004 U.S. Dist. LEXIS 9859, at *31–32. (W.D. Pa. June 2, 2004) (finding that there was no need to reach the issue of admissibility of expert's specific causation opinion since the expert's general causation opinion was inadmissible); *Hall*, 947 F. Supp. at 1413 (holding that testimony regarding specific causation is irrelevant unless general causation is established).

313. Bruce R. Parker, *Understanding Epidemiology and Its Use in Drug and Medical Device Litigation*, 65 DEF. COUNS. J. 35, 57 (1998); *see also* Harvey Brown, *Eight Gates for Expert Witnesses*, 36 HOUS. L. REV. 743, 866 (1999) ("When doctors treat patients, they may not need to reach a conclusion on causation. Only when causation is part of the physician's normal professional conclusion (because a causation finding significantly alters the course of treatment) does the physician utilize the same methodology in his or her practice as he or she does in preparing expert testimony . . . ." (citation omitted)). As Professor Capra points out, "[a]n expert cannot be expected to research a question of specific causation outside the context of litigation. Indeed, to impose such a requirement would lead to the exclusion of every doctor who diagnoses a patient for purposes of litigation." Capra, *supra* note 186, at 709. In contrast, issues of general causation are independent of litigation. Experts should reach general causation opinions as scientists, not witnesses. *Id.* Another commentator distinguished "opinion-based" medicine and "evidence-based" medicine, explaining that most clinicians' practices do not reflect the principles of evidence-based medicine but rather are based upon tradition, their most recent experience, what they learned years ago in medical school, or what they have heard from their friends. John M. Eisenberg, *What Does Evidence Mean? Can the Law and Medicine Be Reconciled?*, Mar. 1, 2004, http://www.ahcpr.gov/clinic/jhppl/eisenberg.htm.

> The archetype of the physician who practices without a foundation of evidence-based medicine is depicted by the old saw about the doctor who describes the rationale for his decisions. When he says "in my experience," he means he has taken care of one patient

exceptions. Some diseases are "pathognomonic," meaning that the patient's signs and symptoms or diagnostic test results are "signatures" of a disease caused by a particular agent. One prominent example is angiosarcoma, a rare type of liver cancer, associated with substantial occupational exposure to vinyl chloride.[314] A diagnosis of "lead poisoning" defines the causative agent, insofar as it requires demonstration of elevated lead levels in bone or blood. Another signature disease, asbestosis, is diagnosed by the presence of "ferruginous bodies" in lung tissues caused exclusively by asbestos inhalation.[315] In the rare pathognomonic disease case, general causation is by definition not the issue.[316] The issue at bar in such a case is the physician's diagnosis.[317]

A court should be very careful, however, when asked to accept a signature disease as proof of causation. First, some signature diseases are not as pathognomonic as once thought. Experts

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like this. If he says "in my series of cases," he means he has taken care of two. And if he says "in case after case after case," he means he has seen three.

Id.

314. In addition, there may be a fingerprint for vinyl chloride-induced angiosarcoma. Specific chromosomal mutation patterns appear to occur in VC-induced angiosarcoma. Sheri Stuver & Dimitrios Trichopoulos, *Cancer of the Liver and Biliary Tract, in* TEXTBOOK OF CANCER EPIDEMIOLOGY 212, 224 (Hans-Olov Adams et al. eds., 2002).

315. *See* Piero Mustacchi, *Lung Cancer Latency and Asbestos Liability*, 17 J. LEGAL MED. 277, 283 (1996) ("[Mesotheliomas] are so rare that, clinically speaking, any case occurring after a well attested and substantial asbestos exposure is commonly accepted as being caused by that exposure."); *see also* Nat'l Bank of Commerce v. Dow Chem. Co., 965 F. Supp. 1490, 1513 (E.D. Ark. 1996) ("Mesothelioma is a 'signature' disease: The injury points directly to the substance that caused it." (quoting David Levy, *Scientific Evidence After* Daubert, A.B.A. J. LITIG., Fall 1995, at 48 (1995))). Note the Bayesian thinking applied in signature disease causation analysis. Given the overwhelming proportion of the disease caused by the subject agent, a very crude test—merely observing the disease—is sufficiently specific to be a reliable predictor of causation.

316. *See, e.g.*, Hose v. Chi. Nw. Transp. Co., 70 F.3d 968 (8th Cir. 1995) (affirming trial court's admission of physician's "manganese encephalopathy" diagnosis based on plaintiff's symptoms, his occupational exposure to manganese fumes, and magnetic resonance imaging consistent with manganese in plaintiff's brain); Reynolds v. S&D Foods, Inc., 162 F.R.D. 661, 669–70 (D. Kan. 1995) (concluding that dog owners failed to demonstrate salmonella-contaminated dog food caused injuries to their dogs in part because, according to one expert, the symptom displayed by the injured dogs was pathognomonic of distemper unrelated to the salmonella). *Compare* Klinglesmith v. HHS, No. 90-677V, 1991 WL 160321, at *2 (Cl. Ct. Aug. 1, 1991) (concluding that vaccine shot did not cause patient's seizure, relying in part on medical expert's opinion that signs displayed by patient " 'are almost pathognomonic of Herpes simplex meningoencephalitis' and a strong indication that other causes of the encephalopathy [such as the vaccine shot] should be excluded" (citation omitted)), *and* Williams v. HHS, No. 94-1005V, 1997 WL 803112 (Fed. Cl. Dec. 10, 1997) (concluding that patient's lymphocytosis was not pathogonomic of vaccine-induced neurologic condition and thus "lymphocytosis has little or no probative value in establishing the DPT's [diphtheria-pertussis-tetanus vaccination's] causative role"), *with* Brennan, *supra* note 6, at 500 ("When a rare tumor is closely associated with a toxic substance, courts generally take the causation issue as a given. This is the case in the asbestos litigation as well as in the diethylstilbesterol/vaginal adenocarcinoma cases." (citations omitted)).

317. *See, e.g.*, *Hose*, 70 F.3d 968 (contesting plaintiff's medical expert's diagnosis of manganese encephalopathy).

believed that mesothelioma, mentioned in the previous paragraph, resulted almost exclusively from asbestos exposure. Now, research shows that mesothelioma is a sequella of exposure to simian virus 40 (SV 40), a contaminant of some polio vaccine batches.[318] In addition, there is a concern that the diagnosis itself may be a self-fulfilling prophecy. For example, a physician, aware of the patient's alleged occupational exposure to silica, may on the strength of that allegation diagnose the patient's pulmonary fibrosis as silicosis. Likewise, a physician may deem, post hoc, a pulmonary fibrosis as asbestosis in a patient claiming prior asbestos exposure, or as "black lung" (coal-workers pneumoconiosis, or CWP) in a patient who is a coal miner. It is tautological that, if one defines the disease by the associated agent, then the agent caused the disease. In a putative signature disease case in which the plaintiff asks the court to accept the disease itself as proof of causation, the court should decline the invitation unless the specific diagnosis is beyond genuine dispute.

b. The Independent Link of General Causation—Probability in the fields of medicine and toxicology is more difficult than in the context of statistics. While the term "probable" in essence means the same thing as in statistics and the law, that is, $P > 0.5$, the quantification of a biological response as the "possible" or "probable" outcome of an exposure is difficult due to the inherent complexity of biological systems, the uncertainties in the extrapolations from species to species, and the physical and physiological variations among individuals in a given species.[319] How, then, is a court to determine whether the plaintiff's expert has reliable scientific evidence demonstrating the high probability that the subject agent

318. *See generally* N.J. Vogelzang, *Emerging Insights into the Biology and Therapy of Malignant Mesothelioma*, SEMINARS IN ONCOLOGY, Dec. 2002, Supp. 18, at 35, 35–42.

319. *See* Eaton & Klaassen, *supra* note 117, at 24–26 (discussing numerous factors inherent in biological systems that influence responses to toxic agents). Courts recognize the inherent weaknesses in animal studies as proof of causation due to "the fact that different species of animals react differently to the same stimuli for reasons not entirely understood. Immune systems, nervous systems, and metabolism (*i.e.*, physical processing of chemical compounds) may differ greatly between species." Turpin v. Merrell Dow Pharms., Inc., 959 F.2d 1349, 1359 (6th Cir. 1992) (footnote omitted); *see also In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 743 (3d Cir. 1994) ("[A]nimal studies may be methodologically acceptable to show that chemical X increases the risk of cancer in animals, but they may not be methodologically acceptable to show that chemical X increases the risk of cancer in humans."); Farber, *supra* note 228, at 1228 ("Animal studies, although useful, generally involve much higher doses that are difficult to extrapolate to low doses over prolonged periods; there is also the question of whether extrapolation of results between species is valid."); Hall & Silbergeld, *supra* note 66, at 443 ("[Toxicological studies] are generally viewed with more suspicion than epidemiological studies, because they require making the assumption that chemicals behave similarly in different species.").

is capable of causing the plaintiff's injury?[320] At this point, the courts must turn to the Bradford Hill criteria.[321]

As discussed in subsection V(A), an epidemiology study showing a statistical association between an agent and a disease is not by itself proof of a causal association. Researchers apply the Bradford Hill criteria, or a variant of these criteria, to determine whether a statistical association is in fact causal.[322]

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320. At this point of the court's scrutiny of the expert's causation analysis, the court should defer the "dose" issue. So long as the expert has scientific evidence that the subject agent is capable of causing the specific disease at *any* dose, the expert's evidence is sufficiently reliable to pass this step of the *Daubert* analysis. Although consideration of dose is crucial for a reliable causation analysis, the court should defer consideration of dose until reaching the "specific causation" phase of the analysis, *see infra* Part VIII.D.3.d, thereby preserving the "general causation" inquiry as an independent link. The court should note the dose or exposure level found in epidemiologic and toxicological studies that elicits the specific disease, then consider whether the plaintiff's dose or exposure was sufficient to elicit the disease at the subsequent specific causation step of the court's inquiry.

321. *See supra* Part V.A (discussing the Bradford Hill criteria).

322. The scientific community widely accepts the Bradford Hill criteria as the measure of a general causation determination. *See, e.g., Guidelines for Classification of Occupational Carcinogenicity, in* AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS, DOCUMENTATION OF THE THRESHOLD LIMIT VALUES AND BIOLOGICAL EXPOSURE INDICES, at i (7th ed. 2001) (relying on many of the Bradford Hill criteria for interpreting epidemiological data, particularly: (1) consistency with other epidemiologic studies, (2) specificity or risk associated with work areas having high exposures, (3) strength of statistical association, (4) dose-response relationship, (5) coherence with known biological mechanism, (6) temporal relationship between exposure and disease, and (7) statistical significance); INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, WORLD HEALTH ORGANIZATION, 60 IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: SOME INDUSTRIAL CHEMICALS 19–20 (1994) (adopting the Bradford Hill criteria for causality, relying upon the criteria of a strong association, the replication of findings from study to study, the need for increasing exposure to lead to increasing disease, the specificity of the association, and the necessity to control for bias and confounding); U.S. ENVIRONMENTAL PROTECTION AGENCY, GUIDELINES FOR CARCINOGENIC RISK ASSESSMENT, EPA/630/P-03/001F, at 2-11 to 2-15 (2005) (following the Bradford Hill criteria for establishing potential causal associations in the course if its regulatory analyses, requiring specifically: (1) the establishment of a temporal relationship; (2) the magnitude of the association, exposure, and dose considerations; (3) the specificity of the association and biological plausibility; and (4) coherence); WORLD HEALTH ORGANIZATION, ENVIRONMENTAL HEALTH CRITERIA NO. 72: PRINCIPLES OF STUDIES ON DISEASES OF SUSPECTED CHEMICAL ETIOLOGY AND THEIR PREVENTION 40–48 (1987) (reiterating most of the Bradford Hill criteria as the necessary elements for establishing a potential causal association).

