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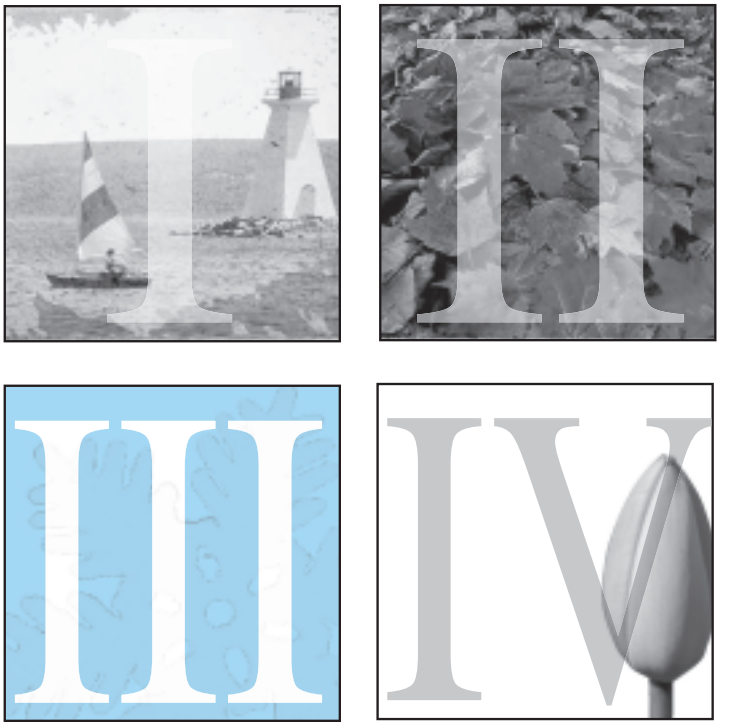


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THE STATEWIDE ASSOCIATION OF ATTORNEYS REPRESENTING THE DEFENSE IN CIVIL LITIGATION

# *DAUBERT* IN TOXIC TORT LITIGATION

**[PART 2 OF 3][1]**

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**"There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact."**
Mark Twain, *Life on the Mississippi* (1874).

**Executive Summary**
Part 2 of 3

Scientific evidence may be derived from any of several sources and each needs to be examined for reliability and fit. Epidemiological studies are generally considered the most reliable source, but it is necessary to distinguish the association of two events from a causal link between them. In addition, the results must be statistically significant and free from bias, that is, a systematic error that makes the two groups being compared different in more ways than just the variable being studied. The Bradford Hill criteria can be used to measure the validity of the result of an epidemiological study, but their application is not mechanical and must itself be scrutinized for validity.

Meta-analyses rarely provide useful information, because they normally are not conducted pursuant to proper scientific methodology. They have frequently reported causal relationships that do not survive scientific scrutiny. By pooling data from different studies, meta-analyses can paper over biases and other weaknesses in the underlying studies, disregard inconsistent findings, and improperly combine divergent population groups.

Animal research is another source of scientific testimony, but the application of the result of any such studies to humans requires express justification. Animal toxicology studies are not designed to establish whether a substance is safe in humans but rather to allow scientists to study the types of effects a substance can produce under specified conditions and therefore animal studies are often conducted with the goal of inducing the greatest number of adverse effects.

## Introduction

The first article in this series discussed the legal standards for admissibility of medical causation expert testimony following the Michigan's Supreme Court's adoption in *Gilbert v. DaimlerChrysler Corp.*[2] of the federal *Daubert* requirements of reliance and relevance. In this second article in our three-part series, we offer detailed guidance on how defense counsel can assist courts in properly interpreting the *Daubert* requirements in relation to specific categories of scientific evidence routinely cited by plaintiffs' experts in support of general causation opinions, *i.e.*, epidemiology, animal studies, chemical analogies, case reports, regulatory findings and other secondary sources. In the final installment, to be published in the next issue of the *Quarterly*, we will discuss how *Daubert* can be used to respond to causation opinions premised on clinical reasoning.

## Evaluating General Causation Evidence Under the Scientific Method

General causation opinions in toxic tort litigation may be based on a wide variety of evidence of differing scientific value, including, *inter alia*, epidemiology, animal studies, chemical analogies, and regulatory findings and other secondary sources. Some legal observers have argued that a medical expert's evaluation of this evidence involves a "complex inferential process" and that the expert accordingly should be allowed to simply lump this evidence together and reach "a subjective judgment about the strength of the evidence."[3] However, *Daubert* clearly requires more. Under *Daubert*, a trial court must consider each of these categories of evidence in light of the scientific method, and the expert's testimony may only be admitted if the expert can establish through scientific evidence that her causal hypothesis has been reliably tested and validated.

