

Journal of Health Law

Winter 2004 Volume 37, No. 1

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The Case Against Differential Diagnosis: *Daubert*, Medical Causation Testimony, and the Scientific Method

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ABSTRACT: For the past decade, federal judges have been obligated to serve as gatekeepers and keep scientifically unreliable and irrelevant expert testimony out of the courtroom. The exacting evidentiary standards set forth in the landmark *Daubert* decision have had a significant impact on numerous areas of legal dispute. Toxic tort litigation, in particular, has been transformed by the standards. This Article reviews the Supreme Court's adoption of the scientific method as the standard for admissibility of expert testimony. It analyzes how a court's proper understanding of the scientific method can guide it in evaluating the different types of causation evidence presented in toxic tort litigation, both with respect to general and specific causation. Throughout this discussion and in the concluding section, the Article reflects the authors' firm's experience as national defense counsel in a series of product liability cases involving the prescription drug Parlodel®, in which these evidentiary issues have been analyzed extensively.

Expert
Testimony

85

There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact.

—Mark Twain¹

As a result of the Supreme Court's landmark ruling in *Daubert v. Merrell Dow Pharmaceuticals, Inc. (Daubert)*,² judges must serve as gatekeepers and keep scientifically unreliable and irrelevant expert testimony out of the courtroom.

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The standards set forth in *Daubert*, which the Supreme Court recently described as “exacting,”³ have had a significant impact on numerous areas of legal dispute. Toxic tort litigation, however, is the one area that has been most affected by the standards. Under *Daubert* and its progeny, *General Electric Co. v. Joiner (Joiner)*⁴ and *Kumho Tire Co. v. Carmichael (Kumho Tire)*,⁵ a plaintiff can no longer bring a toxic tort claim before a jury based solely on an expert’s subjective opinion that the plaintiff’s injury was caused by the substance in question. Rather, the plaintiff must demonstrate that the expert’s opinion is scientifically valid, both on the general causation question of whether the substance could potentially cause the injury, and the specific causation question of whether the substance in fact did cause the plaintiff’s injury.⁶

Daubert has imposed a significant new obligation on trial courts, and many judges have struggled to understand the scientific principles that they must follow in their new role.⁷ Plaintiffs’ counsel and like-minded legal observers have sought to take advantage of this uncertainty by arguing that the Supreme Court provided ambiguous guidance regarding the admissibility of medical causation testimony. Thus, they claim, courts should defer to the judgment of medical experts so long as they follow the same “differential diagnosis” reasoning in their expert testimony as they do in their clinical practice.⁸ These arguments are misplaced. The guidance provided by the Supreme Court is clear: Expert testimony that *Exposure A* caused *Event B* is admissible only if it is based on the scientific method. Evidence is based on the scientific method if it is properly derived through the generating and testing of hypotheses. This guidance provides a simple framework for courts considering the variety of evidence generally presented by causation experts in toxic tort litigation, whether it is epidemiology, animal research, chemical analogies, anecdotal information, or differential diagnosis.

This Article will review the Supreme Court’s adoption of the scientific method as the standard for admissibility of expert testimony. It will analyze how a court’s proper understanding of the scientific method can guide it in evaluating the different types of causation evidence presented in toxic tort litigation, both with respect to general and specific causation. Throughout this discussion and in the concluding section, the Article will draw on the authors’ firm’s experience as national defense counsel in a series of product liability cases involving the prescription drug Parlodel,[®] in which these evidentiary issues have been analyzed extensively. The Parlodel[®] litigation has been described in a recent textbook as “the first significant

products liability causation debate of the 21st century” and one that “will serve as a guide to understanding the significant causation issues that will continue to be involved, at increased rates of complexity in the 21st century products cases.”⁹

I. The Supreme Court’s Directive: Expert Testimony Must be Derived By the Scientific Method

In *Daubert*, the Supreme Court held that scientific testimony is not admissible unless it satisfies the dual requirements of scientific reliability and relevance. Scholarly debate regarding *Daubert* has often focused on the four factors suggested by the Court in determining scientific reliability: (1) testing; (2) peer review; (3) error rate and standards; and (4) general acceptance. A rote discussion of these factors, however, misses the point. These factors are relevant only insofar as they assist the trial court in applying the overarching directive of *Daubert*—that expert testimony must be based on the scientific method. The Supreme Court explained that “in order to qualify as ‘scientific knowledge,’ an inference or assertion must be derived by the scientific method.”¹⁰ The Court defined the scientific method as follows: “Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry.”¹¹ Moreover, “scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes.”¹² In other words, expert testimony is admissible only if empirical testing validates the specific theory to which the expert opines.¹³

Daubert also explains that, while admissible expert testimony must be based on the scientific method, “there are important differences between the quest for truth in a courtroom and the quest for truth in the laboratory. Scientific conclusions are subject to perpetual revision. Law on the other hand, must resolve disputes finally and quickly.”¹⁴ Accordingly, expert testimony must be judged based on the current state of scientific knowledge, not on the possibility that additional knowledge may emerge in the future. The Court recognized that the requirement of existing empirical evidence “on occasion will prevent the jury from learning of authentic insights and innovation,” but held that this “is the balance that is struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for particularized resolution of legal disputes.”¹⁵

Four years after *Daubert*, the Supreme Court provided further guidance on how judges should use the scientific method in evaluating expert testimony. In *Joiner*, the plaintiffs' experts contended that their opinion that PCBs can cause lung cancer should be admitted because they relied on epidemiology and animal studies, which are standard tools used by scientists in testing causal hypotheses.¹⁶ The Court rejected this contention, explaining that a faithful application of the scientific method requires more: "whether animal studies can ever be a proper foundation for an expert's testimony was not the issue. The issue was whether *these* experts' opinions were sufficiently supported by the animal studies on which they purported to rely."¹⁷ In other words, expert testimony must be based on empirical testing that *validates* the conclusions reached.¹⁸

The *Joiner* Court held that the research cited by plaintiffs' experts did not validate their conclusions because the epidemiological studies did not report a statistically significant causal link between PCBs and lung cancer, lacked proper controls, and examined substances other than PCBs.¹⁹ Furthermore, the animal studies involved massive doses of PCBs and a different type of cancer and could not be properly extrapolated to humans.²⁰ Plaintiffs' experts could not support their opinions under the scientific method because their conclusions ultimately rested on subjective leaps from the scientific evidence. "[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* of the expert. A court may conclude that there is simply too great an analytical gap between the data and opinion proffered."²¹

Two years later, in *Kumho Tire*, the Supreme Court held that the *Daubert* requirements of reliability and relevance apply to all expert testimony, including experience-based testimony.²² Even in areas where the four factors proposed in *Daubert* are inapplicable, the Court explained that the overarching question remains the same: Is the expert's testimony supported by a methodology that has been objectively validated and supports the conclusions offered?²³ In evaluating this question, it instructed that courts should consider whether the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."²⁴

II. 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 epidemiology, animal studies, chemical analogies, case reports, 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 lump this evidence together and reach a subjective determination concerning the strength of the evidence.²⁵ *Daubert*, however, clearly requires more. Under *Daubert*, a trial court must consider each of these categories of evidence in light of the scientific method. The expert's testimony may only be admitted if the expert can establish through scientific evidence that his causal hypothesis has been reliably tested and validated.