Numerous textbooks authored by various epidemiologists adhere to the Bradford Hill criteria as the methodological basis for evaluating causality. *See, e.g.*, Elaine M. Faustman & Gilbert S. Omenn, *Risk Assessment, in* CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, *supra* note 117, at 83, 90–91; JUDITH S. MAUSNER & SHIRA KRAMER, EPIDEMIOLOGY: AN INTRODUCTORY TEXT 180–93 (1985); RICHARD R. MONSON, OCCUPATIONAL EPIDEMIOLOGY 99–103 (1980); Kenneth J. Rothman & Sander Greenland, *Causation and Causal Inference, in* MODERN EPIDEMIOLOGY 7, 24–28 (Rothman & Greenland eds., 2d ed. 1998).

Finally, a number of occupational medicine textbooks describe these criteria as the method by which to evaluate epidemiological evidence. Ellen A. Eisen & David H. Wegman,

Courts do the same.[323]

A judge need not "don the scientist's cap" to scrutinize the reliability of an expert's general causation opinion. In some cases, the causation expert will have no support in the scientific literature for the proposition that the subject agent causes the subject disease.[324] That is, the expert will have no epidemiologic studies suggesting a relationship between the agent and the disease, and no toxicological studies showing that animals exposed to the agent develop the disease. In such cases, the judge should bar the proffered general causation testimony as unreliable.

Other cases may present some minimal but still insufficient data to support admissibility. For example, the expert may point to one or more epidemiologic studies showing an elevated risk of disease associated with the agent, but the risk is "statistically nonsignificant."[325] Perhaps the expert will have a toxicological study or two in which mammals exposed to the agent display the subject disease at a statistically greater rate than controls, but no epidemiologic support.[326] Or perhaps the expert will point to a study showing the agent causes a different, but related, disease, or that an agent chemically similar to the subject agent causes the disease at issue (the so-called "analogy" argument).[327] As a rule, such minimal general causation evidence does not satisfy a reasonable application of

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Epidemiology, *in* OCCUPATIONAL HEALTH: RECOGNIZING AND PREVENTING WORK-RELATED DISEASE AND INJURY 143, 143–60 (Barry S. Levy & David H. Wegman eds., 4th ed. 2000); Joseph K. McLaughlin & Loren Lipworth, *Epidemiology and Biostatistics*, *in* A PRACTICAL APPROACH TO OCCUPATIONAL AND ENVIRONMENTAL MEDICINE 571, 579–80 (Robert J. McCunney ed., 3d ed. 2003); OCCUPATIONAL MEDICINE 534–54 (Joseph LaDou ed., 1990).

The consensus opinion in the scientific and medical community is that the Bradford Hill criteria form the cornerstone for the scientific method of establishing general causation. Courts must do the same.

323. *See, e.g.*, Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

324. *See, e.g.*, Black v. Food Lion, Inc., 171 F.3d 308, 314 (5th Cir. 1999) (affirming trial court's exclusion of physician's causation opinion based on a differential diagnosis that linked plaintiff's fall with her fibromyalgia because physician lacked evidence that trauma can cause that disease); Marsh v. W.R. Grace & Co., Nos. 98-1943, 98-1944 & 98-1945, 2003 WL 22718177, at *4 (4th Cir. Nov. 19, 2003) (affirming trial court's summary judgment in favor of defendant in part because plaintiffs' causation expert lacked epidemiologic evidence that agent can cause cancer and instead "started from the conclusion that picloram caused the plaintiffs' cancers and then generated, without testing, the hypothesis to support that conclusion").

325. *See supra* Part V.A.1 (discussing statistical significance); *see also supra* note 103 (citing cases in which the plaintiffs' causation experts relied on epidemiology studies showing statistically insignificant risks in support of their general causation theories).

326. *See supra* Part V.A.4 (discussing "biological plausibility"); *see also supra* note 117 (citing cases in which plaintiffs' causation experts relied on animal studies as a method of establishing general causation).

327. *See supra* Part V.A.4 (discussing the "analogy" argument).

the Bradford Hill criteria. Rarely should a court allow an opinion based on such minimal data to reach the factfinder.

Although courts require reliable evidence of general causation at the *Daubert* phase, the type of general causation evidence that courts will admit into evidence may depend on the natures of the alleged exposures and the injury. In cases involving acute exposures followed immediately by injury, many courts are less demanding of epidemiologic data in support of the general causation theory.[328] Toxicologic data or clinical case reports may suffice to demonstrate that the agent can cause the injury in acute exposure-response cases. Conversely, courts are more demanding of epidemiologic data in support of general causation theories in cases involving chronic exposures followed by latency periods prior to manifestation of injuries.[329] In chronic exposure-response cases, the causal nexus between the agent and the injury is more obscure than in acute exposure-response cases, compelling courts to require more exacting proof of the nexus, often in the form of epidemiologic data showing an association.[330] Also weighing in the

328. *See, e.g.*, Westberry v. Gislaved Gummi AB, 178 F.3d 257 (4th Cir. 1999) (affirming trial court's admission of causation testimony because a strong temporal relationship between occupational exposure to talcum powder, sinus problems, and a physician's differential diagnosis, and the undisputed fact that talcum powder irritates mucous membranes, were sufficient to overcome lack of scientific evidence that talcum powder can cause severe sinus infection); Zuchowicz v. United States, 140 F.3d 381 (2d Cir. 1998) (affirming trial court's admission of testimony that drug overdose caused plaintiff's fatal liver disease despite lack of scientific support that drug was linked with liver disease when the overdose of drug immediately caused serious symptoms and plaintiff was diagnosed with fatal liver disease within months of first dose); Ambrosini v. Labarraque, 101 F.3d 129 (D.C. Cir. 1996) (reversing trial court's exclusion of expert's opinion that mother's ingestion of drug caused birth defects in child exposed in utero despite lack of statistically significant studies associating drug with infant's birth defects); Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378 (4th Cir. 1995) (affirming trial court's admission of expert's causation testimony despite lack of epidemiologic support for expert's opinion that drug caused liver damage when plaintiff consumed drug for five days before entering hospital near death in a coma and underwent a liver transplant two days later); Globetti v. Sandoz Pharms. Corp., 111 F. Supp. 2d 1174 (N.D. Ala. 2000) (denying defendant's motion to exclude plaintiff's causation evidence despite lack of epidemiologic support for expert's opinion when plaintiff suffered myocardial infarct shortly after ingesting drug).

329. For an explanation of what is meant by "acute," "chronic," and things in between, see Eaton & Klaassen, *supra* note 117, at 14 (defining "acute" exposures as continuous for one day or less, "subacute" exposures as repeated for one month or less, "subchronic" exposures as repeated for one to three months, and "chronic" exposures as repeated for more than three months).

330. The pre-*Daubert* Agent Orange cases present an excellent and important example of the use of epidemiology in chronic exposure cases. Agent Orange was a defoliant used by American forces in the Vietnam War. Veterans and their families filed numerous lawsuits against the manufacturers of Agent Orange alleging various ailments as a result of exposures to the agent, and the cases were consolidated in Judge Weinstein's court. *In re* Agent Orange Prods. Liab. Litig., 597 F. Supp. 740 (E.D.N.Y. 1984). As summarized by Daniel Farber:

mix are considerations of whether the particular disease at issue occurs in the absence of exposure to the agent, and whether there is a reasonable biological explanation as to how the agent may cause the disease.[331]

In the former group of "acute" cases appears *Heller v. Shaw Industries, Inc.*[332] In that case, homeowners claimed that organic vapor emissions from their new carpeting caused their respiratory illnesses.[333] The wife's symptoms arose within two weeks of the carpet installation; the husband's symptoms, however, preceded the carpet installation.[334] The homeowners' retained medical expert concluded that the emissions from the new carpet caused the respiratory problems based in part on the strong temporal association between the exposures and the onset of symptoms.[335] Nevertheless, the trial court barred this medical testimony in part because the medical expert had no research demonstrating that the organic vapor emissions from the carpet could cause such respiratory symptoms.[336] On this point, the Third Circuit disagreed, finding that under the circumstances a valid differential diagnosis and a strong temporal relationship can overcome a lack of research in support of general causation.[337] "[I]f a person were doused with

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> The weakness of the plaintiffs' causation evidence persuaded Judge Weinstein to approve a $180 million settlement, which was considered highly favorable to the defendants. . . . The key flaw in the plaintiffs' case was that governmental epidemiological studies showed no statistical link between Agent Orange exposure and significant health effects. . . . In a companion case, involving opt-outs or individuals never included in the class, Judge Weinstein was forced to rule on the merits of the plaintiffs' claims. [Lilley v. Dow Chem. Co (*In re* Agent Orange Prods. Liab. Litig.), 611 F. Supp. 1267 (E.D.N.Y. 1985)]. In these cases, he granted summary judgment for the defendants despite the plaintiffs' tender of expert testimony linking Agent Orange with health effects. The epidemiological studies played a key role in these decisions. . . . Judge Weinstein ruled the plaintiffs' expert testimony inadmissible, and then granted summary judgment because the plaintiffs had no admissible evidence to counter the defendants' epidemiological studies.

Farber, *supra* note 228, at 1234–36 (footnotes omitted).

331. *See* Lofgren v. Motorola, No. CV 93-05521, 1998 WL 299925, at *14 (Ariz. Super. Ct. June 1, 1998) (holding epidemiologic support crucial in non-Hodgkin's lymphoma cases because "doctors and scientists have little knowledge about the etiology of the diseases, have identified other causes of them, or know that all of the diseases occur in the absence of exposure to TCE [the alleged causative agent]").

332. 167 F.3d 146 (3d Cir. 1999).

333. *Id.* at 149.

334. *Id.* at 150.

335. *Id.* at 153–54.

336. *Id.* at 154.

337. *Id.* Note that at several points in its analysis, the *Heller* court confused the medical expert's causation analysis with his differential diagnosis. *Id.* at 153–57; *see also infra* Part VIII.D.3.a (discussing the consequences of this frequent error committed by courts in toxic

chemical X and immediately thereafter developed symptom Y, the need for published literature showing a correlation between the two may be lessened."[338] The *Heller* court's holding is limited to acute exposure situations where the "temporal relationship" between the alleged exposure and the injury is "valid and strong."[339]

At the opposite end of the dose-response spectrum is the "chronic" case of *Mitchell v. Gencorp Inc.*[340] *Mitchell* involved a hematopoietic cancer (chronic myelogenous leukemia, or CML) allegedly caused by a long-term chemical exposure. The plaintiff's experts lacked epidemiologic evidence that the chemicals at issue (toluene, xylene, hexane, and haptene) were capable of causing CML.[341] To fill the void, the plaintiff's experts relied on the "chemical analogy" argument. They argued that a chemical (benzene) structurally similar to the chemicals at issue can cause leukemia and, by analogy, the chemicals at issue can cause leukemia.[342] The Tenth Circuit affirmed the trial court's summary judgment for the defendant, making short work of the plaintiff's experts' lack of epidemiologic support. Without scientific data supporting their conclusions that chemicals similar to benzene cause the same

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tort cases). The court confused the means by which the medical expert diagnosed the homeowners' injuries—medical tests and examinations, personal and medical histories, possible allergenic exposures, etc.—with the expert's means of determining the cause of the diagnosed illness—environmental tests and temporality. *Heller*, 167 F.3d at 153–57. One should read the court's conclusion—that a valid differential diagnosis coupled with strong temporality between the exposure and the onset of symptoms may suffice as general causation evidence—as a medical differential diagnosis, not a causation analysis. Otherwise, the conclusion is a mere tautology, and a valid causation analysis suffices as evidence of causation.

338. *Id.* (quoting Cavallo v. Star Enter., 892 F. Supp. 756, 774 (E.D. Va. 1995), *aff'd in relevant part*, 100 F.3d 1150, 1159 (4th Cir. 1996)). As this generality suggests, cases in which a valid diagnosis and strong temporality suffice for general causation purposes should be limited to those "dousing" cases in which the exposures are not genuinely disputed.