Further, a causation expert cannot satisfy her *Daubert* burden by arguing that the scientific research necessary to test her hypothesis has not been or

cannot be performed. *Daubert* requires trial judges to evaluate expert testimony based on the science that exists at the time, not the possibility of new scientific discoveries in the future or guesswork as to what those discoveries might show.[4] As Judge Posner of the United States Court of Appeals for the Seventh Circuit explained, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science, it does not lead it."[5]

## Epidemiological Studies

Controlled epidemiological studies are generally considered the most reliable evidence for testing a hypothesis that a particular substance causes a particular injury in humans.[6] Epidemiological studies can be especially important in cases where the drug or substance at issue is widely used or where there is a measurable background rate of the alleged injury regardless of exposure. In these situations, epidemiology may be the only way to test the hypothesis that observed injuries in exposed individuals are reflective of an increased risk and a causal connection rather than pure statistical chance.[7] While the absence of epidemiology may not be fatal to a plaintiff's case, numerous courts have held that a plaintiff seeking to establish causation without such evidence will face a high evidentiary hurdle.[8]

When a causation expert relies on epidemiological studies to support her opinions, a trial court must analyze those studies to determine whether they provide a proper foundation for the expert's testimony under the scientific method. The finding in an epidemiological study of an *association* between a substance and an injury is not equivalent of *causation*.[9] There are three reasons that a positive association may be observed in an epidemiological study: (1) chance, (2) bias, and (3) real effect.[10] As the Supreme Court recognized in *Joiner*, epidemiological research cannot provide a scientifically reliable basis for an affirmative causation opinion if it is statistically insignificant or inadequately controlled for bias.[11]

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### i. Confidence Intervals

Epidemiologists attempt to account for the possibility of chance by calculating "confidence intervals" around point estimates of potential increased risk derived from epidemiological studies. An epidemiological study is considered to show a statistically significant association with an increased risk if the confidence interval of upper and lower bound estimates of risk does not include the possibility of no increased risk in the exposed population. The possibility of no increased risk is referred to as the "null" hypothesis, which is generally indicated by a relative risk or odds ratio of 1.0.[12] The generally accepted confidence interval in epidemiological studies is 95%, meaning that a study is not statistically significant unless the "null" hypothesis of no increased (or decreased) risk can be excluded with 95% confidence.[13] If an epidemiological study is not statistically significant, it cannot provide scientifically reliable evidence of an association, let alone causation.[14] Further, numerous courts have held that epidemiological evidence can only support a conclusion that a substance is more likely than not the cause of disease if it establishes a doubling of the risk of the disease.[15] The reasoning behind this requirement is that if exposure does not at least double the risk of injury, then more than half of the population suffering from injuries allegedly caused by the substance would have been injured anyway through pure chance (based on the background risk of injury) thereby disproving "more likely than not" legal causation. Courts have also cautioned against reliance on statistically significant subgroup analyses, given the likelihood that numerous subgroup analyses will result in spurious statistical associations in some endpoints through chance alone.[16]

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### ii. Bias

Bias in epidemiology is any systematic error that makes the two groups being compared different in more ways than just the variable being studied.[17] Common sources of bias include confounding factors (other factors associated with the studied factor that might account for a perceived increased risk), selection bias (uncontrolled differences between the studied populations), and infor-

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mation bias (systematic error in measuring data that results in differential accuracy of information).[18] A court must consider each of these sources of bias in interpreting an epidemiological study because bias can produce an erroneous association.[19] Thus, for example, courts have excluded expert causation testimony based on purported statistically significant epidemiologic evidence where the study failed to account for other confounding exposures that could have accounted for the apparent association.[20] Courts have rejected expert opinions that relied upon epidemiological studies where the subjects were not blinded to the study hypothesis.[21] Courts have rejected expert testimony based on epidemiological studies that failed to adequately address the possibility that injured subjects would be more likely to recall a preceding exposure than healthy controls ("recall bias").[22] Courts have also rejected expert testimony that relied upon epidemiological studies that failed to articulate selection criteria for participants in the study and thus could not account for selection biases "that could lead to erroneous inferences regarding causation."[23]

### iii. Bradford Hill Criteria

The existence of a well-controlled epidemiological study that reports a statistically significant increased association with a specific injury does not, by itself, provide scientifically reliable evidence establishing causation.[24] "The strong consensus among epidemiologists is that conclusions about causation should not be drawn, if at all, until a number of criteria have been considered."[25] In analyzing the scientific reliability of epidemiological evidence under *Daubert*, a number of courts have been guided by a set of criteria published by the noted epidemiologist, Sir Austin Bradford Hill in 1965 ("the Bradford Hill criteria").[26] The Bradford Hill criteria can be summarized as follows: (1) strength of association, (2) consistency and replication of findings, (3) specificity with respect to both the substance and injury at issue; (4) evidence of a dose-response relationship, (5) temporal relationship, (6) biological plausibility, and (7) consideration of alternative explanations.[27]

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In light of these criteria, courts have rejected statistically significant epidemiological research under *Daubert* where the reported relative risk is only slightly elevated[28] and have suggested that epidemiological research reporting a relative increased risk of less than three times indicates only a weak association (strength of association).[29] Courts have also rejected isolated, statistically significant epidemiological findings that are not replicated in other epidemiological research (consistency).[30] Courts have rejected epidemiological studies reporting statistically significant associations with allegedly similar substances or allegedly similar injuries (specificity).[31] And courts have rejected alleged associations in epidemiological studies that did not demonstrate a dose response relationship (dose response).[32] Moreover, courts have not accepted the mere incantation of the name of Bradford Hill as establishing the reliability of a causation hypothesis.[33] These criteria must be applied faithfully or they can also generate unreliable conclusions,[34] as demonstrated by two review papers published in 1989–1990 that both purported to use the Bradford Hill criteria to assess the epidemiological evidence regarding an association between alcohol consumption and breast cancer, but reached dramatically different conclusions.[35]