Further, a causation expert cannot satisfy his *Daubert* burden by arguing that the scientific research necessary to test his 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.²⁶ As Judge Posner explained, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it."²⁷

Expert
Testimony

89

A. Epidemiology

Controlled epidemiological studies are generally considered the most reliable evidence for testing a hypothesis that a particular substance causes a particular injury in humans.²⁸ Epidemiological studies can be especially important in cases in which the substance at issue is widely used or in which 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. While the absence of epidemiology may not be fatal to a plaintiff's case, a plaintiff seeking to establish causation without such evidence will face a high evidentiary hurdle.²⁹

When a causation expert relies on epidemiological studies to support his 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 to *causation*.³⁰ There are three reasons that a positive association may be observed in an epidemiological study: (1) bias; (2) chance; and (3) real effect.³¹ As the Supreme Court recognized in *Joiner*, epidemiological research cannot provide a scientifically reliable basis for an affirmative causation opinion if it is inadequately controlled for bias or statistically insignificant.³²

Bias in epidemiology is any systematic error that makes the two groups being compared different in more ways than just the variable being studied.³³ 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 information bias (systematic error in measuring data that results in differential accuracy of information).³⁴ Thus, a court must consider each of these sources of bias when interpreting an epidemiological study.³⁵

Expert
Testimony

90

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 1.0.³⁶ The generally-accepted confidence interval in epidemiological studies is ninety-five percent, meaning that a study is not statistically significant unless the "null" hypothesis of no increased (or decreased) risk can be excluded with ninety-five-percent confidence.³⁷ If an epidemiological study is not statistically significant, it cannot provide scientifically reliable evidence of an association, let alone causation.³⁸

Further, several 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 that the substance doubled the risk of contracting the disease.³⁹ 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. Thus, “more likely than not” legal causation would be disproved.

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.⁴⁰ “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.”⁴¹ 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”).⁴² 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.⁴³

In light of these criteria, courts have rejected statistically significant epidemiological research under *Daubert* when the reported relative risk is only slightly elevated.⁴⁴ They have suggested that epidemiological research reporting a relative increased risk of less than three times indicates only a weak association (strength of association).⁴⁵ Courts have also discarded isolated, statistically significant epidemiological findings that are not replicated in other epidemiological research (consistency).⁴⁶ Courts have rejected epidemiological studies reporting statistically significant associations with allegedly similar substances or allegedly similar injuries (specificity).⁴⁷ In addition, alleged associations in epidemiological studies that did not demonstrate a dose response relationship have been rejected as well (dose response).⁴⁸

Further, courts have not accepted the mere incantation of the name of Bradford Hill as establishing the reliability of a causation hypothesis.⁴⁹ These criteria must be applied faithfully or they can also generate unreliable conclusions,⁵⁰ as demonstrated by two review papers published in 1989–1990. Both review papers 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.⁵¹

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 was rejected by courts in the Bendectin litigation,⁵² and rightfully so. While meta-analyses can provide useful information if conducted pursuant to proper scientific methodology, they have frequently reported causal relationships that do not survive scientific scrutiny.⁵³ By pooling data from different studies, meta-analyses can discount 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 the studies are then run through computer models of bewildering complexity, which produces results of implausible precision.”⁵⁴ Pursuant to *Daubert*, a court must look behind this “bewildering complexity” and require the expert to establish the reliability and relevance of both the different pieces of information going into the meta-analysis and the calculations used to combine the information into a single result.

Expert
Testimony

92

B. Animal Research

Animal research may be a useful tool for raising suspicions that can then be tested in humans. Significant differences in humans and laboratory animals exist, however, that limit the degree to which animal research can validate a causation hypothesis in humans.⁵⁵ There are many examples of apparent positive findings in animal studies that have subsequently been found inapplicable to humans.⁵⁶ The most commonly cited example, perhaps, is saccharine. Saccharine was linked to bladder cancer in rats over twenty 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 and are accordingly not believed to be at risk. Due to such extrapolation problems, courts repeatedly have held that animal studies alone cannot prove causation in humans.⁵⁷

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.⁵⁸ 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 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.⁵⁹

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.⁶⁰ 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 metabolism.⁶¹ 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.

The existence of a dose-response relationship has been described as “the most fundamental and pervasive concept in toxicology.”⁶² All substances, even water, become toxic at a high enough dose. Conversely, however, “[i]t has long been recognized that acute toxicologic responses are associated with thresholds; that is, there is some dose below which the probability of an individual responding is zero.”⁶³ As stated by the oft-described father of chemical pharmacology, Paracelsus, “What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison.”⁶⁴ Accordingly, 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.⁶⁵ To the contrary, because toxic effects in humans are 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 is more indicative of the safety of the substance in normal use.⁶⁶

The route by which a substance enters the body can have a significant effect on its toxicity. Animal researchers frequently administer chemical agents through special routes, including: (1) intraperitoneal; (2) subcutaneous; (3) intramuscular; and

(4) intravenous.⁶⁷ These routes of administration may bypass the normal mechanisms through which potential toxins are removed before reaching general circulation. For example, many substances are biotransformed and detoxified by the liver. These substances can demonstrate toxic effects when injected either intravenously, intramuscularly, or subcutaneously, yet they are perfectly safe when ingested orally.⁶⁸ Likewise, animal researchers may use genetically designed or physically altered animals whose normal protective body mechanisms are removed.⁶⁹ These types of animal studies are useful in studying how an animal's normal body mechanisms interact and how substances affect isolated physiological systems. These studies, however, do not reflect real-world risks and may not be extrapolated, even among the particular species studied.

In conducting a *Daubert* inquiry, a trial court must determine whether the findings in the animal studies "fit" the expert opinions offered in the case. 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 "[c]ompared to humans much more variation occurs in the cancer sites in animals."⁷⁰ Yet in cases where a chemical is associated with cancers in both animal and epidemiological studies, "the target organs are usually identical."⁷¹ In *Joiner*, the Supreme Court rejected animal research in part because the animals developed a different type of cancer than that of the plaintiff.⁷²

C. 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"⁷³ evidence, especially when there is scientific research that demonstrates differences between the substance at issue and its purported chemical cousins. Small changes in molecular structure can "radically change a particular substance's properties and propensities."⁷⁴ Thus, research in analogous substances does not reliably test the causal hypothesis at issue.