339. *Id.* at 154. The appellate court upheld the trial court's exclusion of the plaintiffs' medical causation expert because, among other reasons, the temporal nexus between the exposure and the symptoms was not strong enough. *Id.* at 158 ("[W]e have no problem concluding that the temporal relationship between the exposure to the Shaw carpeting and the onset of Heller's illness was questionable at best and exculpatory at worst."). The appellate court noted, as did the trial court, that: (1) the wife's symptoms were delayed for two weeks or so after installation of the carpet; (2) the homeowners experienced renewed symptoms after returning home almost a week after removal of the carpeting; and (3) the husband actually began experiencing symptoms prior to the installation of the carpet. *Id.* at 157.

340. 165 F.3d 778 (10th Cir. 1999).

341. *Id.* at 781–82.

342. *Id.*

problems as benzene, the analytical gap in the experts' testing is simply too wide for the opinions to establish causation.[343]

Even in an acute exposure-response case, a court should require the plaintiff to come forward with *some* reliable evidence of general causation, or at least an excuse for its absence. We disagree with the *Heller* view that a valid diagnosis and strong temporality without corroborating published research may be sufficient to admit general causation evidence in an acute exposure-response case. In such a case, a court should also require the plaintiff to produce a convincing explanation for the lack of published research before allowing into evidence a novel general causation theory. For example, a valid excuse for a lack of supporting research could be that the alleged exposure is rare or perhaps among the first. It would follow that relevant epidemiologic studies, toxicologic studies, and case reports would not be available. The *Heller* court alluded to such a situation when it observed that a strict requirement for published, peer-reviewed research in support of a general causation theory "would doom from the outset all cases in which the state of research on the specific ailment or on the alleged causal agent was in its early stages . . . ."[344] This point is true, but the plaintiff should bear the burden of explaining the absence of such research.[345] Conversely, the existence of research refuting general causation should doom the plaintiff's cause even if the diagnosis is undisputed and temporality is strong.

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343. *Id.* at 782; *see also* Wilson v. Merrell Dow Pharms., Inc., 893 F.2d 1149, 1154 (10th Cir. 1990) ("This lack of epidemiological proof for the Wilsons' claims is particularly significant in light of recent decisions of federal courts of appeals granting judgment n.o.v for Merrell Dow based upon the absence of epidemiological evidence showing a causal relationship between Bendectin use and birth defects." (citations omitted)); Cerna v. S. Fla. Bioavailability Clinic, Inc., No. 3D00-2126, slip op. at *3, 7–9 (Fla. Dist. Ct. App. Jan. 30, 2002) (affirming exclusion of ophthalmologist's opinion that ingestion of drugs caused plaintiff's blindness where the expert lacked epidemiologic evidence that drugs could cause blindness in humans at a normal dosage).

344. *Heller*, 167 F.3d at 155. This view excusing a lack of epidemiologic evidence may also apply in chronic-exposure cases. *See* Lakie v. SmithKline Beecham, 965 F. Supp. 49 (D.D.C. 1997). In *Lakie*, the court admitted the general causation testimony of the plaintiff's medical experts despite the paucity of epidemiologic evidence linking benzene exposure with the plaintiff's chronic disease. *Id.* at 56. The court accepted the experts' analogy between the plaintiff's bone marrow disease and other bone marrow diseases associated with benzene because, among other reasons, the plaintiff's bone marrow disease was "extremely rare" and therefore "has not been included in any of the epidemiological studies on benzene exposure." *Id.*

345. *See* Renaud v. Martin Marietta Corp., 749 F. Supp. 1545, 1554 (D. Colo. 1990) (recognizing that epidemiology is required in toxic tort cases "where collection of such evidence is possible"), *aff'd*, 972 F.2d 304, 307 (10th Cir. 1992).

c. The Independent Link of Temporality—Although *post hoc, ergo propter hoc* is a logical fallacy,[346] "post hoc" is a necessary prerequisite for the determination that exposure to an agent caused the injury. That is, the exposure must precede the injury. This link in the plaintiff's causal chain, if true, is easy to demonstrate and is not often challenged by the defendant. In such cases, the court can accept the link as proven, with probability "P" equal to one.

There are exceptions. The most common challenge to the temporality link involves cases in which there is a recognized "latency period" of years, or maybe decades, between the initial exposure and clinical recognition of the disease. For example, causation analyses of cancers require consideration of latency periods.[347] Defendants in toxic tort cases will challenge the temporality link in those cases where the alleged latency period between the initial exposure to the agent and the diagnosis of the injury is too brief. Indeed, courts have viewed truncated latency periods as a factor weighing against the reliability of causation testimony.[348]

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346. *See infra* note 399 and accompanying text (discussing the *post hoc, ergo propter hoc* fallacy).

347. For most cancers, the time from initial exposure to onset of disease is many years, even decades. SILVA, *supra* note 93, at 260. For example, adenocarcinomas of the vagina develop fifteen to thirty years after in utero exposure of female fetuses to diethylstilbestrol. Kenneth J. Rothman & Charles Poole, *Causation and Causal Inference*, *in* CANCER EPIDEMIOLOGY AND PREVENTION, *supra* note 125, at 3, 7. "A toxic tort claim alleging a shorter time period between cause and effect is scientifically untenable." Goldstein & Henifin, *supra* note 292, at 426. Appropriate "time-lag" periods are incorporated with the statistical analysis of epidemiological studies so that the exposure data "refer to the relevant etiological period (for example, 10–20 years before the development of cancer)." SILVA, *supra* note 93, at 260; *see, e.g.*, M. H. Ward et al., *Drinking Water Nitrate and the Risk of Non-Hodgkin's Lymphoma*, 7 EPIDEMIOLOGY 465, 467 (1996) (incorporating a lag time of five years "since exposures just a few years before diagnosis are unlikely to be related to cancer risk").

348. *See, e.g.*, Medalen v. Tiger Drylac, 269 F. Supp. 2d 1118, 1133 (D. Minn. 2003) ("Without knowing the latency period, between the Plaintiff's exposure to one carcinogen, or another, and the onset date of her basal cell carcinoma—and Dr. Martinez provides neither—there is no logical way that the doctor could conclude that a temporal relationship existed between the Plaintiff's non-acute exposure to powdered coatings, as opposed to her exposure to liquid paints, or sunlight, to name but two other complicating environmental agents, and the incurrence of her basal cell carcinoma."); Burleson v. Glass, 268 F. Supp. 2d 699, 707 (W.D. Tex. 2003) (granting defendant's motion to exclude plaintiff's expert testimony in part because two-year latency period from alleged exposure to onset of cancer was unusually short given the scientific literature indicating typical latency of ten to fifteen years for the tumor type); Nat'l Bank of Commerce v. Associated Milk Producers, 22 F. Supp. 2d 942, 975 (E.D. Ark. 1998) (excluding expert testimony because an unusually short latency period "creates one more negative for the plaintiffs"), *aff'd*, 191 F.3d 858 (8th Cir. 1999); Goewey v. United States, 886 F. Supp. 1268, 1280–81 (D.S.C. 1995) (holding that plaintiff failed to establish causation where scientist's testimony concerning latency period conflicted with his research). *But see* Ruff v. Ensign-Bickford Indus., Inc., 168 F. Supp. 2d 1271, 1283–86 (D. Utah 2001) (allowing plaintiffs' causation expert to testify that the plaintiffs' exposure to nitrates in drinking water caused their non-Hodgkin's lymphoma [NHL]).

d. Specific Causation and the Dependent Links—At this stage, the court addresses the causation expert's method of extrapolating from the scientific data to the conclusion that the subject agent caused the specific disease at issue. Here, the court asks: 1) what was the plaintiff's dose or exposure level; 2) does the scientific evidence demonstrate that the plaintiff's dose or exposure level can cause the specific disease in humans so exposed; and 3) did the expert explain on a quantitative basis how he or she eliminated other potential causes of the plaintiff's disease and determined that the subject agent is the most likely cause?

Step three of this inquiry is the point at which Bayes' Law comes into play.[349] The reliability of the causation expert's specific causation analysis depends on the specificity of the analysis—that is, how well does the method detect those in the population with the disease not caused by the agent—and the base rate of the agent-induced disease in the relevant population.[350] Opinions that fail to take into account the specificity of the analysis and the base rate of the agent-induced injury are inherently unreliable.

As noted in the introduction to this Article, we know of no toxic tort case in which the court engaged in a Bayesian analysis of the proffered specific causation testimony, taking into account the base

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In *Ruff*, the court failed to mention the issue of temporality associated with one of the plaintiffs, whose NHL developed possibly within eighteen months after her first potential exposure to the nitrates in her well water. *See id.* at 1283–86. The defendants challenged the plaintiffs' expert's specific causation opinion on the ground that the latency period was too short for that particular plaintiff. Memorandum in Support of Defendants' Motion for Summary Judgment and *Daubert* Motion to Exclude Testimony of Dr. Dennis Weisenburger at 72–74, *Ruff*, 168 F. Supp. 2d 1271 (No. 2:99CV0120B). In fact, the defendants pointed out that the expert had co-authored an epidemiologic study of nitrates in drinking water that incorporated a "lag time" of five years "since exposures just a few years before diagnosis are unlikely to be related to cancer risk." *Id.* at 73 (quoting Ward et al., *supra* note 347, at 467). Despite this published statement in direct conflict with the expert's litigation opinion, the court admitted the expert's specific causation opinion as to that plaintiff. *Ruff*, 168 F. Supp. 2d at 1283–86. In fact, as mentioned, the court did not discuss this contested latency issue. *See id.*

349. Bayesian analysis also bears on the issue of diagnosis. Physicians should, and do, take into account the base rate of the disease in the population when determining the most likely disease afflicting an individual based on the signs and symptoms presented. Henifin et al., *supra* note 276, at 467 ("[P]hysicians frequently rely on the principles of Bayesian reasoning when deciding on a diagnosis. Doctors combine probabilities of disease (prevalence) with their knowledge of the frequency of signs and symptoms in a given disease and competing diseases to progressively modify and ultimately arrive at their view of the likelihood of the disease under consideration.").

350. Two commentators have mused of 100% specificity. *See* Hall & Silbergeld, *supra* note 66, at 442. "In a perfect world, science would be able to locate the people whose injury was caused by a chemical and distinguish them from people whose suffering from a similar disease was caused by other factors." *Id.* In reality, "[h]owever, the etiology of most chemically induced disease will never afford us such precision." *Id.* (citing GARY FRIEDMAN, PRIMER OF EPIDEMIOLOGY 1–4 (2d ed. 1980)).

rate of the disease and the specificity of the expert's methods. Nevertheless, there are examples of courts engaging in a crude type of analysis indicating an inchoate understanding of the importance of base rates and specificity. For example, in *Wade-Greaux v. Whitehall Laboratories, Inc.*, the court recognized that there are numerous agents capable of causing birth defects such as the plaintiff's, including genetic and chromosomal abnormalities, bacterial and viral infections, chemicals, radiation, drugs and "unknown" causes.[351] Although the court did not conduct a Bayesian analysis per se, it noted the probabilities that these alternative agents may have caused the plaintiff's defect by noting that such birth defects are common and that "environmental agents" may account for ten to twenty percent of human malformations.[352] The court held that the plaintiff's causation experts did not account for these alternative agents, rendering unreliable their proffered specific causation testimony.[353]

Although courts such as *Wade-Greaux* may not be thinking in terms of Bayes' Law, the requirement that the causation expert address alternative explanations for the injury is a rudimentary approach to the base-rate problem. Courts have held that the failure of a health expert to address alternative causes of a plaintiff's injury is grounds for excluding the expert's specific causation testimony.[354] Generally, the more alternative possible causes there are

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351. 874 F. Supp. 1441, 1449, 1483, 1485 (D.V.I. 1994), *aff'd*, 46 F.3d 1120 (3d Cir. 1994).