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### iv. Meta-Analyses

Causation experts sometimes attempt to bolster individually weak epidemiological studies by relying on "meta-analyses" in which otherwise insignificant or inconsistent findings are pooled to generate a single purportedly significant finding. This approach has been rejected by courts in the Bendectin, breast implant, and SSRI litigations among others,[36] and rightly so. Meta-analyses rarely provide useful information, because they normally are not conducted pursuant to proper scientific methodology. They have frequently reported causal relationships that do not survive scientific scrutiny.[37] While government agencies will sometimes rely on meta-analyses to satisfy the lower evidentiary burden used for regulatory findings, *see supra*, they also have recognized the scientific limitations

of such analyses:

> Where FDA evaluates a meta-analysis, the Agency considers such an analysis primarily as supporting evidence, rather than as primary evidence, that can confirm the validity of data concerning a hypothesis. The Agency must carefully scrutinize each meta-analysis to assess the soundness of its design and the quality of the data from individual studies to determine the significance of the data. Such scrutiny requires review of the original studies used for the meta-analysis.[38]

By pooling data from different studies, meta-analyses can paper over biases and other weaknesses in the underlying studies, disregard inconsistent findings, and improperly combine divergent population groups. As one commentator has explained, "[m]eta-analyses begin with scientific studies, usually performed by academics or government agencies, and sometimes incomplete or disputed. The data from these studies are then run through computer models of bewildering complexity, which produces results of implausible precision."[39] After finding that meta-analyses were frequently contradicted by subsequent large, randomized controlled trials, another investigator cautioned: "The popularity of meta-analysis may at least partly come from the fact that it makes life simpler and easier for reviewers as well as readers. However, simplification may lead to inappropriate conclusions."[40] Pursuant to *Daubert*, a court must look behind the "bewildering complexity" of meta-analysis and protect against "inappropriate conclusions" by requiring the expert to establish the reliability and relevance both of the different pieces of information going into the meta-analysis and the calculations used to combine the information into a single result.

## Animal Research

Animal research may be a useful tool for raising suspicions that can then be tested in humans, but there are significant differences in humans and laboratory animals that limit the degree to which animal research can validate a causation hypothesis in humans.[41] There are numerous examples of apparent positive findings in animal studies that have subsequently been found inapplicable to humans. The most commonly cited example, perhaps, is saccharine, which was linked to bladder cancer in rats over 20 years ago but was recently removed from the National Toxicology Program list of potential human carcinogens after years of subsequent research failed to find any health risk in humans. Similarly, scientists have determined that a common insecticide, carbaryl, causes fetal abnormalities in dogs because dogs lack a specific enzyme involved in metabolizing carbaryl. Humans have the enzyme at issue and are accordingly not believed to be at risk.[42] Because of numerous such problems of extrapolation, courts repeatedly have held that animal studies alone cannot prove causation in humans.[43]

*At a minimum, extrapolations from animal studies to humans are not considered reliable in the absence of a credible scientific explanation why such extrapolation is warranted.*

### i. Requirements for Extrapolation

At a minimum, extrapolations from animal studies to humans are not considered reliable in the absence of a credible scientific explanation why such extrapolation is warranted.[44] In evaluating whether animal studies can form a reliable foundation for a causation opinion, trial courts should consider such factors as: (1) whether the results followed a dose response curve; (2) whether the animal studies involved massive doses, (3) whether the studies involved different routes of administration, (4) whether the studies are conducted in intact animals (as opposed, *e.g.*, to isolated animal parts), (5) whether the results have been replicated in different animal species, and (6) whether the animal models have been shown to be reliable predictors of human experience.[45]

Animal toxicology studies are not designed to establish whether a substance is safe in humans but rather to allow scientists to study the types of effects a substance can produce under specified conditions.[46] Accordingly, animal studies are often conducted with the goal of inducing the greatest number of adverse effects. This is accomplished in a number of ways, including the use of extremely high doses and exposures through special routes designed to deliver the substance directly to a particular organ without allowing for normal absorption and metabolization.[47] While these models are useful and appropriate in the laboratory as a means to generate hypotheses for further testing, they create additional problems for extrapolating study findings to humans.