The difficulty in relying on chemical analogies is demonstrated by attempts to create computerized programs to assess the toxicity of chemical agents based on structure-activity relationships. These computerized models are far more sophisticated than the

simplistic chemical analogies often relied on by causation experts in toxic tort litigation. In addition, these models often rely on information regarding a substance beyond its chemical structure. While these models may prove helpful in setting research priorities or generating hypotheses, they have failed to provide reliable predictions as to a chemical's toxic effect.⁷⁵ As reported in a recent survey article, two prediction toxicity exercises conducted under the aegis of the National Toxicology Program found that models which attempt to predict carcinogenicity "based solely on information derived from chemical structure" are particularly unreliable. The first exercise reported that "overall accuracy in terms of positive or negative predictions was in the range 50-65%," and the ongoing second exercise reported even higher error rates in preliminary results.⁷⁶ Moreover, "[a] clear limitation of almost all the prediction systems . . . was their excessive sensitivity, *i.e.*, incorrectly predicting many non-carcinogens as positive."⁷⁷ Efforts to predict toxicity based on structure activity relationships have resulted in similar problems.⁷⁸

D. Case Reports/Case Series

Case reports and case series are anecdotal observations of adverse effects occurring in coincidence with exposure to a given substance. If a sufficient body of similar case reports appear in medical literature, they can spur epidemiological or other controlled research on whether a causal link exists.⁷⁹ As most courts have properly recognized, however, under *Daubert*, case reports themselves do not test the causal hypothesis and accordingly cannot support a causation opinion.⁸⁰ Case reports are merely anecdotal accounts of observations in particular individuals. They are not controlled tests, frequently lack analyses, and often make little attempt to screen out alternative causes for a patient's condition.⁸¹ As discussed above, when a substance is widely used, it is statistically certain, given general background rates of injury, that there will be case reports in which an exposure and injury coincidentally coincide. Thus, the existence of such case reports is of little scientific value.⁸²

In drug product-liability cases, causation experts can rely on "causality assessments" of individual case reports. Causality assessments are algorithms used in some European pharmacovigilance regulatory schemes. They seek to impose structure on evaluation of individual case reports by creating standardized questions to be used in reviewing such reports. Examples of questions used in causality assessments include the following.

- Was the adverse event a known consequence of the drug?
- Did the event occur in temporal proximity to the use of the drug?
- Did the symptoms disappear upon withdrawal of the drug (dechallenge)?
- Did the symptoms reappear following reintroduction of the drug (rechallenge)?
- Are there alternative causes for the adverse event?

Reviewers grade individual case reports using such terms as “not possible,” “unlikely,” “possible,” and “probable.”⁸³ Causality assessments are used by some regulatory agencies as a signaling tool, but they “have no objective reliability which would render them useful in a wider environment.”⁸⁴ “None of the available causality assessment systems has been validated . . . [i]n other words, uncertainty [inherent in case reports] is not reduced, but categorised (at best, in a semiquantitative way).”⁸⁵ Studies of standardized causality assessments repeatedly find significant disagreements between graders using the same assessment methodology.⁸⁶ Accordingly, causality assessments carry no greater scientific weight than other case reports and thus cannot provide the type of evidence required under *Daubert*.⁸⁷

Expert
Testimony

96

Some case reports include information regarding purported dechallenges or rechallenges—reports that a patient’s condition improved when the substance was removed or worsened when the substance was reintroduced. When the dechallenge/rechallenge report is merely an after-the-fact account of an anecdotal observation, it suffers from similar reliability problems as other case reports. Many medical conditions result in fluctuations in symptomology in the ordinary course, and apparent temporal associations with exposure can be due purely to chance. Even if the dechallenge or rechallenge is conducted prospectively with the intent of testing a causal hypothesis, a perceived effect in one person has limited scientific value at best.⁸⁸ A trial court must be particularly diligent in determining whether the dechallenge/rechallenge was conducted under strict controls to account for potential confounding influences, because the data are limited to a single observation. Prospective dechallenge/rechallenge experiments—sometimes referred to as “single subject” or “n of 1” experiments—have numerous limitations that preclude general causation conclusions.⁸⁹ “[W]ithout strong assumptions regarding how an intervention on one individual relates to its effects on others, the results from a single-subject design provide little useful information . . . [and] [e]xamination of a single subject cannot verify these as-

sumptions.”⁹⁰ A prospective dechallenge/rechallenge report “constitutes but one single, uncontrolled experiment.”⁹¹

E. Secondary Source Materials

In addition to actual scientific or anecdotal data, causation experts sometimes rely on secondary source materials that cite to the primary evidence. These materials include regulatory materials, textbooks, and internal company documents. Secondary source materials do not add additional scientific knowledge and are no more reliable than the evidence they cite.⁹² They do not test a causal hypothesis. Rather, secondary sources 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.”⁹³ A recent article reported that the vast majority of regulatory withdrawals of approvals for drugs in Spain during the 1990s was based solely on case reports.⁹⁴ 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 regulatory decision-maker in setting regulatory standards and make such standards problematic as reference points in litigation.”⁹⁵

Expert
Testimony

97

III. Causation Opinions Based on Clinical Reasoning

The question whether clinical reasoning can reliably support a causation opinion must be considered separately from both general and specific causation. Doctors do not ordinarily make scientifically reliable determinations regarding general causation in their daily clinical practice. Instead, doctors make individualized treatment decisions based on the exigencies of the moment. As a result, clinical reasoning cannot reliably support a general causation opinion. On the other hand, clinical reasoning through a differential diagnosis may provide reliable support for a specific causation opinion, so long as the diagnosis is reached in a manner that it is faithful to the scientific method. Differential diagnoses conducted for tort-litigation purposes can raise unique issues of reliability, though, because they are generally conducted *post hoc* and not in the context of medical treatment.

A. Clinical Reasoning and General Causation

Physicians are required to make treatment decisions for individual patients based upon the clinical information before them. These clinical judgments do not provide a reliable basis for a general causation opinion.⁹⁶ Physicians do not conduct scientific testing in their daily practice to determine whether particular substances cause particular injuries. Indeed, few have “more than rudimentary training” in the scientific methods used to determine causation.⁹⁷ Instead, they make working diagnoses and conservative medical judgments based on their Hippocratic Oath to “first, do no harm.”⁹⁸ Thus, for example, when a physician orders a patient to avoid further exposure to a new medication or chemical substance, it is a no-risk prophylactic measure and not a scientific determination of causality.⁹⁹

While doctors may reach tentative opinions regarding causation in the course of providing treatment, their opinions are not reached pursuant to the scientific method. Rather, they are based on inferential leaps, which allow them to provide immediate therapeutic care. A clinical causation opinion based on differential diagnosis is “a mixture of science and art, far too complicated for its accuracy to be assessed quantitatively or for a meaningful error rate to be calculated.”¹⁰⁰ Moreover, differential diagnosis only “follow[s] the causal stream up to a point where intervention is possible” because typically physicians are only interested in a disease’s etiology if it would assist in diagnosis and treatment.¹⁰¹ As one court recently explained,

Doctors in their day-to-day practices stumble upon coincidental occurrences and random events and often follow human nature, which is to confuse association and causation. They are programmed by human nature and the rigors and necessities of their clinical practices to conclude that temporal association equals causation, or at least that it provides an adequate proxy in the chaotic and sometimes inconclusive world of medicine. This shortcut aids doctors in their clinical practices because their most important objective day-to-day is to help their patients and “first, do no harm,” as their Hippocratic oath requires. Consequently, they make a leap of faith. . . . [This type of] clinical impression is not the sort of scientific methodology that *Daubert* demands.¹⁰²

Plaintiffs' counsel will often cite to the language in *Kumho Tire* that an expert must employ "in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field"¹⁰³ when arguing for clinical reasoning to support a general causation opinion. This argument is misplaced because, as has been explained, "the relevant field[s]" for a general causation opinion are epidemiology and toxicology, not clinical medicine.¹⁰⁴ Plaintiffs' counsel will also argue that differential diagnosis is a well-recognized, scientifically reliable technique. Yet differential diagnosis is a reliable methodology only in "ruling out" alternative causes of injury from a list of possible causes; it does not "rule in" a substance as a potential cause in the first instance.¹⁰⁵

B. Clinical Reasoning and Specific Causation

Although insufficient for purposes of general causation, differential diagnosis may provide a scientifically reliable basis for a specific causation opinion that an established toxin in fact caused a plaintiff's injury. An expert's assertion that he applied a differential diagnosis, however, is not sufficient to satisfy *Daubert*. A trial court must determine whether the differential diagnosis is based on a reliable methodology. Accordingly, the expert must demonstrate that the differential diagnosis was based on a sufficient and valid clinical investigation.¹⁰⁶ The expert must also have a scientifically reliable basis for excluding alternative causes of the plaintiff's injury, including the possibility that the injury was idiopathic.¹⁰⁷

A trial court must also evaluate an expert's differential diagnosis in light of the artificial circumstances in which the expert reached his opinion. Unlike differential diagnoses conducted by physicians in their day-to-day practice, a differential diagnosis in a litigation context is often conducted in support of an already asserted legal claim of causation. This raises myriad possibilities of bias, both intentional and unintentional.