352. *Id.* at 1449.

353. *Id.* at 1485; *see also* Newton v. Roche Labs., Inc., 243 F. Supp. 2d 672 (W.D. Tex. 2002) (barring specific causation testimony that acne drug caused plaintiff's schizophrenia in part because expert failed to rule out other risk factors for schizophrenia such as a family history of schizophrenia in plaintiff's mother, sister, and uncle, plaintiff's personal history of malnutrition, and her father's age of sixty when she was born).

354. *See, e.g.*, Moore v. Ashland Chem. Co., 151 F.3d 269, 279 (5th Cir. 1998) (affirming trial court's finding that plaintiff's causation theory was unreliable because, among other reasons, expert did not account for plaintiff's personal habits and medical history as alternative explanations for plaintiff's disease); Claar v. Burlington N. R.R., 29 F.3d 499, 502 (9th Cir. 1994) (holding doctor's testimony inadmissible because doctor failed to rule out alternative possible causes for plaintiffs' injuries, even though the doctor admitted that this step is standard procedure before each diagnosis); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 610 (D.N.J. 2002) (excluding plaintiff's medical causation testimony because, among other reasons, expert failed to address plaintiff's smoking history and family history of cancer as alternative causes of plaintiff's cancer); Wills v. Amerada Hess Corp., 98 Civ. 7126(RPP), 2002 WL 140542 (S.D.N.Y. Jan. 31, 2002) (excluding toxicologist's proffered testimony that decedent's occupational exposures caused his cancer because, among other reasons, expert failed to explain how he eliminated decedent's cigarette smoking as a possible cause of decedent's cancer even though cigarette smoking was a major risk factor for decedent's type of cancer); Cloud v. Pfizer, 198 F. Supp. 2d 1118, 1136 (D. Ariz. 2001) (excluding psychiatrist's opinion that drug caused decedent to commit suicide because, among other

for the injury, or the more likely an alternative possible cause explains the injury, the more explanation (specificity) courts should require from the causation expert as to why the subject agent is the probable cause. The causation expert's failure to address a major cause of the disease in the population,[355] or failure to consider idiopathic disease, should be fatal to the plaintiff's claim.[356] If there are other risk factors present in a case, courts should require the causation expert to conduct reliable quantitative risk analyses to demonstrate the most likely causal factor. When there is epidemiologic evidence available, the risk analyses can, and should, include Bayesian analysis to determine the most likely cause of the injury among the potential agents.

e. The Exposure Links: Actual Exposure and Hazardous Exposure—"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."[357] So said Philippus Aureolus Theophrastus Bombastus von Hohenheim, known as Paracelsus, the Renaissance man in the history of science and medicine. Paracelsus was speaking of a "threshold" dose required for an observable biological response, whether remedial or toxic.[358] To demonstrate that an exposure to an agent caused a

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reasons, psychiatrist did not fully explore other potential causes of the suicide, such as alcohol consumption and family problems); Aldridge v. Goodyear Tire & Rubber Co., 34 F. Supp. 2d 1010, 1024 (D. Md. 1999) (excluding causation testimony because experts did not explain how they concluded that a particular chemical caused the particular disease when other occupational and environmental exposures have similar effects); Reiff v. Convergent Techs., 957 F. Supp. 573, 583 (D.N.J. 1997) (excluding expert's testimony because expert was unable to discount alternative causes and did little, if anything, to rule them out); Diaz v. Johnson Matthey, Inc., 893 F. Supp. 358, 376–77 (D.N.J. 1995) (citing *In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 760 (3d Cir. 1994)) (holding that expert's opinion on specific causation was unreliable because expert failed to account for alternative causes); Praytor v. Ford Motor Co., 97 S.W.3d 237 (Tex. App. 2002) (barring plaintiff's causation experts because they failed to rule out possible causes of plaintiff's asthma other than the chemicals in the deployed air bag).

355. *See, e.g., In re* Swine Flu Immunization Prods. Liab. Litig., 508 F. Supp. 897, 906–07 (D. Colo. 1981) (barring experts' proffered testimony that swine flu caused plaintiff's neurological disorder in part because experts failed to account for plaintiff's pre-existing viral infection, a risk factor of the illness), *aff'd sub nom.*, Lima v. United States, 708 F.2d 502, 507 (10th Cir. 1983).

356. *See* discussion *supra* Part VIII.C.3.a. Many courts do not require physicians to explain their causation analyses. Instead, these courts incorrectly label the physicians' causation analyses as "differential diagnoses." *See supra* note 286. Then, these courts apply no scrutiny at all to the physicians' causation analyses, believing that "diagnoses" by physicians, even those reached in the course of litigation, are inherently reliable and seldom wrong. *See supra* note 302 and accompanying text. Such judicial deference to physicians' causation analyses is the most glaring abdication of the courts' gatekeeping duty routinely found in toxic tort cases.

357. Michael A. Gallo, *History and Scope of Toxicology, in* CASARETT & DOULL'S TOXICOLOGY, *supra* note 117, at 3, 4.

358. Eaton & Klaassen, *supra* note 117, at 13.

deleterious response in an exposed person, one must be able to demonstrate that the dose received by the person was sufficient to cause the response. The burden of proof in a toxic tort case requires the plaintiff to show with reasonable certainty that the subject exposures resulted in a dose sufficient to produce the injury suffered.[359]

To survive *Daubert* scrutiny, the plaintiff must have reliable scientific evidence that the exposure to the subject agent exceeded the level of exposure sufficient to cause the injury. For example, in *Sutera v. The Perrier Group of America, Inc.*, the plaintiff claimed that his leukemia, a type of cancer, resulted from his consumption of the defendant's bottled water that contained low levels of benzene.[360] The plaintiff's medical expert was prepared to opine that the benzene in the bottled water caused the plaintiff's leukemia.[361] The plaintiff's medical theory in *Sutera* was based on the "no threshold" model, which holds that there is no safe level of exposure to a carcinogen and, therefore, any exposure to a carcinogen no matter how low is sufficient to cause leukemia.[362] The *Sutera* court found that the no-threshold model "cannot be

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359. *See supra* note 131 (discussing the differences between "dose" and "exposure"). The distinction between dose and exposure is important in many toxic exposure cases, particularly in those cases in which the agent is poorly absorbed by the human body, resulting in low doses despite high exposures. For example, while lead is a well-recognized toxin, the human intestines absorb some forms of lead so poorly that exposures via ingestion to such forms of lead present low health risks. *See generally* Ilene Danse et al., *Blood Lead Surveys of Communities in Proximity to Lead-Containing Mill Tailings*, 56 AM. INDUS. HYGIENE ASS'N J. 384 (1995); Martha J. Steele et al., *Assessing the Contribution from Lead in Mining Wastes to Blood Lead*, 11 REG. TOXICOLOGY & PHARMACOLOGY 158 (1990). Consequently, despite heavy soil lead contamination in some communities surrounding lead mines, the levels of lead in the blood of children remain surprisingly low. *See generally* Danse et al., *supra*; Stelle et al., *supra*.

360. 986 F. Supp. 655, 657–58 (D. Mass. 1997). Perrier's troubles began in January 1990 when laboratory workers in North Carolina, using Perrier water as a quality control for analysis, got some odd readings from their spectrometer. *Perrier Woes Began with Blip on Carolina Screen*, N.Y. TIMES, Feb. 12, 1990, at A18. The "pure" French mineral water contained benzene at levels ranging from 12.3 to 19.9 parts per billion, in excess of the five parts per billion standard set for public drinking water by the EPA. G. James, *Perrier Recalls Its Water in U.S. After Benzene Is Found in Bottles*, N.Y. TIMES, Feb. 10, 1990, at A1. Although the U.S. Food and Drug Administration (FDA) emphasized that the risk presented by the low levels of benzene in water was small, Perrier recalled its entire inventory of over seventy-two million bottles. Barry Meier, *Perrier Production Halted Worldwide*, N.Y. TIMES, Feb. 11, 1990, at A26. Then-Senator Al Gore stated: "I am not going to be satisfied until thousands of rats have consumed millions of bottles of Perrier and survived." Maureen Dowd, *What, No Perrier? Status Bubble Bursts*, N.Y. TIMES, Feb. 11, 1990, at A26. It turned out that benzene was naturally present in the spring from which Perrier drew its water. Barbara Wickens, *Bursting the Bubble*, MACLEAN'S, Feb. 26, 1990, at 34, 34.

361. *Sutera*, 986 F. Supp. at 656–57.

362. *Id.*

falsified, nor can it be validated."[363] Since the plaintiff in *Sutera* had no testimony that his low-level exposure to benzene is hazardous to humans other than his expert's unproved "no threshold" theory, the court excluded this unreliable testimony and granted summary judgment for the defendant.[364]

Courts do not require claimants to prove the exact dose or exposure. Courts do require, however, evidence that the alleged exposure was sufficient to cause the injury at issue.[365] In the best of circumstances, actual dose data are available. For some agents, scientists can determine the actual dose by measuring the agent or its metabolite in biological tissue such as blood, urine, or hair. In most circumstances, however, actual dose data are unavailable, and the experts must use whatever exposure information is available as a surrogate for dose.[366] Sometimes exposure measurements from which an industrial hygiene or toxicology expert can extrapolate reliable dose or exposure estimates are available. In other cases, experts can estimate historical exposures based on data and testimony less reliable than actual exposure measurements, but reliable enough for present purposes. Experts can extrapolate reliable exposure estimates from data and testimony such as duration of exposure; distance from the source of the agent; volatility of the agent; environmental conditions such as temperature and wind speed and direction; presence or absence of mechanical ventilation; extent of skin contact with the agent and dermal permeability to the agent;[367] odor

363. *Id.* at 667 (quoting Whiting v. Boston Edison Co., 891 F. Supp. 12, 25 (D. Mass. 1995)); *see also* Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 593 (1993) (stating that scientific status of a theory stems from its falsifiability because testing a hypothesis to see if it is false is the method that distinguishes science from other fields of inquiry).

364. *Sutera*, 986 F. Supp. at 667–68; *see also* Wills v. Amerada Hess Corp., 98 Civ. 7126(RPP), 2002 WL 140542, at *8, 13–14 (S.D.N.Y. Jan. 31, 2002) (excluding the plaintiff's causation expert's "oncogene theory," where a single exposure is sufficient to initiate cell transformation leading to cancer, which is both untested and untestable); *supra* Part V.A.7 (summarizing cases in which the courts have demanded information concerning plaintiff's levels of exposures to the alleged causative agent).

365. *Id.* (discussing the "threshold dose" concept).

366. *See* ENVIRONMENTAL & OCCUPATIONAL MEDICINE 40 (William N. Rom ed., 3d ed. 1998) ("In most instances, doses and dose rates cannot be measured directly, and surrogate measures must be developed from data on exposures observed in the environment external to the worker. Exposure concentration or intensity is used as a surrogate for dose rate . . . .").