### ii. Dosage and Toxicity

The existence of a dose-response relationship has been described as the most fundamental and pervasive concept in toxicology.[48] All substances, even water, become toxic at a high enough dose. Conversely, however, "it has long been recognized that acute toxicological responses are associated with thresholds; that is, there is some dose below which the probability of an individual responding is zero."[49] As stated by the oft-described father of chemical pharmacology, Paracelsus (1493–1541), "What is there that is not poison? All things are poison and

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nothing [is] without poison. Solely a dose determines that a thing is not a poison."[50] Accordingly, even leaving to one side the issue of inter-species variations, the fact that a high-dose study results in adverse effects in animals cannot be extrapolated into a scientifically reliable conclusion that the substance can cause such effects at normal exposure levels in humans.[51] To the contrary, because toxic effects in humans are generally expected to appear in the same range on the basis of dose per unit of body surface as in experimental animals, a finding of adverse events in animals at only very high doses may be more indicative of the safety of the substance in normal use.[52]

### iii. Path of Entry and Toxicity

The route by which a substance enters the body can also have a significant effect on its toxicity. Animal researchers frequently administer chemical agents through special routes, including, *inter alia*, (1) intraperitoneal, (2) subcutaneous, (3) intramuscular, and (4) intravenous.[53] These routes of administration may bypass the normal mechanisms through which potential toxins are removed before reaching the general circulation. For example, many substances are biotransformed and detoxified by the liver; while these substances may demonstrate toxic effects when injected intravenously, intramuscularly, or subcutaneously, they are perfectly safe if ingested orally.[54] Likewise, animal researchers also use genetically designed or physically altered animals in which normal protective body mechanisms are removed.[55] These types of animal studies can be useful in studying how an animal's normal body mechanisms interact and how substances can affect isolated physiological systems, but they do not reflect real world risks, even in the species being studied.

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In conducting its *Daubert* inquiry, a trial court also must determine whether the findings in the animal studies "fit" the opinions being offered in the case. Thus, an expert cannot rely on animal research that relates to a different injury than the one at issue. For example, animal carcinogenicity studies indicate that animals "react differently and in much more diverse ways than man" and that "compared to humans much more variation occurs in the cancer sites in animals."[56] However, in cases in which a chemical has been associated with cancers in both animal studies and epidemiological studies, "the target organ is usually identical."[57] In *Joiner*, the Supreme Court thus rejected animal research in part because the animals had developed a different type of cancer than the cancer at issue in the plaintiff.[58]

### Chemical Analogies

Causation opinions derived from chemical analogies rely on the hypothesis that a substance's effects can be predicted based on the established effects of similarly structured compounds. Trial courts should be very wary of such "guilt-by-association" evidence,[59] particularly where there is scientific research involving the actual substance at issue that demonstrates differences between it and its purported chemical cousins. Because even small changes in molecular structure can radically change a particular substance's properties and propensities, research in analogous substances does not reliably test the causal hypothesis at issue.[60]

The difficulty in relying on chemical analogies has been demonstrated by attempts to create computerized programs to assess the toxicity of chemical agents based on structure-activity relationships ("SARs"). These computerized models are far more sophisticated than the simplistic chemical analogies often relied on by causation experts in toxic tort litigation, and often rely on additional information regarding a substance beyond its chemical structure. Even so, while these models ultimately may prove helpful in setting research priorities or generating hypotheses, they have failed to provide reliable predictions as to a chemical's toxic effect.[61] As reported in a recent survey article, two prediction toxicity exercises conducted in recent years under the aegis of the National Toxicology Program have found that models that attempt to predict carcinogenicity "based solely on information derived from chemical structure" have been particularly unreliable, with the first exercise reporting that "overall accuracy in terms of

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positive or negative predictions was in the range 50–65%" and the ongoing second exercise reporting even higher error rates in preliminary results.[62] Moreover, "[a] clear limitation of almost all the prediction systems ... was their excessive sensitivity, *i.e.*, incorrectly predicting many non-carcinogens as positive."[63] Efforts to predict toxicity based on structure activity relationships have resulted in similar problems.[64]

## Secondary Source Materials

In addition to actual scientific data, causation experts will sometimes rely on secondary source materials that cite to the primary evidence, such as regulatory materials, textbooks, and internal company documents. These secondary materials do not add any additional scientific knowledge and are no more reliable than the evidence they cite.[65] They do not test a causal hypothesis; they merely report the findings of others.

In particular, regulatory findings do not provide relevant "peer review" for a causation opinion, because they are based on a risk-utility analysis that involves a much lower standard of proof than that which is demanded by a court of law.[66] For example, a recent article reported that the vast majority of regulatory withdrawals of approvals for drugs in Spain during the 1990s were based solely on anecdotal case reports.[67] As one commentary observed, "law, societal considerations, costs, politics, and the likelihood of litigation challenging a given regulation all influence the level of scientific proof required by the regulator decision-maker in setting regulatory standards and make such standards problematic as reference points in litigation."[68]

## Conclusion

The *Daubert* requirement that expert causation evidence be derived through the scientific method of hypothesis testing and validation provides a consistent guide for determining admissibility of the different categories of scientific evidence discussed in this article. In the final article in this series, we will address how this requirement comes into play in assessing what is far less scientific, but often more viscerally compelling, evidence of specific individuals who experience an adverse event in close proximity to an exposure at issue.