Consider a hypothetical example of typical large-scale drug product liability litigation. Based on anecdotal reports of adverse events and possibly pressure from special interest organizations like Public Citizen, the Food and Drug Administration (FDA) recommends labeling changes or withdraws approval of a drug.¹⁰⁸ The same day, if not before, plaintiffs' firms begin advertising for potential plaintiffs utilizing various forms of media, including internet, television, radio, and print. Provided that the drug is or was used by a relatively large number of patients, there will be a ready population of people who had

adverse events while taking the drug solely due to a statistical chance. By using this method, plaintiffs' counsel can quickly gather a large pool of potential plaintiffs.

Plaintiffs' counsel will then begin weeding through the pool of individuals, excluding those with obvious alternative causes for their injuries and those whose injury did not emerge in temporal proximity to their ingestion of the drug. At first blush, this appears to be a reliable method for determining which individuals have injuries that are likely due to the drug. This interpretation, however, is based on the false premise that medicine can always find a cause for an injury. In fact, there are many conditions for which medicine frequently cannot find a cause.¹⁰⁹ In other words, there is often a measurable background rate of *idiopathic* injuries—injuries with unknown causes. This weeding-out process often only identifies the statistically-expected population of patients who coincidentally had adverse events of unknown cause while taking the drug.

At the same time plaintiffs' counsel is reviewing the potential plaintiff pool, they are also looking for an expert witness who will provide a specific causation opinion. Generally, plaintiffs' counsel will select an expert who is already prepared to offer a favorable general causation opinion. This expert witness is often predisposed towards providing a favorable specific causation opinion. "Predisposed" does not mean that the expert is intentionally biased or insincere in his opinion, but it does mean that the expert enters the litigation process with a preconceived assumption of causality.

By the time the expert and plaintiff are brought together for purposes of a differential diagnosis, the result is effectively preordained. The expert starts the examination from the premise that the substance at issue is dangerous and a likely cause of injury regardless of potential alternative causes. The plaintiff will not ordinarily present with obvious alternative causes of injury sufficient to shake the expert from his initial presumption. Moreover, in cases in which the expert is not the patient's treating physician, the expert does not test the initial diagnosis through ongoing observation and medical treatment.

This "differential diagnosis" method bears little resemblance to a differential diagnosis conducted by physicians in their regular practice, and therefore cannot provide the type of objective validation that *Daubert* requires for admissibility of an expert causation opinion. Accordingly, trial courts must evaluate carefully the expert's conclusion to determine whether it is based on

“the same level of intellectual rigor” that characterizes a differential diagnosis conducted in normal clinical practice.

IV. The Parlodel® Litigation

Over the past decade, plaintiffs have filed a number of product liability cases involving the prescription drug Parlodel.® This litigation established a body of *Daubert* case law that squarely addresses the issues of medical causation expert testimony and provides a detailed analysis of “all of the components of the ‘causation’ argument that are available to litigators in the most contentious of products liability case[s].”¹¹⁰

There is now an emerging judicial consensus that the expert causation opinions offered by plaintiffs in the Parlodel® litigation do not satisfy the *Daubert* requirements. In the past two years, three federal appellate courts, the Eighth, Tenth, and Eleventh Circuits, unanimously affirmed district court opinions that excluded the causation opinions of plaintiffs’ experts. In addition, four other published district court opinions excluding this testimony were not appealed.¹¹¹ A few earlier district court opinions, two of which were drafted by the same magistrate judge, allowed plaintiffs’ expert causation opinions.¹¹² The Parlodel® opinions provide a useful *Daubert* case study of courts that properly evaluate medical causation testimony based on the scientific method and those that do not.

Expert
Testimony

101

A. Plaintiffs’ Allegations Regarding Parlodel®

Parlodel® (bromocriptine mesylate) is an FDA-approved drug used for a variety of conditions, including Parkinson’s Disease, amenorrhea/galactorrhea (lack of menses), infertility, and acromegaly (a growth disorder).¹¹³ Between 1980 and 1994, Parlodel® was also approved for the prevention of postpartum lactation (PPL) in women who elected not to breast-feed. Parlodel’s® manufacturer withdrew the drug from the market for treatment of PPL following the receipt of case reports describing strokes, seizures, and myocardial infarctions, as well as an FDA advisory committee determination that there was limited need for pharmaceutical treatment of PPL.¹¹⁴ The FDA withdrew its approval of Parlodel® for the PPL indication in 1995, based on its conclusion that the limited utility of the drug for PPL did not outweigh the possible risks.¹¹⁵

Plaintiffs’ experts claimed that Parlodel® causes vasoconstriction (a narrowing of blood vessels) which can allegedly cause strokes, seizures, and myocardial infarction. Plaintiffs’ experts

concede that current epidemiological studies conducted on the drug do not establish a causal link with the above injuries. These experts also concede that there is a body of controlled clinical human research indicating that Parlodel® causes vasodilation (a widening of blood vessels), the exact opposite of vasoconstriction. In addition, controlled intact animal research does not show a causal link between Parlodel® and strokes, seizures, or myocardial infarctions in animals. Consequently, the causation opinions of plaintiffs' experts have been based on anecdotal case reports (including alleged dechallenge/rechallenge reports), animal research involving limited endpoints, chemical analogies, a variety of secondary source materials, and differential diagnoses.¹¹⁶

B. Opinions Admitting Causation Opinions of Plaintiffs' Experts

The district courts that admit plaintiffs' expert causation opinions primarily rely on differential diagnoses and a determination that lesser scientific evidence of general causation should be accepted because it allegedly is not possible to conduct an epidemiological study of sufficient strength to adequately test the causation hypothesis. Thus, one magistrate judge dismissed the lack of any direct scientific evidence supporting plaintiffs' expert causation opinion. The judge reasoned that "[s]cience, like many other human endeavors, draws conclusions from circumstantial evidence when other, better forms of evidence [are] not available."¹¹⁷ In a subsequent opinion, the same magistrate judge sounded a similar theme: "In science, as in life, where there is smoke, fire can be inferred, subject to debate and further testing."¹¹⁸ This court was similarly deferential in its review of plaintiffs' expert specific causation opinions. While noting that there were a number of alternative causes for the injuries at issue, the court found that the "debate creates a question about the weight to be accorded the plaintiffs' experts' opinions, but it does not affect the admissibility."¹¹⁹

Missing in these opinions is any recognition of the requirement in *Daubert* that an expert's causation opinion be based on the scientific method of testing and validating hypotheses. *Daubert* does not permit expert testimony to be admitted based on the "smoke" of anecdotal reports and inferences, nor does *Daubert* allow courts to lower the bar of scientific reliability based on a perceived lack of relevant scientific evidence. Courts abdicate their gatekeeping responsibility when accepting a lower showing of evidence.