367. Sound logic dictates that reliable dose data trump exposure estimates. *Compare* Lakie v. SmithKline Beecham, 965 F. Supp. 49 (D.D.C. 1997) (admitting plaintiff's expert's benzene dose estimates based on the skin absorption rate of benzene through human skin, the concentration of benzene in defendant's dental adhesive, and the frequency of plaintiff's use of the product), *with* Bourne v. E.I. DuPont De Nemours & Co., 189 F. Supp. 2d 482, 499–501 (S.D. W. Va. 2002) (excluding as unreliable plaintiff's expert's dermal absorption rate estimate based on the permeability of rat skin because, among other things, the

thresholds;[368] the quantity of the agent present and the concentration of the agent in mixtures;[369] whether the agent is heated; and other data and testimony. Whatever the means of estimating doses, a transparent and valid scientific methodology, not exactitude, is required.[370]

There is a temptation to assume that the dose was sufficient to cause the injury because the plaintiff displayed injury after the exposure. This circular logic is akin to the *post hoc, ergo propter hoc* fallacy sometimes used to justify a finding of general causation where epidemiologic evidence is lacking.[371] Where causation is at

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expert failed to adjust for the lower permeability of human skin as compared with rat skin), *aff'd*, 85 F. App'x 964 (4th Cir. 2004), Mancuso v. Consol. Edison Co. of N.Y., 56 F. Supp. 2d 391, 399–401 (S.D.N.Y. 1999) (excluding plaintiff's expert's opinion based in part on the assumption that the plaintiffs came in skin contact with PCB-contaminated mud and water "on pretty much a daily basis" because the assumption did not fit the facts of the case and a better measure of the plaintiff's dose was available—blood tests indicated that the plaintiffs' PCB body burden was less than the typical New York adult), *aff'd in relevant part*, 216 F.3d 1072 (2d Cir. 2000), *and* Leija v. Marathon Oil, No. 96-617531 (Mich. Cir. Ct. Feb. 15, 2000) (excluding plaintiff's benzene dose estimate based on an unreliable dermal absorption model used by plaintiff's experts).

368. *See, e.g.*, Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 614 (D.N.J. 2002) (holding that the method of estimating concentrations of air contaminants by use of published odor thresholds "has been subject to peer review and is a generally accepted way of estimating exposure levels in the absence of air sampling").

369. *See, e.g.*, Amorgianos v. National R.R. Passenger Corp., 137 F. Supp. 147, 158 (E.D.N.Y. 2001) (calculating potential xylene exposure levels based on the amount of paint used, its xylene content, the volume of the containment area in which the plaintiff worked, and other factors because measurements of the xylene concentration in air were lacking).

370. One commentator disagrees. John Hein, *When Reliable Is Reliable Enough: The Use of Expert Testimony After* Kumho v. Carmichael, 6 WASH. U. J.L. & POL'Y 223, 231–33 (2001) (citing Goeb v. Tharaldson, No. CX-98-2275, 1999 WL 561956 (Minn. Ct. App. Oct. 21, 1999), *aff'd*, 615 N.W.2d 800 (Minn. 2000)) ("In toxic substance exposure litigation, an expert's failure to identify the precise exposure dose level can be fatal to an expert's qualification and to the plaintiff's case."). Contrary to Hein's analysis, however, the *Goeb* court did not apply so strict a test. Pursuant to the *Frye* "general acceptance" standard as applied by the Minnesota courts, the *Goeb* court excluded the plaintiffs' causation experts for a plethora of reasons, the inexactitude of the experts' exposure quantification not being one of them. *Goeb*, 1999 WL 561956, at *3. Indeed, the Minnesota Supreme Court, in affirming the exclusion of the plaintiffs' experts, eschewed the "exposure level" issue and relied instead on the remaining shortcomings in the experts' methodologies, including their failure to review the plaintiffs' medical records before reaching their causation opinions or produce medical and scientific support for their diagnostic techniques. *Goeb*, 615 N.W.2d at 815–16. Neither the district court, the appellate court, nor the Minnesota Supreme Court required the Goebs to present evidence of their exact exposures, an impossible evidentiary hurdle. *See also Lakie*, 965 F. Supp. at 58 (rejecting defendant's argument that plaintiff's dose expert's opinion was unreliable because he did not know plaintiff's precise exposure level) ("The law does not hold the plaintiff to such an exacting standard of proof.").

371. *See, e.g.*, Marsh v. W.R. Grace & Co., Nos. 98-1943, 98-1944 & 98-1945, 2003 WL 22718177, at *4 (4th Cir. Nov. 19, 2003) (affirming trial court's summary judgment in favor of defendant in part because plaintiffs' causation expert lacked epidemiologic evidence that agent can cause cancer, instead "start[ing] from the conclusion that picloram caused the

issue, sound science does not allow the retroactive calculation of dose based on the injury. To do so is a self-fulfilling prophecy, as recognized in *Wright v. Willamette Industries, Inc.*[372] In *Wright*, the court found that the testimony of plaintiffs' experts, including an industrial hygienist, "failed to produce evidence that they were exposed to a hazardous level of formaldehyde . . . ."[373] The industrial hygienist in *Wright* offered testimony about the levels of formaldehyde that *might* be expected to cause symptoms like the ones that plaintiffs claimed to have experienced.[374] Such testimony was insufficient evidence of the level of formaldehyde the plaintiffs incurred. The court stated:

> It is therefore not enough for a plaintiff to show that a certain chemical agent sometimes causes the kind of harm that he or she is complaining of. *At a minimum, we think that there must be evidence from which the factfinder can conclude that the plaintiff was exposed to levels of that agent that are known to cause the kind of harm that the plaintiff claims to have suffered.* We do not require a mathematically precise table equating levels of exposure with levels of harm, but there must be evidence from which a reasonable person could conclude that a defendant's emission has probably caused a particular plaintiff the kind of harm of which he or she complains before there can be a recovery.[375]

Similarly, in *O'Conner v. Commonwealth Edison Co.*, a nuclear power plant worker sued the plant licensee alleging that occupational exposures to radiation caused his cataracts.[376] The trial court granted the defendant's motion in limine to exclude the testimony

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plaintiffs' cancers and then generated, without testing, the hypothesis to support that conclusion"); *see also* Ballentine v. The Terminix Int'l Co., No. 98C-836, slip op. at 11 (Tenn. Cir. Ct. June 25, 2004) ("Here, Dr. Calabrese formed his [causation] opinion and only when the weaknesses and, perhaps, scientific invalidity of his opinions were exposed in his deposition did he do any serious research. It was too little, too late, to convince the Court of his reliability.").

372. 91 F.3d 1105 (8th Cir. 1996).

373. *Id.* at 1107.

374. *Id.*

375. *Id.* (emphasis added) (citation omitted); *see also Marsh*, 2003 WL 22718177, at *5 (affirming trial court's summary judgment in favor of defendant in part because plaintiffs' causation expert could not state the "no effect" level of the subject agent or whether plaintiffs' exposures exceeded that level, instead "assum[ing] the plaintiffs had received adequate exposure to picloram to cause cancer"); Payne v. Union Pac. R.R., No. 8:00CV337, slip op. at 11–12 (D. Neb. Oct. 9, 2001) (quoting *Wright*, 91 F.3d 1105, and granting defendant's motion for summary judgment because plaintiff failed to produce evidence of his level of exposure to creosote).

376. 807 F. Supp. 1376, 1378 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994).

of the plaintiff's ophthalmologist.[377] The *O'Conner* court found that the ophthalmologist's methodology was "to first uncritically accept what Mr. O'Conner told him about receiving a high dose and then to assume that radiation induced cataracts are pathognomonic."[378] The court found that "[b]oth parts of [the ophthalmologist's] methodology are errors and are not a methodology which any reasonable expert in radiation doses or radiation effect on humans would use."[379] The Court elucidated the flaw in the expert's methodology, noting:

> Dr. Scheribel failed to assess properly O'Conner's radiation dose before concluding that the radiation caused his cataracts. As set forth previously, any expert with even rudimentary knowledge of this field would know that radiation induced cataracts require a certain threshold dose and would carefully seek to discover the exact dose involved *before* giving a causation opinion. Dr. Scheribel did the opposite: he presumed that the cataracts were radiation induced, and then presumed that the plaintiff must have somehow been exposed to a high enough dose to exceed the threshold in order to have caused the cataracts, thereby justifying his initial diagnosis. This is circular reasoning. . . .
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> . . . .
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> An expert in radiation induced cataracts would require knowledge of a patient's radiation dose *before* finding causation. He would not rely only on the story told by the patient to determine the patient's radiation dose. Rather, the expert would review the patient's actual dosimetry records, and examine (or perform) the appropriate medical tests to determine the dose received. He would also review the scientific literature to learn the threshold dose of radiation and minimum latency period required to cause cataracts.[380]

Courts tend to be more lenient when considering the plaintiff's exposure evidence in acute exposure cases where the agent is well

377. *Id.* at 1404. Since the remaining evidence was insufficient for plaintiff to establish the essential elements of his negligence claims, the court also granted the defendant's motion for summary judgment. *Id.*

378. *Id.* at 1397.

379. *Id.*

380. *Id.* at 1396 (citations omitted) (emphases added).

known to cause the injury and the manifestation of the injury is immediate, or nearly so.[381] For example, in *Louderback v. Orkin Exterminating Co.*, the plaintiffs suffered symptoms following accidental exposure to an organophosphate pesticide with well-known, acute toxic properties.[382] The plaintiffs' causation expert could not estimate the levels of exposures to the pesticide, nor did he consider known safe levels of exposure for the pesticide.[383] The district court recognized that the expert's failure to quantify the exposures and hazard weighed against admission of the proffered testimony. Nevertheless, under the facts of that case, the district court determined that this failing was not crucial. The well-known toxic properties of the chemical, the strong temporality of symptoms, and the expert's "differential diagnosis" overcame the expert's lack of dose-response data.[384]

Falling somewhere between the chronic and acute exposure scenarios are cases such as *Amorgianos v. National Railroad Passenger Corp.*[385] In that case, a railroad worker and his wife sued the worker's employer, claiming that he suffered permanent neurological damage as a result of intermittent occupational exposures to xylene (and maybe other organic solvents) during a 30-day period of spray-painting a bridge.[386] The worker's exposures fit into the "sub-acute" category.[387] The jury returned a verdict for the plaintiffs in the amount of $2.3 million. The trial court subsequently granted the railroad's motion for a new trial, "finding that the verdict was 'fundamentally against the overwhelming weight of the evidence' and represented a 'miscarriage of justice.'"[388] Subsequently, another judge granted the railroad's motion to exclude the proffered testimony concerning the worker's permanent neurological

381. *See supra* Part VIII.D.3.b (discussing the analogous view that a court's scrutiny of general causation evidence may be lenient in acute exposure/acute effects cases).

382. 26 F. Supp. 2d 1298, 1306 (D. Kan. 1998).

383. *Id.* at 1305–06.

384. *Id.* at 1306. *Compare id.* at 1298 (admitting causation expert's opinions in "strong temporality" case even though expert did not quantify exposures or risk), *with* Polaino v. Bayer Corp., 122 F. Supp. 2d 63, 69 (D. Mass. 2000) (excluding the causation experts' opinion in a "strong temporality" case because they had failed to conduct reliable exposure estimates or demonstrate that the plaintiff had actually been exposed to the subject toxins even though the injury followed soon after the putative exposure).

385. 137 F. Supp. 2d 147 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

386. *Id.* at 150–51, 177. The worker's wife joined him as a plaintiff. *Id.* at 149.

387. *See supra* note 329 (citing Eaton & Klaassen, *supra* note 117, at 14) (defining "acute," "subacute," and "chronic" exposures).

388. *Amorgianos*, 137 F. Supp. 2d at 159 (quoting Trial Transcript Sept. 29, 1998 at 67, *Amorgianos*, 137 F. Supp. 2d 147 (No. CIV A. CV-96-2745 (DGT))).

conditions.[389] In part, the court excluded this causation testimony because the court found unreliable the plaintiffs' industrial hygiene expert's exposure estimates.[390] Despite the close temporality of the worker's sub-acute exposures and the onset of his neurological symptoms, the *Amorgianos* court demanded reliable scientific support for the worker's claim that his exposures to the organic solvents were sufficient to cause the alleged neurological damage.[391]

Why did the *Amorgianos* court demand strict proof of exposure levels and duration despite the strong temporality between the subacute exposures and the symptoms? Since the exposures were subacute, the *Amorgianos* court could have followed the lenient *Louderback* model and excuse the plaintiffs' weak exposure evidence. Instead, it followed the *Wright* model and demanded more exacting evidence relating to exposures. One reason may be the many weaknesses in the worker's evidence that he suffered permanent neurological damage, casting in doubt the diagnosis of neurological damaged reached by the plaintiff's medical experts. While the worker complained of worsening neurological symptoms, supported by his wife's testimony, all the objective neurological tests were either negative or, if positive, had a more plausible explanation.[392] In

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389. *Id.* at 191. The court denied the defendant's motion insofar as it attempted to exclude testimony concerning the plaintiff's claim that he suffered acute effects during the few days following his exposures, including eye irritation, nausea, and fever. *Id.* The court, however, demanded reliable estimates of the plaintiff's exposures to support these claims of acute effects. *Id.* The court granted the plaintiff leave to supplement the industrial hygienist's report to give that expert a chance to perform a "proper exposure assessment." *Id.* at 175, 191. If the plaintiff failed to submit a supplemental report addressing the issue of exposures, the court would grant leave to the defendant to move for summary judgment on the acute claims. *Id.* at 191.