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## Endnotes

1. Editor's Note: Earlier versions of this series have appeared as an article in the *Journal of Health Law,* published by the American Health Lawyers Association, and will be included in the *Drug Abuse Handbook,* 2nd Edition, published by Taylor and Frances/CRC Press and edited by Steven Karch and Michael Peat (expected publication December 2006, available at www.crcpress.com and through other distributors.) Both AHLA and Frances/CRC Press have granted permission for the publication of this series.
2. 470 Mich. 749, 685 N.W.2d 391 (2004).
3. J. Kassirer & J. Cecil, *Inconsistency in Evidentiary Standards for Medical Testimony: Disorder in the Courts*, 288(11) JAMA 1382-87 (Sept. 2002), at 1384, 1386; *see also* M. Berger, *Upsetting the Balance Between Adverse Interests: The Impact of the Supreme Court's Trilogy on Expert Testimony in Toxic Tort Litigation*, 64 SUM Law & Contemp. Probs. 289 (Spring/Summer 2001).
4. 509 U.S. at 597.
5. *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).
6. *See, e.g., Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 532 (W.D. Pa. 2003) (epidemiology is "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease") (quoting *Conde v. Velsicol Chem. Corp.*, 804 F. Supp. 972, 1025-26 (S.D. Ohio 1992), aff'd, 24 F.3d 809 (6th Cir. 1994)); *Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1235, n.14 (W.D. Okla. 2000) ("In the absence of an understanding of the biological and pathological mechanisms by which disease develops, epidemiological evidence is the most valid type of scientific evidence of toxic causation"), *aff'd*, 289 F.3d 1193 (10th Cir. 2002); *Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224-25 (D. Colo. 1998) (same, citing cases).
7. There has been recent controversy regarding whether certain types of epidemiological studies should be considered inherently more reliable than others in establishing causation. Historically, courts have understood that randomized controlled clinical trials are less likely to report erroneous associations than observational epidemiological studies, like cohort or case control studies. *See In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 406 (S.D.N.Y. 2005); *see also* David H. Kaye & David A. Freeman, *Reference Guide on Statistics*, Reference Manual on Scientific Evidence (2d ed. 2000) at 94-95. However, recent research suggests that this understanding may be mistaken, *see* John Concato, *et. al., Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Design*, 342(25) New Eng. J. Med. 1887 (2000); John Concato, *Observational Versus Experimental Studies: What's the Evidence for a Hierarchy?*, 1 J. Am. Soc. Experimental NeuroTherapeutics 341 (2004). In a recent review of the most highly cited clinical research (defined as studies cited more than 1,000 times in the literature), a scientist concluded that 16% of the top-cited clinical research studies relating to medical interventions had been contradicted within the following 15 years and another 16% were followed by subsequent research suggesting that the initial findings may have been overstated. John P.A. Ioannidis, *Contradicted and Initially Stronger Effects in Highly Cited Clinical Research*, 294(2) JAMA 218 (2005). While epidemiological evidence can provide the best evidence of causation, as explained below, even the best study cannot establish that causation in fact exists.
8. *See, e.g., Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1358 ((N.D. Ga. 2001), *aff'd sub. nom Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194 (11th Cir. 2002).
9. *See* Michael D. Green, *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence (2d ed. 2000) at 336.
10. *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D.N.J. 2002), *aff'd*, 68 Fed. Appx. 356 (3d Cir. 2003)); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp

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2d 1026, 1032 (S.D. Ill 2001); *see also* Eddy A. Bresnitz, *Principles of Research Design* in Goldfrank's Toxicologic Emergencies 1827-28 (Goldfrank, *et al.* eds. 6th ed. 1998).