Expert
Testimony

C. Opinions Excluding Opinions of Plaintiffs' Experts

By contrast, in the Parlodel® cases, the courts that evaluate plaintiffs' expert's opinions based on the scientific method exclude the expert testimony. These courts conduct detailed analyses of each of the different categories of evidence discussed earlier, and incorporate their reasoning and conclusions into that discussion. The overarching theme in these opinions is that medical causation opinions are not admissible unless the opinions are based upon scientifically tested and validated hypotheses.

As these courts explain, *Daubert* does not establish a "best efforts test."¹²⁰ An expert cannot satisfy *Daubert* by arguing that he used the "best methodology"¹²¹ available under the circumstance, or that the expert did the "best [he] could with the available data and the scientific literature."¹²² Rather, the expert must answer the key question: Whether the "theory being advanced by the expert is testable or has been tested, the methodology of which is 'what distinguishes science from other fields of human inquiry.'"¹²³ "The hallmark of [*Daubert's*] reliability prong is the scientific method, *i.e.*, the generation of testable hypotheses that are then subjected to the real world crucible of experimentation, falsification/validation, and replication."¹²⁴ The "testing of hypotheses [is] a critical aspect of the application of the scientific method."¹²⁵ Expert opinions "reposed in the realm of 'may cause' or 'possibly could cause'"¹²⁶ must be excluded. "While hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination of whether liability exists."¹²⁷

The Parlodel® cases forcefully answer the *Daubert* critics who argue for a lower standard based on deferential review of medical-causation testimony:

The *Daubert* trilogy, in shifting the focus to the kind of empirically supported, rationally explained reasoning required in science, has greatly improved the quality of the evidence upon which juries base their verdicts. Although making determinations of reliability may present a court with the difficult task of ruling on matters that are outside of its field of expertise, this is "less objectionable than dumping a barrage of scientific evidence on a jury, who would likely be less equipped

than the judge to make reliability and relevancy determinations."¹²⁸

The scientific method serves as a bulwark against subjective judgments and inspired guesswork masquerading as scientific knowledge. Courts that ignore the scientific method when reviewing medical causation opinions do a disservice to the legal system and disregard the Supreme Court's mandate.

V. Conclusion

Faced with the exacting standards of *Daubert*, plaintiffs' causation experts often respond with a "spaghetti-on-the-wall" strategy in the hope that something will "stick." The Supreme Court's adoption of the scientific method as the central guide to admissibility provides district courts with the solution they need to untangle the mess. For each strand in plaintiffs' expert's analysis, the questions are the same: Is the expert relying on evidence that has been tested and validated, and does the evidence fit the question at issue? Unless an expert can answer both of these questions in the affirmative, he should not be allowed to present his opinions to a jury.

Expert
Testimony

104

Endnotes

- ¹ MARK TWAIN, *LIFE ON THE MISSISSIPPI* 156 (Harper and Brothers 1950) (1874).
- ² *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).
- ³ *Weisgram v. Marley Co.*, 528 U.S. 440, 455 (2000).
- ⁴ *General Elec. Co. v. Joiner*, 522 U.S. 136 (1997).
- ⁵ *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137 (1999).
- ⁶ *See Raynor v. Merrell Pharm. Inc.*, 104 F.3d 1371, 1376 (D.C. Cir. 1997).
- ⁷ A recent survey of 400 state trial judges found that while a large majority of judges agreed that the role of "gatekeeper" was an appropriate one for a judge, most judges did not have a proper understanding of the scientific principles set forth in *Daubert*. *See Sophia I. Gatowski et al., Asking the Gatekeepers: A National Survey of Judges on Judging Expert Evidence in a Post-Daubert World*, 25 *LAW & HUM. BEHAV.* 433, 433 (2001).
- ⁸ *See Jerome P. Kassirer & Joe S. Cecil, Inconsistency in Evidentiary Standards for Medical Testimony: Disorder in the Courts*, 288 *J.A.M.A.* 1382 (Sept. 2002).
- ⁹ TERENCE F. KIELY, *SCIENCE AND LITIGATION: PRODUCTS LIABILITY IN THEORY AND PRACTICE* 177 (CRC Press 2002).
- ¹⁰ *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 590 (1993).
- ¹¹ *Id.* at 593. The Supreme Court cited to two philosophical texts on the nature of scientific evidence. *See id.* (citing CARL G. HEMPEL, *THE PHILOSOPHY OF NATURAL SCIENCE* 49 (Prentice-Hall 1966) ("[T]he statements constituting a scientific explanation must be capable of empirical test"); KARL R. POPPER, *CONJECTURES AND REFUTATIONS: THE GROWTH OF SCIENTIFIC KNOWLEDGE* 37 (5th ed., Routledge 1989) (1963) ("[T]he criterion of the scientific status of a theory is its falsifiability, or refutability, or testability").
- ¹² *Daubert*, 509 U.S. at 591.
- ¹³ The four factors discussed in *Daubert* provide different methods by which an expert's opinion can be analyzed for adherence to the scientific method.

Two of the factors, testing and error rates, are integral parts of the scientific method itself. The other two factors, peer review and general acceptance, can provide independent support that the opinion was properly derived by the scientific method. Peer review, however, should not be mindlessly equated with publication. As the Supreme Court noted, publication “is but one element of peer review.” *Id.* at 593. Peer review, like general acceptance, refers more broadly to the concept that the theory at issue has been subjected to and found valid through empirical testing by the broader scientific community. See generally William L. Anderson et al., *Daubert’s Backwash: Litigation-Generated Science*, 34 U. MICH. J.L. REFORM 619 (2001); Effie J. Chan, *The “Brave New World” of Daubert: True Peer Review, Editorial Peer Review, and Scientific Validity*, 70 N.Y.U. L. REV. 100 (1995).

¹⁴ *Daubert*, 509 U.S. at 596-97.

¹⁵ *Id.* at 597.

¹⁶ *General Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997).

¹⁷ *Id.*

¹⁸ See *id.* at 146 (“conclusions and methodology are not entirely distinct from one another”).

¹⁹ *Id.* at 144.

²⁰ *Id.*

²¹ *Joiner*, 522 U.S. at 146.

²² *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999).

²³ See *Kumho Tire Co., Ltd.*, 526 U.S. at 157 (noting with respect to challenged tire expert’s testimony that “despite the prevalence of tire testing,” plaintiffs did not “refer to any articles or papers that validate [the expert’s] approach”).

²⁴ *Id.* at 152.

²⁵ *Kassirer & Cecil*, *supra* note 8, at 1384, 1386.

²⁶ See *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993).

²⁷ *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

²⁸ See, e.g., *Soldo v. Sandoz Pharm. 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 Pharm. 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); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224-25 (D. Colo. 1998) (citations omitted).

²⁹ See *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001), *aff’d*, *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002).

³⁰ Michael D. Green et al., *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 336 (2d ed. 2000).