390. *Amorgianos*, 137 F. Supp. 2d at 170–77, 188–90. In addition, the court found the proffered expert testimony unreliable and inadmissible because the expert lacked scientific evidence of a causal link between the alleged exposures and permanent neurological damage—that is, the expert lacked evidence of general causation. *Id.* at 177–91.

In many cases in which the plaintiff alleges that occupational exposures caused the injuries, experts in the field of industrial hygiene provide exposure testimony. The industrial hygienist may offer opinions as to the level and extent of exposure based on actual exposure monitoring data or, if such data is unavailable, exposure models using principles of chemistry and physics; in either case, the industrial hygienist's methods must pass the court's scrutiny for reliability. *See, e.g.*, Nook v. Long Island R.R., 190 F. Supp. 2d 639, 642 (S.D.N.Y. 2002) (excluding exposure estimates offered by industrial hygienist because he did not validate his estimates by collecting data); Castellow v. Chevron USA, 97 F. Supp. 2d 780, 787–93 (S.D. Tex. 2000) (excluding industrial hygienist's exposure model testimony under *Daubert* because industrial hygienist revised his estimates several times during the course of litigation and admitted at one point that his estimates were improbable).

391. *Amorgianos*, 137 F. Supp. 2d at 169–78.

392. *Id.* at 154–59.

addition, surveillance videotape showed the plaintiff walking about town with no apparent difficulty, in direct conflict with his testimony.[393] Finally, emergency room medical records following a car accident, which occurred after the subject exposures, indicated that the worker was suffering no neurological problems, again in direct conflict with the plaintiffs' testimony.[394] For these reasons, the court appeared skeptical of the medical experts' diagnoses.[395]

An analysis of the *Amorgianos* case and other toxic tort cases in which doses are at issue suggests a concordance. The plaintiff's claim will pass *Daubert* scrutiny without direct exposure (dose) data only where the temporality of the exposures and the symptoms is strong, general causation is well established, and the medical expert's differential diagnosis is valid.[396] In other words, strong temporality, well-established general causation, and a valid diagnosis are sufficient proof of harmful dose in toxic exposure cases. This view does not suggest that plaintiff need not produce reliable evidence of exposure at the *Daubert* stage. Rather, this view suggests that the plaintiff's evidence of exposure may be indirect, but nevertheless reliable, in limited circumstances.[397] In generic toxic tort cases, direct evidence of exposure is required.

The same leniency arguably applies in a few chronic, "weak temporality" cases involving "signature" diseases.[398] If the disease is

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393. *Id.* at 156. The trial judge cited this videotape as a basis of his decision to grant the railroad's motion for a new trial. *Id.* at 159.

394. *Id.* at 155. The trial judge also cited these emergency room medical records as a ground to allow the railroad a new trial. *Id.* at 159.

395. *Id.* at 157–59.

396. In *Amorgianos*, the lack of a reliable diagnosis doomed the plaintiff's case. There was evidence refuting the plaintiff's claim that he actually incurred neurological damage. *See supra* notes 392–395 and accompanying text. This doubtful diagnosis proved an insufficient basis for the plaintiff's indirect proof of his dose.

397. For a similar analysis, see Note, *supra* note 6, at 1476 (suggesting that toxic tort cases involving close temporality coupled with reliable diagnoses present a situation more akin to "slip and fall" cases than "generic" toxic tort cases and therefore justify relaxed rules of admissibility bearing on causation opinions). On the flip side of the coin are the so-called "trauma cancer" cases, which are "slip and fall" cases more akin to "generic" toxic tort cases. *See supra* note 202.

Bocanegra v. Vicmar Services, Inc. presents an interesting corollary of the "indirect proof of dose" view. 320 F.3d 581 (5th Cir. 2003). In *Bocanegra*, the appellate court reversed a "take-nothing" verdict, holding that the trial court should have admitted a toxicologist's testimony concerning the defendant motorist's mind-altering dose of marijuana prior to a traffic accident. *Id.* at 590. Addressing the trial court's view that the toxicologist did not know the defendant's dose of marijuana, the appellate court noted that marijuana users smoke until they achieve the desired mind-altering dose, a view with which defense experts agreed. *Id.* at 588–90. A truism—dopers smoke dope until they are doped—was sufficient corroboration of the toxicologist's dose opinion.

398. *See supra* notes 315–318 and accompanying text (discussing signature, or pathognomonic, diseases).

rarely, or never, caused by anything other than the subject agent, proof of dose may be unnecessary. In such cases, the reasoning that the disease proves the sufficiency of the exposure is reliable, at least reliable enough to establish the plaintiff's prima facie case. Since the presence of a signature disease, correctly diagnosed, proves specific causation, it follows that it proves sufficiency of the dose, an element of specific causation, at least so long as the plaintiff can establish *some* threshold exposure to the agent.

In any event, most toxic tort cases involve no signature disease, meaning that there are many possible causes of the subject injury. In such cases, courts should, and do, bar evidence based on *post hoc, ergo propter hoc* logic (that is, circular reasoning) that the person's exposure must have been sufficient to cause the disease because the person developed the disease after the alleged exposure.[399]

f. The Most Likely Cause—Finally, at the *Daubert* stage the causation expert must address alternative causes of the subject disease, and explain through a reliable quantitative analysis the predominance of the subject agent as the most likely cause of the disease. It is at this specific causation stage that Bayesian analysis applies. Crucial to this quantitative analysis is consideration of the base rate of the agent-induced disease.

Good scientific methodology requires that a scientist conduct a valid risk assessment to arrive at an opinion concerning causation of disease. "[T]he question for causation purposes is: At what levels of exposure do what kinds of harm occur?"[400] Risk assessment requires a determination of what dose-response relationship exists

399. *See, e.g.*, Washburn v. Merck & Co., Inc., No. 99-9121, 2000 WL 528649, at *2 (2d Cir. 2000) (affirming exclusion of expert testimony based "on little more than temporal correlation between [plaintiff's] vaccination and the onset of symptoms" (citing Cavallo v. Star Enter., 892 F. Supp. 756 (E.D. Va. 1995), *aff'd in relevant part*, 100 F.3d 1150 (4th Cir. 1996); Conde v. Velsicol Chem. Corp., 804 F. Supp. 972, 1023 (S.D. Ohio 1992), *aff'd*, 24 F.3d 809 (6th Cir. 1994))); Austin v. Children's Hosp. Med. Ctr., No. 95-3880, 1996 U.S. App. LEXIS 22329, at *7 (6th Cir. July 26, 1996) (citing Abbott v. Fed. Forge, Inc., 912 F.2d 867, 875 (6th Cir. 1990); Hasler v. United States, 718 F.2d 202, 205 (6th Cir. 1983)) (finding that temporality alone is not sufficient to create a material issue of causation); Cerna v. S. Fla. Bioavailability Clinic, Inc., 815 So. 2d 652, 655 (Fla. Dist. Ct. App. 2002) ("Expert causation theories based solely on the temporal proximity between an ingested pharmaceutical and the resulting injury are not methodologically sound."); Hannan v. Pest Control Servs., Inc., 734 N.E.2d 674, 682 (Ind. Ct. App. 2000) (excluding plaintiffs' experts' testimony because they "were relying on a mere temporal coincidence of the pesticide application" and the plaintiffs' alleged illnesses).

400. Cartwright v. Home Depot U.S.A., Inc., 936 F. Supp. 900, 906 (M.D. Fla. 1996).

between the substances and injuries in question.[401] As explained in *Cavallo v. Star Enterprise*:

> [T]here are certain scientific principles and methods upon which a toxicologist must rely in forming an opinion regarding whether exposure to specific chemicals could cause certain maladies in individuals. Specifically, the methodology . . . endorsed by the World Health Organization, the National Academy of Sciences, and various agencies of the United States Government, calls for the following "risk assessment":
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> [(1)] First, an evaluation is made of the chemicals to which the individual might have been exposed, and of the concentrations of these chemicals in air breathed by the individual. [(2)] The second step involves an evaluation, based on the published scientific literature, of the exposures necessary to produce the adverse effects associated with the chemicals to which individuals may be exposed. [(3)] These two evaluations are then combined in the final step of the risk assessment to provide an estimate of the likelihood that any of the harmful properties of any or all of the chemicals might have been expressed in the exposed individual.
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> . . . [A]ll chemicals can cause health problems at some level or concentration of exposure, but they vary widely in the types of harm caused and in the levels of exposure required to trigger those harms. In addition, all chemicals have thresholds of exposure that must be exceeded before the harms will occur, and these thresholds may be identified through scientific studies and literature. The task of the toxicologist, therefore, is to identify a dose-response relationship for a particular chemical (or chemical mixture) and illness and analyze the results to determine whether the duration and concentration of exposure in a given instance could have caused the alleged harms.[402]

Risk assessment is the sum and substance of causation evidence offered by a scientist. A court's *Daubert* analysis must focus on

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401. Cuevas v. E.I. DuPont De Nemours & Co., 956 F. Supp. 1306, 1312 (S.D. Miss. 1997).

402. 892 F. Supp. 756, 764 (E.D. Va. 1995) (citations omitted), *aff'd in relevant part*, 100 F.3d 1150, 1159 (4th Cir. 1996).

whether the scientist conducted a valid risk assessment to reach his or her conclusions.

E. An Example: Lakie v. Smithkline Beecham

The toxic tort case *Lakie v. SmithKline Beecham* presents facts well suited for application of the *Daubert* technique suggested in this Article.[403] In that case, a denture wearer claimed that she developed myelodysplastic syndrome (MDS) 5 q-minus, a rare type of bone marrow disorder, due to benzene contamination in the defendant manufacturer's denture adhesive.[404] The plaintiff's "dose" expert calculated that plaintiff absorbed between 550 and 4200 milligrams (mg) of benzene from the denture adhesive over a six-year period of use.[405] The plaintiff's causation experts determined that this calculated, cumulative benzene dose was sufficient to cause, and did cause, the plaintiff's disease.[406] The defendant moved the court for summary judgment on the ground that the plaintiff's proffered causation testimony was inadmissible pursuant to *Daubert.*[407] The court denied the defendant's motion.[408]

Use of the *Daubert* technique suggested in this Article likely would have led the *Lakie* court to grant the defendant's summary judgment motion. The proffered causation testimony would fail because one of the three independent causal links—temporality—lacked the requisite scientific support. In addition, the plaintiff's experts produced no scientific substantiation of their specific causation analysis. That is, there is no quantitative risk analysis set forth in the court's opinion supporting the experts' opinion that the plaintiff's benzene dose from the dental adhesive most likely caused her disease.

The analysis begins with consideration of the three independent links in the plaintiff's causal chain: diagnosis, general causation, and temporality. Then, the analysis turns to a consideration of the dependent links of specific causation—that is, whether 1) the actual dose 2) exceeded the level generally considered harmful

403. 965 F. Supp. 49 (D.D.C. 1997).
404. *Id.* at 51.
405. *Id.* at 57.
406. *Id.*
407. *Id.* at 54.
408. *Id.* at 58.

and 3) was sufficient to conclude that the subject agent was the most likely cause of the injury, considering all potential causes.