11. *See Joiner*, 522 U.S. at 145-46.
12. *See Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1353 n.1 (6th Cir. 1992).
13. *Id.*, at 723 (citing *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1046 (D.N.J. 1992), *aff'd*, 6 F.3d 778 (3d Cir. 1993)).
14. *See Joiner,* 522 U.S. at 145; *see also Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 681 (M.D.N.C. 2003) ("statistically insignificant results do not constitute proof" of causation); *Soldo*, 244 F. Supp. 2d at 533 ("Courts have emphasized that epidemiologic proof must be statistically significant,") (citing cases); *Caraker*, 188 F. Supp. 2d at 1034 (rejecting experts' causation opinions "inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies").
15. *See Magistrini,* 180 F. Supp. 2d at 591; *Siharath*, 131 F. Supp. 2d at 1356; *In re Breast Implant Litig.*, 11 F. Supp. 2d at 1225-26; *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1403-04 (D. Or. 1996); *see also Daubert v. Merrell Dow Pharms., Inc,* 43 F.3d 1311, 1321 (9th Cir. 1995) ("*Daubert* II") ("A relative risk of less than two may suggest teratogenicity, but it actually tends to disprove legal causation as it shows that Bendectin does not double the likelihood of birth defects"). *But cf. In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1137 (9th Cir. 2002) (plaintiffs did not need to present epidemiological evidence showing a doubling of risk cancer from ionizing radiation at specific exposure levels because capability of ionizing radiation to cause cancer generally has been recognized by scientific and legal authority).
16. *See Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 779 (D. Md. 2002), *aff'd* 62 Fed. R. Evid. Serv. 1289 (4th Cir. 2003).
17. *See Magistrini,* 180 F. Supp. 2d at 592.
18. *See Merrell Dow Pharms. v. Havner*, 953 S.W.2d 706, 719 (Tex. 1997); *see also* Bresnitz, *supra* note 10, at 1831-32; Michael D. Green, et al., *Reference Guide on Epidemiology*, Reference Manual on Scientific Evidence at 389, 392, & 395 (2d ed. 2000) (discussing sources of bias); David A. Grimes & Kenneth F. Schuls, *Bias and causal associations in observational research*, 359 The Lancet 248 (Jan. 19, 2002) (same, including real world examples of confounding errors).
19. *Magistrini*, 180 F. Supp. 2d at 591; *Caraker*, 188 F. Supp. 2d at 1032; *see also Havner,* 953 S.W.2d at 719 ("Bias can dramatically affect the scientific reliability of an epidemiological study.").
20. *Nelson v. Tennessee Gas Pipeline Co.*, 243 F.3d 244, 252-54 (6th Cir. 2001) (expert's failure to account for confounding factors in cohort study or alleged PCB exposures rendered his opinion unreliable).
21. *See Allison v McGhan Med. Corp.*, 184 F.3d 1300, 1315 (11th Cir. 1999) (noting that the women participating in the study at issue "were aware of the hypothesis, a factor which could have created bias, skewing the results and ultimately making the conclusions suspect").
22. *See Newman*, 218 F. Supp. 2d at 778; *see also Maras v. Avis Rent A Car Sys., Inc.*, No. Civ. 03-6191, 2005 WL 83828, * 5 (D. Minn. Jan. 14, 2005) (rejecting expert testimony based on epidemiological study that, among other failures, may have been influenced by recall bias).
23. *In re TMI Litig.*, 193 F.3d 613, 707-08 (3d Cir. 1999); *see also Bouchard v. Am. Home Prods. Corp.*, 213 F. Supp. 2d 802, 809-10 (N.D. Ohio 2002) (excluding expert causation testimony to the extent based on epidemiological study tainted with selection bias).
24. *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).
25. *Havner*, 953 S.W.2d at 718.
26. *See Dunn*, 275 F. Supp 2d at 677-78; *Magistrini*, 180 F. Supp. 2d at 592-93; *Amorgianos*, 137 F. Supp. 2d at 168; *Castellow v. Chevron* USA, 97 F. Supp. 2d 780, 786-87 & n.2 (S.D. Tex. 2000); *In re Breast Implants*, 11 F. Supp. 2d at 1233 n.5; *Havner*, 953 S.W.2d at 718 & n.2.
27. *Id.; see also* Bresnitz, supra note 10 at 1827-28 (describing Bradford Hill criteria in detail); David A. Grimes & Kenneth F. Schulz, *Bias and causal associations in observational research*, 359 The Lancet 248 (Jan. 19, 2002) (same, including real world examples of confounding errors); Douglas L. Weed, *Underdetermination and Incommensurability in Contemporary Epidemiology*, 7(2) Kennedy Institute of Ethics Journal 107, 113-15 (1997) (same).
28. *See Allison*, 184 F.3d at 1315 (noting that statistically significant epidemiological study reporting an increased risk of marker of disease of 1.24 times in patients with breast implants was so close to 1.0 that it "was not worth serious consideration for proving causation."); *In re Breast Implants Litig.*, 11 F. Supp. 2d at 1227 (same).
29. *See Havner*, 953 S.W.2d at 719.
30. *See, e.g., Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, (D. Kan. 2002) (expert failed to address "fact that other research is contrary to his conclusion), *aff'd*, 356 F.3d 1326 (10th Cir.), *cert denied*, 125 S. Ct. 40 (2004); *Havner*, 953 S.W.2d at 727 ("if scientific methodology is followed, a single study would not be viewed as indicating that it is 'more probable than not' that an association exists").
31. *See Joiner*, 522 U.S. at 145-46 (studies proffered as evidence of PCB-lung cancer link involved exposures to mineral oils or other potential carcinogens); *Burleson v. Tex. Dep't. of Criminal Justice*, 393 F.3d 577, 585-86 (5th Cir. 2004) (rejecting expert testimony where expert could not point to epidemiological studies demonstrating statistically significant link between thorium dioxide exposure and plaintiff's type of lung or throat cancer); *Allison*, 184 F.3d at 1315 (studies reported link to injuries not suffered by plaintiff); *Schudel v. Gen. Elec. Co.*, 120 F.3d 991, 997 (9th Cir. 1997) (studies involved exposures to organic solvents other than those at issue); *Magistrini*, 180 F. Supp. 2d at 603-04 (to same effect).
32. *See Newman*, 218 F. Supp. 2d at 778 (no dose response relationship found in study involving cell phone use and cancer); *Kelley v. Am. Heyer-Schulte Corp.*, 957 F. Supp. 873, 879 (W.D. Tex. 1997).
33. *See Hollander*, 289 F.3d at 1204 (rejecting expert's causation testimony despite his claimed adherence to the Bradford Hill methodology): *Dunn*, 275 F. Supp. 2d at 677-78 (same).
34. *See Lust v. Merrell Dow Pharms. Inc.*, 89 F.3d 594, 598 (9th Cir 1996) ("the district court should be wary that the [expert's] method has not been faithfully applied"); *O'Conner v. Commonwealth Edison Co.*, 13 F.3d 1090, 1106-07 (7th Cir. 1994) (excluding opinion where expert did not follow his own expressed methodology for establishing causation); *Knight v. Kirby Inland Marine, Inc.*, 363 F. Supp. 2d 859, 864 (N.D. Miss. 2005) (expert's "Bradford-Hill analysis is only as reliable as the underlying data upon which it is based"); *Hall*, 947 F. Supp. at 1400 (quoting *Lust*).
35. *See* Weed, (1997) *supra* note 27 at 115, 116-18 (discussing Robert A. Hiatt, *Alcohol Consumption and Breast Cancer*, 7 Medical Oncology Tumor Pharmacotherapy 143 (1990) (concluding that women with risk factors for breast cancer should limit alcohol use) and Ernst L. Wynder & Randall E. Harris, *Does Alcohol Consumption Influence the Risk of Developing Breast Cancer?* in Important Advances in Oncology 283 (V.T. Devita, S. Hellman, and S.A. Rosenberg eds. 1989) (concluding that there was no evidence of a causal link)).
36. *See Miller v. Pfizer, Inc*, 356 F.3d 1326, 1331 (10th Cir. 2004) (affirming *Daubert* exclusion of expert who relied upon meta-analyses of data regarding alleged relationship between Zoloft and suicide); *Allison*, 184 F.3d at 1315 (affirming exclusion of expert causation testimony based on "reanalysis of other studies that had found no statistical correlation between