³¹ *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D. N.J. 2002); *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1032 (S.D. Ill. 2001). See Eddy A. Bresnitz, *Principles of Research Design*, in GOLDFRANK’S TOXICOLOGIC EMERGENCIES 1827-28 (Goldfrank et al. eds. 6th ed. 1998).

³² See *General Elec. Co. v. Joiner*, 522 U.S. 136, 145-46 (1997).

³³ See *Magistrini*, 180 F. Supp. 2d at 592.

³⁴ See *Merrell Dow Pharm., Inc. v. Havner*, 953 S.W.2d 706, 719 (Tex. 1997). See also Bresnitz, *supra* note 31, at 1831-32; Green et al., *supra* note 30, at 389, 392, 395; David A. Grimes & Kenneth F. Schulz, *Bias and Causal Associations in Observational Research*, 359 THE LANCET, Jan. 19, 2002, at 248-51.

³⁵ *Magistrini*, 180 F. Supp. 2d at 592. See *Havner*, 953 S.W.2d at 719 (“bias can dramatically affect the scientific reliability of an epidemiological study”).

- ³⁶ See *Turpin v. Merrell Dow Pharm., Inc.*, 959 F.2d 1349, 1353 n.1 (6th Cir. 1992).
- ³⁷ *Havner*, 953 S.W.2d at 723.
- ³⁸ See *General Elec. Co. v. Joiner*, 522 U.S. 136, 145 (1997). See also *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 681 (M.D. N.C. 2003) (“statistically insignificant results do not constitute proof” of causation); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 533 (W.D. Pa. 2003) (“Courts have emphasized that epidemiologic proof must be statistically significant.”); *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1034 (S.D. Ill. 2001) (rejecting experts’ causation opinions “inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies”).
- ³⁹ See *Magistrini*, 180 F. Supp. 2d at 591; *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1356 (N.D. Ga. 2001); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1225-26 (D. Colo. 1998); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1403-04 (D. Or. 1996). See also *Daubert v. Merrell Dow Pharm., 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).
- ⁴⁰ See *Amorgianos v. Nat’l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 168 (E.D. N.Y. 2001).
- ⁴¹ *Merrell Dow Pharm., Inc. v. Havner*, 953 S.W.2d 706, 718 (Tex. 1997).
- ⁴² See *Dunn*, 275 F. Supp. 2d at 677-680; *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. 2002); *Breast Implant Litig.*, 11 F. Supp. 2d at 1233 n.5; *Havner*, 953 S.W.2d at 718 n.2.
- ⁴³ See *Dunn*, 275 F. Supp. 2d at 677-680; *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. 2002); *Breast Implant Litig.*, 11 F. Supp. 2d at 1233 n.5; *Havner*, 953 S.W.2d at 718 n.2. See also *Bresnitz*, *supra* note 31, at 1827-28 (describing Bradford Hill criteria in detail); Douglas L. Weed, *Underdetermination and Incommensurability in Contemporary Epidemiology*, 7 KENNEDY INST. ETHICS J. 107, 113-15 (1997) [hereinafter *Weed*, *Underdetermination*].
- ⁴⁴ See *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1315 (11th Cir. 1999) (noting that statistically significant epidemiological study reporting an increased risk of marker of disease of 1:24 in patients with breast implants was so close to 1.0 that it “was not worth serious consideration for proving causation”); *Breast Implant Litig.*, 11 F. Supp. 2d at 1227.
- ⁴⁵ See *Havner*, 953 S.W.2d at 719.
- ⁴⁶ See, e.g., *id.* 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”).
- ⁴⁷ See *General Elec. Co. v. Joiner*, 522 U.S. 136, 145-47 (1997) (revealing that studies relied upon by the respondent as evidence of PCB-lung cancer involved exposure to mineral oils and other potential carcinogens and made no mention of PCB); *Allison*, 184 F.3d at 1315 (demonstrating a study that reported a link to injuries that were not suffered by the plaintiff); *Schudel v. Gen. Elec. Co.*, 120 F.3d 991, 997 (9th Cir. 1997) (reporting that studies involved exposures to organic solvents other than those at issue); *Magistrini*, 180 F. Supp. 2d at 603-04.
- ⁴⁸ See *Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 778 (D. Md. 2002) (reporting a lack of dose-response relationship in a study involving cell

- phone use and cancer); *Kelley v. Am. Heyer-Schulte Corp.*, 957 F. Supp. 873, 879 (W.D. Tex. 1997).
- ⁴⁹ See *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1204 (10th Cir. 2002) (rejecting expert's causation testimony despite his claimed adherence to the Bradford Hill methodology); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 678 (M.D. N.C. 2003).
- ⁵⁰ See *Lust v. Merrell Dow Pharm., 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).
- ⁵¹ See *Weed, Underdetermination*, *supra* note 43, at 115 (discussing Robert A. Hiatt, *Alcohol Consumption and Breast Cancer*, 7 MED. ONCOLOGY AND 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? Two Views*, in *IMPORTANT ADVANCES IN ONCOLOGY* 283 (V.T. Devita et al. eds., 1989) (concluding that there was no evidence of a causal link)).
- ⁵² See, e.g., *DeLuca v. Merrell Dow Pharm., Inc.*, 791 F. Supp. 1942, 1046-59 (D. N.J. 1992).
- ⁵³ See generally Douglas L. Weed, *Interpreting Epidemiological Evidence; How Meta-Analysis and Causal Inference Methods are Related*, 29 INT'L. J. EPIDEMIOLOGY 387, 387 (2000); Samuel Shapiro, *Is Meta-Analysis a Valid Approach to the Evaluation of Small Effects in Observational Studies?*, 50 J. CLINICAL EPIDEMIOLOGY 223 (1997); Samuel Shapiro, *Meta-Analysis/Shmeta-Analysis*, 140 AM. J. EPIDEMIOLOGY 771 (1994) [hereinafter Shapiro, *Meta-Analysis/Shmeta Analysis*].
- ⁵⁴ Shapiro, *Meta-Analysis/Shmeta-Analysis*, *supra* note 53, at 771.
- ⁵⁵ See Irva Hertz-Picciotto, *Epidemiology and Quantitative Risk Assessment: A Bridge from Science to Policy*, 85 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.") (citation omitted).
- ⁵⁶ Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, in *REFERENCE MANUAL ON SCIENTIFIC EVIDENCE* 420 (2nd ed. 2000), available at [www.fjc.gov/public/pdf.nsf/lookup/sciman00.pdf/\\$file/sciman00.pdf](http://www.fjc.gov/public/pdf.nsf/lookup/sciman00.pdf/$file/sciman00.pdf) (last visited Jan. 1, 2004). 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., 2001); Elaine M. Faustman & Gilbert S. Omenn, *Risk Assessment*, in *CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS* 88-90 (Curtis D. Klaassen, 6th ed. 2001); Jan M. Meijers et al., *The Predictive Value of Animal Data in Human Cancer Risk Assessment*, 25 REGULATORY TOXICOLOGY & PHARMACOLOGY 94, 94 (1997); Lorenz Rhomberg, *Risk Assessment and the Use of Information on Underlying Biological Mechanisms: A Perspective*, 365 MUTATION RESEARCH 175, 179-80 (1996).
- ⁵⁷ See *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1367 (N.D. Ga. 2001) (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 opinion*, 46 F.3d 1120 (3d Cir. 1994).
- ⁵⁸ See *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 565 (W.D. Pa. 2003); *Siharath*, 131 F. Supp. 2d at 1366-67.
- ⁵⁹ See, e.g., *General Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997); *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1209 (10th Cir. 2002); *Turpin v. Merrell Dow Pharm., Inc.*, 959 F.2d 1349, 1358-61 (6th Cir. 1992); *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1037 (S.D. Ill. 2001); *Wade-Greaux*, 874 F. Supp. at 1477.
- ⁶⁰ See *Eaton & Klaassen*, *supra* note 56, at 27.