1. Diagnosis—The defendants did not challenge the "differential diagnosis" that the plaintiff had MDS 5 q-minus. Unchallenged, one can accept the truth of the diagnosis beyond a reasonable doubt, with probability (P) equal to 1.0.

2. General Causation—In contrast, the defendants genuinely challenged the scientific adequacy of the plaintiff's experts' general causation opinions. The experts had scant epidemiologic evidence demonstrating an association between benzene exposures and MDS 5 q-minus.[409] Instead, the experts relied on the analogy argument[410] that benzene is associated with other, related bone marrow diseases.[411] In addition, the court excused the paucity of epidemiologic evidence offered by the experts on the ground that the plaintiff's disease was rare, and had just recently been recognized as a distinct disease entity.[412] This evidence in support of the plaintiff's general causation argument does not place the issue beyond genuine dispute, but arguably provides sufficient evidence of a probable causal association between benzene exposure and MDS. Lack of evidence that benzene causes the "5 q-minus" variant of the disease is troubling, though excusable for the reasons the court gave. The best (from the plaintiff's view) that one can reasonably

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409. *Id.* at 56. The court noted that there was one Chinese epidemiologic study demonstrating an association between occupational exposure to benzene and MDS, though apparently not the 5 q-minus variant displayed by the plaintiff. *Id.* at 56 & n.10 (citing Lois B. Travis et al., *Hematopoietic Malignancies and Related Disorders Among Benzene-Exposed Workers in China*, 14 LEUKEMIA & LYMPHOMA 91 (1994)). There was no discussion in the court's opinion concerning the comparison between the exposures of the workers in the study and the plaintiff's exposures, an important consideration for the "exposure/dose" causation link. *See supra* note 224 (discussing "external validity").

410. *See supra* Part V.A.4 (discussing the analogy argument as a means of establishing general causation).

411. *Lakie*, 965 F. Supp. at 55–56. The analogy argument adopted by the experts, and accepted by the court, was as follows:

> [S]ince the types of biological lesions which cause leukemia are very similar to the lesions which cause MDS, [one] would expect that what causes one lesion would cause the other. Drs. Swerdlow and Hess also claimed that a significant percentage (10–30%) of leukemia patients undergo a myelodysplastic syndrome before they progress to leukemia.

Id. at 56. The defendants' experts agreed that benzene is a bone-marrow toxin. *Id.* at 55. A well-respected textbook states that "[b]enzene, in particular is known to induce MDS as well as leukemia." *Id.* at 55 n.7 (quoting Andrew Deiss, *Non-neoplastic Diseases, Chemical Agents, and Hematologic Disorders that May Precede Hematologic Neoplasms*, *in* 2 WINTROBE'S CLINICAL HEMATOLOGY, *supra* note 125, at 1946, 1949).

412. *Id.* at 56. This is a valid excuse. *See supra* Part VIII.D.3.b.

conclude is that benzene is probably capable of causing the plaintiff's disease.

Accepting the probability of the general causation link, the plaintiff's claim can survive the tripartite "independent link" inquiry if the experts can substantiate the temporality link to a clear and convincing degree.

3. Temporality—At this point of the *Daubert* analysis, however, the plaintiff's claim begins to erode. There was no dispute that there was an exposure to the defendant's product and it occurred before the development of the plaintiff's MDS. But there is a problem with temporality when one considers the latency period.[413] The plaintiff claimed that she began to use the defendant's product in the spring of 1985.[414] In February 1989 she was diagnosed with macrocytic anemia, then in October 1990 she was diagnosed with MDS 5 q-minus.[415] Thus, the "latency period" as measured from the time of the first exposure was five and a half years, an unlikely and brief latency period under the circumstances. The low-level, chronic benzene dose alleged by the plaintiff is unlikely to result in a shorter latency period than observed in the acutely and massively exposed survivors of the Hiroshima nuclear detonation.[416] It is not impossible that benzene-induced MDS could occur within five and

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413. *See supra* Part VIII.D.3.c (discussing the latency period concept).

414. *Lakie*, 965 F. Supp. at 51.

415. *Id.*

416. Shorter latency periods are possible following massive, acutely toxic doses of the causative agents. For example, survivors of the Hiroshima nuclear detonation displayed six-to-ten-year latencies for MDS. Richard M. Stone, *Acute Leukemias, in* HOSPITAL PHYSICIAN HEMATOLOGY BOARD REVIEW MANUAL, HEMATOLOGY SPECIAL ISSUE 1, 2 (Arthur T. Skarin ed., 1998). Similarly, certain chemotherapeutic agents may cause MDS in treated patients with a latency period of three to eight years. *Id.* It is well recognized in the medical and toxicological communities that latency periods are inversely proportional to the dose of the causative agent. *See, e.g.*, Masayuki Arai et al., *Long Term Dose Response Study of N-[4-(5-Nitro-2-Furyl)-2-Thiazolyl] Formamide-Induced Urinary Bladder Carcinogenesis*, 18 CANCER LETTERS 261 (1983) (showing an inverse relationship between dose of agent in laboratory animals and latency period for bladder cancer); Wolfgang H. Fischer & Werner K. Lutz, *Influence of Diet Restriction and Tumor Promoter Dose on Cell Proliferation, Oxidative DNA Damage and Rate of Papilloma Appearance in the Mouse Skin After Initiation with DMBA and Promotion with TPA*, 98 TOXICOLOGY LETTERS 59 (1998) (showing that the median latency time (t50) for the appearance of skin papilloma in the high-, intermediate-, and low-dose groups fed cancer agent was 9, 15.5, and 23.5 weeks, respectively); E.J. O'Flaherty & M.L. Dourson, *Relationship Between Urethan Dose Rate and Adenoma Latency: Relevance of Tumor Growth Rate and Target Cell Number*, 69 J. NAT'L CANCER INST. 859 (1982) ("The relationship between dose per unit time, or DR, and time (t1) needed for the development of a mean of one observable tumor per mouse was: $DR \times t1^n = k$, where k and n are constants."). More particularly, this inverse relationship between the extent of the dose and the length of the latency period holds for MDS. *See* Deiss, *supra* note 411, at 1956 ("Latency may decrease as a function of the intensity of treatment [in relation to medical treatment-induced MDS].").

a half years of the first exposure, but it is unlikely.[417] There is no discussion of this latency issue in the court's opinion and no apparent substantiation of the plaintiff's theory that benzene caused her disease despite this truncated latency. The "temporality" link of the plaintiff's causation chain fails.

4. Specific Causation—At this point the inquiry focuses on the dependent links of specific causation. The specific causation links are: 1) the actual exposure/dose 2) exceeded the level generally considered harmful and 3) was sufficient to conclude that the subject agent was the most likely cause of the injury, considering all potential causes.

In *Lakie*, the dose expert did estimate the plaintiff's dose to benzene as somewhere between 550 and 4200 mg over the six years the plaintiff used the defendant's dental adhesive. Although the defendant challenged the dose estimates of the plaintiff's expert, the expert's estimates were defensible. The expert relied on the plaintiff's use history and documents demonstrating the concentrations of benzene in the dental adhesive through the years of the plaintiff's use.[418] The expert assumed that the plaintiff absorbed all of the benzene in the adhesive she applied. This plaintiff-friendly assumption seemed reasonable, given animal studies on which the expert relied showing the high permeability of skin to benzene.[419]

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417. Although scientists customarily measure latency periods from the time of first exposure, this method is probably inappropriate for low-level, chronic exposures such as presented in the *Lakie* case.

> For exposures that are continuous or intermittent, there remains the difficulty in determining when the exposure acts etiologically. Customarily, epidemiologists measure induction periods from the time of first exposure, because the relevant time of action is unknown, whereas the time of first exposure can usually be determined. A better practice, however, is to choose an arbitrary accumulation of exposure, and determine the time at which that level is reached.

Rothman & Poole, *supra* note 347, at 7.

Applying the "cumulative exposure" approach to determine commencement of the latency period in the *Lakie* case, one could decide arbitrarily to commence the latency period at the time the plaintiff's cumulative benzene exposure resulted in an Attributable Risk (AR) of one in one hundred (0.01), a very plaintiff-friendly approach. Using the formula derived in the Rinsky Study, *see supra* text accompanying note 157, and the risk calculations discussed in the next subsection, it would take the plaintiff eight years to absorb enough benzene to achieve an AR of 0.01, assuming the plaintiff's actual dose equaled the highest dose estimated by her expert. Thus, using the more appropriate "cumulative dose" approach for determining commencement of the latency period, the plaintiff's disease manifested itself prior to the time that the latency period began, in contravention of the essential temporality criterion of causation.

418. *Lakie*, 965 F. Supp. at 57–58.

419. The "dose" expert reasoned that highly vascularized human gum and mouth tissue would be less resistant to absorption than skin. *Id.* at 58.

The "dose" expert's conclusions were a rational inference based on the data.

Was the calculated dose sufficient to cause the plaintiff's disease, as the plaintiff's causation experts concluded? As mentioned, the plaintiff's "dose" expert calculated that plaintiff absorbed between 550 and 4200 milligrams (mg) of benzene from the denture adhesive over a six-year period of use.[420] But what scientific evidence did the experts present to substantiate their specific causation conclusion that this dose caused the plaintiff's disease? There is no scientific support cited in the court's decision. The conclusion appears to be the *ipse dixit* (bare authority) of the plaintiff's experts. Failing to present the court with any scientific substantiation for their "harmful dose" conclusion, the court should have granted judgment in favor of the defendant.[421]

It was not the defendant's burden at the *Daubert* stage to come forward with scientific evidence to substantiate its defense that the plaintiff's estimated benzene dose was unlikely the cause of her disease. To the contrary, it was the plaintiff's burden to demonstrate that her proffered opinion testimony was admissible.[422] We, however, present here an analysis that the defendant could have offered to substantiate its defense. This analysis demonstrates the type of quantitative risk assessment and Bayesian inquiry that courts should demand of an expert offering specific causation testimony. In the *Lakie* case, a quantitative analysis demonstrates that the plaintiff's specific causation theory was unsubstantiated for a reason.

As discussed above, benzene is arguably the most studied chemical toxin.[423] There are data available to make a scientific judgment as to the level of risk presented by the dose estimate calculated in the *Lakie* case. As a scientific basis of this analysis, we turn again to the Rinsky Study, an epidemiologic study in which the researchers reconstructed the cohort's benzene exposures and, based on these calculated exposures, estimated the risk of contracting leukemia per unit cumulative exposure of benzene as measured in parts per

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420. *Id.* at 57.

421. Courts should not accept an expert's unsubstantiated assertions. The purpose of the *Daubert* inquiry is to require the experts to come forward with their scientific evidence in support of their assertions. *See* Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 592 n.10 (1993). There is no discussion in the *Lakie* opinion concerning any scientific support for the opinion that the plaintiff's dose was sufficient to cause her disease, rendering the opinion an unreliable *ipse dixit.*

422. *See supra* note 190 and accompanying text (addressing the burden of proof at the *Daubert* stage).

423. *See supra* Part VI (discussing benzene toxicology and epidemiology).

million•years (ppm•yrs).[424] The researchers derived the following formula for determining the Odds Ratio (OR) of contracting leukemia:

$$OR = e^{(0.0126 \times ppm\bullet yrs)}$$

There are two obstacles to clear before using this formula to calculate the *Lakie* plaintiff's risk. First, the variable "ppm•yrs" in this formula involves cumulative occupational inhalation exposure in terms of air concentration, while the plaintiff's exposure was oral. There is, however, a valid method to convert the cumulative oral dose estimated for the *Lakie* plaintiff to ppm•yrs, and then plug this calculated dose equivalent into the Rinsky Study formula to derive a risk associated with the plaintiff's accumulated dose. The second obstacle to clear is the fact that the Rinsky Study researchers calculated an exposure risk for leukemia, not for the plaintiff's disease, MDS 5 q-minus. Nevertheless, it is reasonable to use the Rinsky Study formula to calculate the plaintiff's risk, given the plaintiff's general causation theory based on the "analogy" argument that benzene likely causes MDS because it causes leukemia. The Rinsky Study presents the best available risk analysis for use in this case, certainly better than the plaintiff's unsubstantiated theory.