silicone implants and disease"); *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1046-59 (D.N.J. 1992) (excluding expert testimony based on meta-analysis in Bendectin litigation), *aff'd without op.*,6 F.3d 778 (3d Cir. 1993); *see also Daubert II,* 43 F.3d at 1321 n.14 (noting that Bendectin plaintiff causation expert's metaanalysis "rested on demonstrably faulty methodology"); Knight, 363 F. Supp. 2d at 866 (rejecting causation opinion based on meta-analyses of cancer risks to chemical industry employees); *Black v. Rhone Poulenc, Inc.*, 19 F. Supp.2d 592, 604 (S.D.W.Va. 1998) (excluding expert testimony that relied heavily on meta-analysis, noting "a meta-analysis does not normally validate the individual studies it looks at").

37. For examples, see Douglas L. Weed, *Interpreting epidemiological evidence; how meta-analysis and causal inference methods are related*, 29 Int'l J. Epidemiol. 387 (2000); Jacques LeLorier, *et. al., Discrepancies Between Meta-Analyses and Subsequent Large Randomized, Controlled Trials*, 337(8) New Eng. J. Med. 336 (1997); Samuel Shapiro, *Is Meta-Analysis a Valid Approach to the Evaluation of Small Effects in Observational Studies?* 50(3) J. Clin. Epidemiol. 223 (1997); Samuel Shapiro, *Meta-analysis/Shmeta-analysis,* 140(9) Am. J. Epid. 771 (Nov. 1994).
38. EPA Office of Food Additive Safety, Redbook 2000: Toxicological Principles for the Safety Assessment of Food Ingredients, at VI.B.2(d) (Oct. 2001) (available at http://www.cfsan.fda.gov/~redbook/red-vib.html#vib2d) .
39. Shapiro (1994), at 771 *supra* note 37.
40. LeLorier (1997), at 541 *supra* note 37.
41. See, *e.g.*, Irva Hertz-Picciotto, *Epidemiology and Quantitative Risk Assessment: A Bridge from Science to Policy*, 85(4) Am. J. Public Health. 484, 485 (1995) ("The uncertainty stemming from interspecies extrapolation is far larger than the uncertainty resulting from uncontrolled bias or errors in exposure information in epidemiological studies").
42. *See* Bernard D. Goldstein & Mary Sue Henifen, *Reference Guide on Toxicology*, Reference Manual on Scientific Evidence 420 n.48 (2d ed. 2000). For additional examples of the often dramatic differences in responses among animal species and between animals and humans, see David L. Eaton & Curtis D. Klaassen, *Principles of Toxicology* in Casarett & Doull's Toxicology: The Basic Science of Poisons 25-26 (Curtis D. Klaassen ed., 6th ed. 2001); Elaine M. Faustman & Gilbert S. Omenn, *Risk Assessment*, in Casarett & Doull's Toxicology: The Basic Science of Poisons, *supra*, at 88-90; Lorenz Rhomberg, *Risk Assessment and the use of information on underlying biological mechanisms: A perspective,* 365 Mutation Research 175, 179-80 (1996); Jan M. M. Meijers, *et al., The Predictive Value of Animal Data in Human Cancer Risk Assessment*, 25 Regulatory Toxicology & Pharmacology 94 (1997).
43. *See Siharath*, 131 F. Supp. 2d at 1367 (quoting *Bell v. Swift Adhesives, Inc.,* 804 F. Supp. 1577, 1579-80 (S.D. Ga. 1992)); *Wade-Greaux v. Whitehall Labs.,Inc.,* 874 F. Supp. 1441, 1483-84 (D.V.I. 1994), *aff'd without op.,* 46 F.3d 1120 (3d Cir. 1994).
44. See *Soldo*, 244 F. Supp. 2d at 565; *Siharath*, 131 F. Supp. 2d at 1366-67 (citing cases).
45. *See, e.g., Joiner*, 522 U.S. at 144; *Hollander*, 289 F.3d at 1209; *Turpin*, 959 F.2d at 1358-61; *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d at 406-07; Caraker, 188 F. Supp. 2d at 1037; *Wade-Greaux*, 874 F. Supp. at 1477.
46. *See* Eaton & Klaassen, at 27, *supra* note 42.
47. *See* Eaton & Klaassen, at 27, *supra* note 42; Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants*, in Casarett & Doull's Toxicology: The Basic Science of Poisons, at 111.
48. *See* Eaton & Klaassen, at 17-18, *supra* note 42.
49. *Id.*, at 21.
50. *Id.*, at 13.