- ⁶¹ See *id.*; Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants*, in CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS 111 (Curtis D. Klaassen, 6th ed. 2001).
- ⁶² See Eaton & Klaassen, *supra* note 56, at 17–18.
- ⁶³ *Id.* at 21.
- ⁶⁴ *Id.* at 13.
- ⁶⁵ See, e.g., Meijers et al., *supra* note 56, at 100 (Based on a comparison of animal and epidemiological studies for specific chemicals, “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.”).
- ⁶⁶ See Eaton & Klaassen, *supra* note 56, at 26. Federal regulatory agencies such as the Environmental Protection Agency use high dose animal research as a basis for establishing conservative regulatory safe exposure levels for humans (albeit at levels several multiples below that which is found to have no effect in animals). See, e.g., Faustman & Omenn, *supra* note 56, at 92–94.
- ⁶⁷ See Rozman & Klaassen, *supra* note 61, at 111; Irva Hertz-Picciotto, *supra* note 55, at 485. See also Meijers et al., *supra* note 56, at 98.
- ⁶⁸ See Eaton & Klaassen, *supra* note 56, at 14; Rozman & Klaassen, *supra* note 61, at 111–14.
- ⁶⁹ See, e.g., Rhomberg, *supra* note 56, at 181–83 (discussing carcinogenicity testing in animals that are engineered to be more susceptible to tumors).
- ⁷⁰ Meijers et al., *supra* note 56, at 98.
- ⁷¹ *Id.*
- ⁷² See *General Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997).
- ⁷³ *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1038 (S.D. Ill. 2001). “Other federal courts facing proffered expert testimony based on the effects of allegedly similar chemicals 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.” *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 549 (W.D. Pa. 2003) (emphasis in original).
- ⁷⁴ *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002). See *Schudel v. Gen. Elec. Co.*, 120 F.3d 991, 997 (9th Cir. 1997).
- ⁷⁵ See, e.g., J. Ashby & R.W. Tenant, *Prediction of Rodent Carcinogenicity for 44 Chemicals: Results*, 9 MUTAGENESIS 7, 7–15 (1994); Faustman & Omenn, *supra* note 56, at 86–87; A.M. Richard & R. Benigni, *AI and SAR Approaches for Predicting Chemical Carcinogenicity: Survey and Status Report*, 13 SAR AND QSAR IN ENVIRONMENTAL RESEARCH 1, 1–19 (2002).
- ⁷⁶ See Richard & Benigni, *supra* note 75, at 8, 10.
- ⁷⁷ *Id.* at 8. “Carcinogenicity tends to be overpredicted by this integrated technique” of basing predictions on chemical structure, genotoxicity, and rodent toxicity. Ashby & Tenant, *supra* note 75, at 7.
- ⁷⁸ See generally James D. McKinney et al., *Forum: The Practice of Structure Activity Relationships (SAR) in Toxicology*, 56 TOXICOLOGICAL SCIENCES 8 (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.” *Id.* at 15.
- ⁷⁹ “Case reports either sent to local authorities or published in the literature often prompt follow-up studies that can lead to the identification of new hazards.” Howard Hu & Frank E. Speizer, *Influence of Environmental and Occupational Hazards on Disease*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 19, 19 (Braunwald, et al. eds., 15th ed. 2001). “Epidemiologists and clinicians generally use descriptive reports to search for clues of cause of disease—i.e., generation of hypotheses.” David A. Grimes & Kenneth F. Schulz, *Descriptive Studies: What*

They Can and Cannot Do, 359 THE LANCET 145, 148 (2002). See generally J.A. Arnaiz et al., *The Use of Evidence in Pharmacovigilance: Case Reports as the Reference Source for Drug Withdrawals*, 57 EUR. J. CLINICAL PHARMACOLOGY 89 (2001).

- ⁸⁰ See *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 989–90 (8th Cir. 2001); *Hollander v. Sandoz Pharma. Corp.*, 289 F.3d 1193, 1211 (10th Cir. 2002); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 541 (W.D. Pa. 2003); *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1034–35 (S.D. Ill. 2001); *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1361–62 (N.D. Ga. 2001); *Brumbaugh v. Sandoz Pharma. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999).
- ⁸¹ *Glastetter*, 252 F.3d at 989. See *Rider*, 295 F.3d at 1199; *Soldo*, 244 F. Supp. 2d at 539 (citation omitted). “Case reports demonstrate a temporal but not necessarily causative relationship between exposure and health effects. This information is often confounded by the inability to exclude other causes of illness.” MATTHEW J. ELLENHORN, ELLENHORN’S MEDICAL TOXICOLOGY: DIAGNOSIS AND TREATMENT OF HUMAN POISONING 3 (Ellenhorn ed., 2d ed. 1997).
- ⁸² Case reports, case series, and other descriptive studies “do not allow conclusions about cause of disease.” Grimes & Schulz, *supra* note 79, at 148.
- ⁸³ GRAHAM DUKES ET AL., RESPONSIBILITY FOR DRUG-INDUCED INJURY: A REFERENCE BOOK FOR LAWYERS, THE HEALTH PROFESSIONALS AND MANUFACTURERS 46 (IOS Press 2d ed. 1998). See Ronald H.B. Meyboom et al., *Causal or Casual? The Role of Causality Assessments in Pharmacovigilance*, 17 DRUG SAFETY 374, 375–81 (1997).
- ⁸⁴ DUKES ET AL., *supra* note 83, at 46.
- ⁸⁵ Meyboom et al., *supra* note 83, at 382.
- ⁸⁶ See *id.* at 381; G. Miremont et al., *Adverse Drug Reactions: Physicians’ Opinions Versus A Causality Assessment Method*, 46 EUR. J. CLINICAL PHARMACOLOGY 285, 288 (1994).
- ⁸⁷ See, e.g., *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 1037 n.21 (8th Cir. 2001) (“like case reports . . . a causality assessment involves only one individual, and, in any event, is not sufficient to establish causation”); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 545 (W.D. Pa. 2003) (Plaintiff failed to show that the causality assessment “methodology—adopted for foreign regulatory purposes—meets any of the *Daubert* criteria, nor has plaintiff shown any other indicia of reliability.”).
- ⁸⁸ See *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 682–83 (M.D. N.C. 2003); *Soldo*, 244 F. Supp. 2d at 541–42; *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1035–36 (S.D. Ill. 2001); *Revels v. Novartis Pharm. Corp.*, No. 03-98-00231-CV, 1999 WL 644732, at *5 (Tex. App. Ct. Aug. 26, 1999).
- ⁸⁹ See David M. Reboussin & Timothy M. Morgan, *Statistical Considerations In the Use and Analysis of Single-Subject Designs*, 28 MED. & SCI. IN SPORTS AND EXERCISE 639, 640–42 (1996) (discussing limitations).
- ⁹⁰ *Id.* at 639.
- ⁹¹ *Soldo*, 244 F. Supp. 2d at 541 (quoting *Revels*, No. 03-98-00231-CV, 1999 WL 644732, at *5).
- ⁹² See *Soldo*, 244 F. Supp. 2d at 542; *Caraker*, 188 F. Supp. 2d at 1039; *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1370 (N.D. Ga. 2001).
- ⁹³ *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002). See *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1215 (10th Cir. 2002); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001); *Conde v. Velsicol Chem. Corp.*, 24 F.3d 809, 814–15 (6th Cir. 1994); *Dunn*, 275 F. Supp. 2d at 683–84; *Soldo*, 244 F. Supp. 2d at 513. See also Richard A. Merrill, *Regulatory Toxicology*, in CASARETT & DOULL’S TOXICOLOGY: THE BASIC SCIENCE OF POISONS 1141–43 (Curtis D. Klaassen, 6th ed. 2001) (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 REG. TOXICOLOGY & PHARMACOLOGY 21, 27 (1998) (“The public health-oriented resolution of scientific uncertainty [used by regulators] is not especially helpful to the problem faced by a court.”).