The plaintiff's estimated cumulative dose was between 550 and 4200 mg of benzene during six years of use.[425] Taking the highest estimated cumulative dose, the plaintiff's average annual dose was 700 mg per year (mg/yr).[426] Her corresponding estimated average daily exposure was 1.92 mg/day[427]; however, since the objective is to convert the plaintiff's dose to an equivalent occupational dose, one should divide the annual dose not by 365.25 days, but by 200 "working days" per year. Following this procedure, the plaintiff's daily occupational dose equivalent comes out to 2.7 mg/day.[428]

The challenge at this point is to convert a daily oral dose of 2.7 mg into a daily occupational inhalation exposure. In other words, the question is what concentration of benzene in air will result in a daily dose of 2.7 mg benzene in a worker so exposed? This step requires knowledge of a basic rule-of-thumb used in the fields of industrial hygiene and toxicology, to wit: an average worker breathes

424. Rinsky et al., *Risk Assessment*, *supra* note 155, at 1048.
425. *Lakie*, 965 F. Supp. at 57.
426. I.e., 4200 mg divided by six years.
427. I.e., 700 mg/yr divided by 365.25 days per year.
428. I.e., 700 mg/yr divided by 200 working days per year.

about ten cubic meters of air during an eight-hour workshift.[429] Based on this breathing air volume, and assuming that an exposed worker absorbs one hundred percent of the benzene from inhaled air,[430] the plaintiff's calculated occupational dose equivalent of 0.27 mg/m^3 would effect a daily dose of 2.7 mg benzene.[431]

Since the Rinsky Study formula uses units of parts per million (ppm), one must next convert the concentration of 0.27 mg/m^3 into ppm. This step is simple, since it is known that one ppm of benzene in air is equivalent to 3.2 mg benzene per cubic meter of air (mg/m^3).[432] As a consequence, 0.27 mg/m^3 benzene in air equals about 0.1 ppm benzene in air.[433] The *Lakie* plaintiff's high-end estimated dose of 4200 mg benzene over six years converts to a daily occupational exposure of 0.1 ppm benzene in air. The equivalent cumulative exposure over six years is 0.6 ppm•yrs.[434]

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429. Hon-Wing Leung, *Methods For Setting Occupational Exposure Limits, in* HUMAN AND ECOLOGICAL RISK ASSESSMENT 647, 654 (Dennis J. Paustenbach ed., 2002)("A volume of 10 m^3 of inspired air per 8-hour work shift has been most frequently used for OEL [occupational exposure limit] calculations. This figure is derived by assuming that a man engaging in light-duty work has a tidal volume of 1000 cm^3 and a breathing rate of 20 breaths per minute for 8 hours." (citation omitted)).

430. This is a fair assumption, given the dose expert's assumption that Mrs. Lakie absorbed 100% of the benzene in the defendant's product. Lakie v. SmithKline Beecham, 965 F. Supp. 49, 57–58 (D.D.C. 1997).

431. I.e., 2.7 mg/day divided by 10 m3 breathed per day.

432. The formula for converting parts per million (ppm) of a vapor or gas in air to milligrams per cubic meter of air (mg/m3) is:

ppm = [(mg/m3) (24.45)] ÷ gram molecular weight of the substance.

See AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS, 2002 THRESHOLD LIMIT VALUES FOR CHEMICAL SUBSTANCES AND PHYSICAL AGENTS & BIOLOGICAL EXPOSURE INDICES 11 (2002). The gram molecular weight of benzene is 78.11. *Id.* at 16. Thus, the gram-weight equivalent of 1 ppm benzene in air is 3.2 mg/m3.

433. I.e., 0.27 mg/m3 benzene divided by 3.2 mg benzene per ppm benzene.

434. I.e., 0.1 ppm benzene over six years. In comparison, the epidemiologic literature indicates benzene-induced blood dyscrasias occurs only at much higher levels of exposure. *E.g.*, Muzaffer Aksoy & Sakir Erdem, *Followup Study on the Mortality and the Development of Leukemia in 44 Pancytopenic Patients with Chronic Exposure to Benzene*, 52 BLOOD 285, 288 (1978) ("[A]ll pancytopenic patients in whom leukemia developed were heavily exposed to benzene during long working hours. Although in one of these patients the duration of exposure was only 6 mo, his daily exposure was over 8 hr at a benzene concentration of 150 ppm.").

A six-month occupational exposure at 150 ppm, as seen in the Aksoy & Erdem study, results in a cumulative dose of 75 ppm•years. Thus, the *lowest* cumulative exposure in the Aksoy & Erdem study among patients who developed leukemia is 125-fold higher than Ms. Lakie's *highest* estimated cumulative exposure. Furthermore, the benzene levels in all the workplaces examined by Aksoy & Erdem were 150 ppm or greater. *Id.* Consequently, there is no "fit" between the plaintiff's allegation of a benzene-induced MDS and the relied-on data. *See supra* note 224 (discussing "external validity" and the need to explain how the plaintiff's exposure circumstances were similar to those examined in the relied-upon epidemiology studies). Ironically, to find that benzene is capable of causing MDS, the *Lakie* court quoted

Plugging the plaintiff's equivalent inhalation cumulative exposure into the Rinsky Study formula yields a Relative Risk (RR) of 1.008. The Attributable Risk (AR)[435] associated with this RR is 0.008. Accepting this AR as the true measure of benzene-induced MDS at this dose, eight out of one thousand persons with MDS who received the same benzene dose as did the plaintiff developed their disease as a result of their benzene dose.[436] Applying Bayes' Law, this base rate of benzene-induced MDS among comparably exposed persons would require the plaintiff's causation experts to apply tests with a specificity of over 99% to conclude that the plaintiff's disease was more likely than not caused by that benzene dose.[437] In other words, the plaintiff's experts must be able to identify more than 99%of those persons with MDS exposed to benzene as was the plaintiff whose disease was not caused by benzene. Such specificity is impossible to achieve without an immunologic test for benzene-induced MDS or some other "fingerprint" of benzene-induced MDS.[438]

In *Lakie*, the plaintiff's experts failed to explain how they were able to conclude that the plaintiff's benzene dose was sufficient to

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academic text that later cites the Aksoy and Erdem study. *Lakie*, 965 F. Supp. at 55 n.7 (quoting Deiss, *supra* note 411, at 1949); Deiss, *supra* note 411, at 1949 n.128 (citing Aksoy & Erdem, *supra*).

435. *See supra* Part V.B (discussing AR).

436. Approaching this quantitative risk estimate from another angle, one could ask how long it would take for the plaintiff to absorb enough benzene to yield an AR for benzene-induced MDS of 50% (0.5, correlating to an RR > 2.0). Based on the Rinsky Study formula and the plaintiff's highest estimated dose, and applying the same risk analysis as discussed in this Part, it would take 550 years for the plaintiff to absorb enough benzene to exceed an AR of 0.5.

437. The required specificity is determined by applying a base rate of 0.01 in the formula derived in Part VII. *See supra* Part VII. Note that, in reaching this risk estimate, the authors applied the highest dose calculated by the plaintiff's experts. Given that it is the plaintiff's burden to prove admissibility of her proffered expert opinions, it is arguable that a court should use the lowest, reliable, calculated dose in a quantitative risk estimate. In *Lakie*, the lowest calculated benzene dose was 550 milligrams total dose, which would lead to a calculated Attributable Risk of 0.0002, or two benzene-induced cases out of 10,000 individuals exposed at the same level as was the plaintiff. *Lakie*, 965 F. Supp. at 57. With an AR of 0.0002, the specificity required to achieve "more likely than not" reliability is greater than 99.9%.

438. Note the 99.8% specificity of the test for HIV, a highly specific immunologic test. Cleary et al., *supra* note 37, at 1758; *see also supra* text accompanying notes 37–40. Even if the plaintiff's experts had an immunologic test for benzene-induced MDS with a specificity of 98%, a positive test result would not be sufficient to prove that the plaintiff had benzene-induced MDS under these circumstances—that is, a base rate of less than 0.01. Applied to this population, a test with 98% specificity would yield more false positives than true positives, resulting in a Predictive Value of less than 0.5, insufficient to meet the plaintiff's burden of proof.

cause her MDS.[439] To the contrary, a quantitative causation analysis shows that the plaintiff's MDS was probably, almost certainly, not a result of her benzene exposure. Regardless of this quantitative analysis, the failure of the plaintiff's causation experts to provide substantiation of their causation opinion warranted summary judgment for the defendant.[440] Most toxic exposures do not provide an opportunity to conduct a causation analysis as precise and as well-studied as benzene. Nevertheless, all toxic tort cases present the plaintiff's causation experts with the burden to substantiate in a quantitative way their opinions that the dose of the agent at issue more likely than not caused the plaintiff's injury.

IX. CONCLUSION

Daubert introduced a new era of sophisticated court scrutiny of proffered scientific and technical testimony. No longer are federal courts and state courts following *Daubert* to exclude proffered expert opinions simply because the relevant scientific community generally does not accept the expert's methods and conclusions. Instead, the courts are to examine directly the reliability of the expert's methods and conclusions by considering the underlying scientific data. The *Frye* "generally accepted" test, a useful surrogate for reliability of scientific and technical testimony, is no longer the court's sole gatekeeping tool.

This Article describes Bayes' Law and its impact on the reliability of causation testimony in the context of toxic tort cases. This Article also discusses the impact of other uncertainties attendant to expert opinion testimony in toxic tort cases and how these uncertainties compound to make the proffered causation opinions less reliable. Then, this Article suggested a probabilistic approach for

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439. There is no explanation in the court's opinion. It appears that the court simply accepted the expert's *ipse dixit* that the plaintiff's benzene dose was sufficient to cause the plaintiff's MDS.

440. Given the failure of the plaintiff's causation experts to present a transparent quantitative causation analysis, there is no need to consider the presence or absence of alternative risk factors. It is noteworthy, however, that most cases of MDS 5 q-minus are elderly females with macrocytic anemia. Deiss, *supra* note 411, at 1949, 1953. Ms. Lakie was diagnosed with macrocytic anemia in February 1989, approximately twenty-one months prior to her diagnosis with MDS. *Lakie*, 965 F.Supp. at 51. The court stated that Ms. Lakie was sixty-eight years old, though the reference date is unclear. *Id.* Thus, Ms. Lakie displayed risk factors for MDS 5 q-minus—sex, age, and macrocytic anemia—auguring against a finding of benzene causation.

use by judges or their appointed special masters for evaluating the reliability of proffered expert causation opinions in toxic tort cases pursuant to FRE Rules 104 and 702, and *Daubert*. The suggested approach calls for recognition of these uncertainties and evaluation of the reliability of proffered causation opinions based on fundamental scientific principles. At the *Daubert* stage, the expert asserting a causal link between an exposure and an injury has the burden to show that there is reliable scientific data supporting the opinion that each causal factor (diagnosis, dose, temporality, general causation and specific causation) analyzed independently is true to a high probability. The expert's failure to produce reliable scientific evidence supporting each causal link between the subject toxic agent and the plaintiff's injury renders the expert's opinions unreliable and inadmissible.

It is time for the courts to take the next step in sophisticated analysis of expert testimony. Courts must consider the impact of sequential uncertainties and Bayes' Law on the reliability of the proffered causation opinions in toxic tort cases. Aware of these fundamental scientific principles, courts can dispatch at the *Daubert* stage toxic tort cases lacking reliable evidence and direct judicial resources to tenable claims of harm caused by toxic substances.