51. *See, e.g.,* Meijers, *supra* note 42, at 100 (concluding based on a comparison of animal and epidemiological studies for specific chemicals that "chemicals with little or no cancer potential in humans have been tested at too high concentrations in rodents … which resulted in the observed carcinogenic effect").
52. *Id.*, at 27. Federal regulatory agencies such as the Environmental Protection Agency thus use high dose animal research as a basis for establishing conservative regulatory safe exposure levels for humans (albeit at levels several multiples below that found to have no effect in animals). *See, e.g.,* Faustman & Omenn, *supra* note 42, at 92-94.
53. *See* Rozman & Klaassen, *supra* note 47, at 111; see also Meijers, *supra* note 42 at 95-98; Irva Hertz-Picciotto, *supra* note 41, at 485.
54. *See* Eaton & Klaassen, *supra* note 42, at 14; Rozman & Klaassen, *supra* note 47, at 111-14.
55. *See*, e.g., Rhomberg, *supra* note 42, at 181-83 (discussing carcinogenicity testing in animals engineered to be more susceptible to tumors).
56. Meijers, *supra* note 42, at 98.
57. *Id*.
58. *See Joiner*, 522 U.S. at 145; *see also Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001).
59. *Caraker*, 188 F. Supp. 2d at 1038; *see also Soldo*, 244 F. Supp. 2d at 549 ("Other federal courts facing proffered expert testimony based on the effects of allegedly similar compounds have reached the same conclusion and rejected such contentions: these courts have found that consideration of the effects of other drugs can only lead away from the truth.") (citing cases).
60. *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005); Rider, 295 F.3d at 1200-01; *Glastetter*, 252 F.3d at 990; *Schudel*, 120 F.3d at 996-97.
61. *See, e.g.,* Faustman & Omenn, *supra* note 42, at 86-87; A.M. Richard & R. Benigni, *AI and SAR Approaches for Predicting Chemical Carcinogenicity: Survey and Status* Report, 13(1) SAR and QSAR in Environmental Research 1 (2002); J. Ashby & R.W. Tenant, *Prediction of rodent carcinogenicity for 44 chemicals: results*, 9(1) Mutagenisis 7 (1994).
62. *See* Richard & Benigni, *supra* note 61, at 8, 10.
63. Richard & Benigni, *supra* note 61, at 8; see also Ashby & Tenant, *supra* note 60, at abstract ("carcinogenicity tends to be overpredicted by this integrated technique" of basing predictions on chemical structure, genotoxicity and rodent toxicity).
64. *See* James D. McKinney, *et al., Forum: The Practice of Structure Activity Relationships (SAR) in Toxicology,* 56 Toxicological Sciences 8, 15 (2000) ("Given the huge range and variability of possible interactions of chemicals in biological systems, it is highly unlikely that SAR models will ever achieve absolute certainty in predicting a toxicity outcome, particularly in a whole-animal system.").
65. *See Soldo*, 244 F. Supp. 2d at 513, 542; *Caraker*, 188 F. Supp. 2d at 1039; *Siharath*, 131 F. Supp. 2d at 1370; *Glastetter*, 107 F. Supp. 2d at 1034 n.18.
66. *See McLain*, 401 F.3d at 1248-50; *Rider*, 295 F.3d at 1201; *Glastetter*, 252 F.3d at 991; *Hollander*, 289 F.3d at 1215; *Conde*, 24 F.3d at 814; Dunn, 2003 WL 21856420, at * 10; *Soldo*, 244 F. Supp. 2d at 513; see *also* Richard A. Merrill, *Regulatory Toxicology*, in Casarett & Doull's Toxicology: The Basic Science of Poisons 1041-43, (discussing federal regulator's conservative risk-utility analysis); Joseph V. Rodricks & Susan H. Rieth, *Toxicological Risk Assessment in the Courtroom: Are Available Methodologies Suitable for Evaluating Toxic Tort and Product Liability Claims?* 27 Regulatory Toxicology and Pharmacology 21, 27 ("The public health-oriented resolution of scientific uncertainty [used by regulators] is not especially helpful to the problem faced by a court").
67. See J.A. Arnaiz, *et al., The use of evidence in pharmacovigilence: Case reports as the reference source for drug withdrawals*, 57 Eur. J. Clin. Pharmacol 89-91 (2001).
68. Rodricks & Rieth, *supra* note 66, at 30.