- ⁹⁴ See Arnaiz et al., *supra* note 79, at 89.
- ⁹⁵ Rodricks & Rieth, *supra* note 93, at 30.
- ⁹⁶ See *Soldo*, 244 F. Supp. 2d at 508; *Siharath*, 131 F. Supp. 2d at 1362; *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1230 (D. Colo. 1998); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1414 (D. Or. 1996).
- ⁹⁷ Hu & Speizer, *supra* note 79, at 19.
- ⁹⁸ *Siharath*, 131 F. Supp. 2d at 1372. See Miremont et al., *supra* note 86, at 288 (explaining finding that physicians are more likely to attribute causation to a drug resulting from their “necessarily more pragmatic approach to patients and diseases”).
- ⁹⁹ See Kassirer & Cecil, *supra* note 8, at 1384.
- ¹⁰⁰ John M. Conley & John B. Garver, III, *Tribute to Judge William C. Keady: Judge William C. Keady and the Law of Scientific Evidence*, 68 MISS. L.J. 39, 51 (1998).
- ¹⁰¹ Herbert A. Simon, *Artificial-Intelligence Approaches to Problem Solving and Clinical Diagnosis*, in LOGIC OF DISCOVERY AND DIAGNOSIS IN MEDICINE 72, 87 (Kenneth F. Schaffner ed. 1985).
- ¹⁰² *Siharath*, 131 F. Supp. 2d at 1372.
- ¹⁰³ *Kumho Tire Company LTD v. Carmichael*, 526 U.S. 137, 152 (1999).
- ¹⁰⁴ See *Siharath*, 131 F. Supp. 2d at 1362; Michael B. Kent, Jr., *Daubert, Doctors and Differential Diagnosis: Treating Medical Causation Testimony as Evidence*, 66 DEF. COUNS. J. 525, 533 (1999).
- ¹⁰⁵ See *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1412 (D. Or. 1996); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 524 (W.D. Pa. 2003); *Siharath*, 131 F. Supp. 2d at 1362–63; *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 1027 (8th Cir. 2001).
- ¹⁰⁶ See *Soldo*, 244 F. Supp. 2d at 551–552; *Pick v. American Medical Systems, Inc.*, 958 F. Supp. 1151, 1168 (E.D. La. 1997).
- ¹⁰⁷ See *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1319 (9th Cir. 1995); *Soldo*, 244 F. Supp. 2d at 551; *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 609 (D. N.J. 2002); *Nelson v. American Home Prods. Corp.*, 92 F. Supp. 2d 954, 969 (W.D. Mo. 2000).
- ¹⁰⁸ As discussed in *Soldo*, such regulatory action is not the equivalent of a finding of causation. See *Soldo*, 244 F. Supp. 2d at 513.
- ¹⁰⁹ For example, despite neurologists’ careful review, in 50.5% of cases, no probable cause of stroke could be identified. See Steven A. Kittner et al., *Cerebral Infarction in Young Adults: The Baltimore-Washington Cooperative Young Stroke Study*, 50 NEUROLOGY 890, 890 (1998).
- ¹¹⁰ KIELY, *supra* note 9, at 178. In addition to being used as a case study for legal scholars, the Parlodel® litigation was recently discussed in an article published in the *Journal of the American Medical Association* by an unsuccessful *amicus* for plaintiffs appealing a Parlodel® *Daubert* exclusionary ruling to the Eleventh Circuit Court of Appeals in *Rider*. See J. Kassirer & J. Cecil, *supra* note 8, at 1384–85.
- ¹¹¹ See *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1195–96 (11th Cir. 2002); *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1195 (10th Cir. 2002); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 684 (M.D. N.C. 2003); *Soldo*, 244 F. Supp. 2d at 577; *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1028 (S.D. Ill. 2001); *Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 1153, 1154 (D. Mont. 1999). See also *Revels v. Novartis Pharm. Corp.*, No. 03-98-00231-CV, 1999 WL 644732, at *5 (Tex. App. Ct. Aug. 26, 1999) (excluding Parlodel® causation opinions on Texas version of *Daubert*).
- ¹¹² See *Brasher v. Sandoz Pharm. Corp.*, 160 F. Supp. 2d 1291, 1292 (N.D. Al. 2001); *Globetti v. Sandoz Pharms. Corp.*, 111 F. Supp. 2d 1174, 1175 (N.D.

- Al. 2000); *Eve v. Sandoz Pharms. Corp.*, No. 98-1429, 2001 U.S. Dist. LEXIS 4531, at *97–*98 (S.D. Ind. March 7, 2001).
- ¹¹³ See KIELY, *supra* note 9, at 177.
- ¹¹⁴ See *id.*
- ¹¹⁵ See *id.*
- ¹¹⁶ See *Rider*, 295 F.3d at 1198; *Glastetter*, 107 F. Supp. 2d at 1019–1021; *Caraker*, 188 F. Supp. 2d at 1031.
- ¹¹⁷ *Globetti*, 111 F. Supp. 2d at 1180. See also *Eve*, No. 98-1429, 2001 U.S. Dist. LEXIS 4531, at *75 (quoting *Globetti*).
- ¹¹⁸ See *Brasher v. Sandoz Pharm. Corp.*, 160 F. Supp. 2d 1291, 1296 (N.D. Al. 2001). “Given the practical unavailability of other forms of scientific evidence, reliance on those that are available is all the more reasonable.” *Id.* at 1297.
- ¹¹⁹ *Id.* at 1299.
- ¹²⁰ *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1373 (N.D. Ga. 2001).
- ¹²¹ *Id.* at 1371.
- ¹²² *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1213 (10th Cir. 2002).
- ¹²³ *Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999).
- ¹²⁴ *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1030 (S.D. Ill. 2001).
- ¹²⁵ *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 529 (W.D. Pa. 2003).
- ¹²⁶ *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 1025 (8th Cir. 2001).
- ¹²⁷ *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 684 (M.D. N.C. 2003).
- ¹²⁸ *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002) (quoting *Allison v. Mcghan Med. Corp.*, 184 F.3d 1300, 1310 (11th Cir. 1999)).