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RESTATEMENT OF THE LAW THIRD

The American Law Institute

RESTATEMENT OF THE LAW

TORTS: LIABILITY FOR PHYSICAL HARM

PROPOSED FINAL DRAFT NO. 1

(APRIL 6, 2005)

SUBJECTS COVERED:

Submitted by the Council to the Members of

The American Law Institute

for Discussion at the Eighty-Second Annual Meeting

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§ 28. Burden of Proof

(a) Subject to Subsection (b), the plaintiff has the burden to prove that the defendant's tortious conduct was a factual cause of the plaintiff's physical harm.

(b) When the plaintiff sues all of multiple actors and proves that each engaged in tortious conduct that exposed the plaintiff to a risk of physical harm and that the tortious conduct of one or more of them caused the plaintiff's harm but the plaintiff cannot reasonably be expected to prove which actor caused the harm, the burden of proof, including both production and persuasion, on factual causation is shifted to the defendants.

Comment on Subsection (a):

* * *

c. Toxic substances and disease

(1) Introduction. Cases involving toxic substances often pose difficult problems of proof of factual causation. These problems can also arise in cases involving activities that may cause disease, such as continued repetitive motion. Sometimes it is difficult to prove which

defendant was connected to the toxic agent, see Comment *o*, or whether an adequate warning would have prevented the plaintiff's harm. See Comment *b*. The special problem in these cases, however, is proving the connection between a substance and development of a specific disease. In all of these cases, the requirement to prove factual causation remains the same; the plaintiff must prove it by a preponderance of the evidence, and the standards for factual causation set forth in §§ 26-27 continue to apply.

In most traumatic-injury cases, the plaintiff can prove the causal role of the defendant's tortious conduct by observation, based upon reasonable inferences drawn from everyday experience and a close temporal and spatial connection between that conduct and the harm. Often, no other potential causes of injury exist. When a passenger in an automobile collision suffers a broken limb, potential causal explanations other than the collision are easily ruled out; common experience reveals that the forces generated in a serious automobile collision are capable of causing a fracture. By contrast, the causes of some diseases, especially those with significant latency periods, are generally much less well understood. Even known causes for certain diseases may explain only a fraction of the incidence of such diseases, with the

remainder due to unknown causes. Causal agents are often identified in group (epidemiologic) studies that reveal an increase in disease incidence among a group exposed to the agent as compared to a group not exposed. Biological mechanisms for disease development — i.e., a series of causally linked physiological changes from exposure to disease developments — are frequently complicated and difficult to observe. Science continues to develop a better understanding of the biological steps in the development of diseases, but current knowledge in this respect is considerably more modest than for traumatic injury. As a consequence, courts in toxic-substances cases often must assess various alternative methods proffered with regard to factual causation.

Over the past several decades, courts have devoted a great deal of energy to the issue of causation in toxic-tort cases. Causation is a question of fact normally left to the jury, unless reasonable minds cannot differ. Appellate or trial-court review of jury findings affects the allocation of power between judges and juries. Until the early 1980s, a qualified expert witness's opinion that a toxic agent was a factual cause of the plaintiff's disease was treated

as sufficient evidence. A few celebrated cases and case congregations, such as the Agent Orange and Bendectin litigations, led some courts to distrust juries' ability to resolve cases based on conflicting general expert-opinion evidence. Courts began to scrutinize the scientific evidence employed and to examine carefully the bases for an expert's opinion on factual causation. Some courts then tried to develop bright-line rules based on science for adequate proof of factual causation. The high water mark for this overreliance on scientific thresholds occurred in the Bendectin litigation when one court announced a blanket rule that a plaintiff could not make out a sufficient case without statistically significant epidemiologic evidence.

These courts may be relying on a view that "science" presents an "objective" method of establishing that, in all cases, reasonable minds cannot differ on the issue of factual causation. Such a view is incorrect. First, scientific standards for the sufficiency of evidence to establish a proposition may be inappropriate for the law, which itself must decide the minimum amount of evidence permitting a reasonable (and therefore permissible) inference as opposed to speculation that is not permitted. See Comment *b*. Second, scientists report that an evaluation

of data and scientific evidence to determine whether an inference of causation is appropriate requires judgment and interpretation. Scientists are subject to their own value judgments and preexisting biases that may affect their view of a body of evidence. There are instances in which although one scientist or group of scientists comes to one conclusion about factual causation, they recognize that another group that comes to a contrary conclusion might still be "reasonable." These scientists' views reflect their scientific experience outside the courtroom. They may have different views about specific instances of conflicting scientific testimony in a courtroom. Judgments about causation may also be affected by the comparative costs of errors, as when caution counsels in favor of declaring an uncertain agent toxic because the potential harm it may cause if toxic is so much greater than the benefit foregone if it were not introduced. Courts, thus, should be cautious about adopting specific "scientific" principles, taken out of context, to formulate bright-line legal rules or conclude that reasonable minds cannot differ about factual causation.

This Comment is necessarily general. It addresses how methods of proof for traumatic

injuries and for diseases may differ. Toxic-substance cases often involve statistical and group-based scientific studies that courts seldom confronted when the Restatement Second of Torts was published. Toxic agents and the diseases they cause differ, and methods of proof may vary accordingly. The law continues to evolve as courts are confronted with a variety of different circumstances related to different toxic substances, different disease, and the varieties of available evidence.

Scientific methods may advance in the future to better facilitate causation determinations for individuals, thereby obviating the need for statistically based group studies. While such techniques are largely unavailable today, dramatic advances in microbiology, genetics, and related fields have been made. These developments may produce new forms of evidence to which courts will adapt legal treatment of proof of causation.

Proof of causation often involves the admissibility of expert-witness opinions. Admissibility is governed by the law of evidence, and nothing in this Comment addresses that law. However, admissibility cannot be determined without reference to the substantive law.

Moreover, courts may be required to examine scientific evidence when it is offered to prove agent-disease causation. That examination may occur either in the admissibility determination or in the determination whether the evidence is sufficient to meet the burden of production. These usually are separate issues and are subject to different legal standards. Courts, however, sometimes conflate these issues in the process of determining whether there is an adequate basis for an expert's opinion. When courts collapse the sufficiency determination into the question of the admissibility of an expert's testimony no subsequent inquiry into sufficiency is necessary, and the appropriate weight to give to an expert's opinion once it is deemed admissible is for the factfinder. The requirement of causation, the elements of agent-disease causation that are sometimes required when group studies are employed as proof, and the sufficiency of the evidence to meet the burden of production on causation are matters of substantive tort law, and they are addressed in the Restatement.

Most causation issues are resolved under the "but-for" standard for factual cause. See § 26. The plaintiff must prove by a preponderance of the evidence that, but for the

defendant's tortious conduct with respect to the toxic substance, the plaintiff would not have suffered harm. When group-based statistical evidence is proffered in a case, this means that the substance must be capable of causing the disease ("general causation") and that the substance must have caused the plaintiff's disease ("specific causation"). In other cases, when group-based evidence is unavailable or inconclusive, and other forms of evidence are used, the general and specific causation issues may merge into a single inquiry. In any case, plaintiff's exposure to the toxic agent must be established.

Thus, courts often address "exposure," "general causation," and "specific causation." Nevertheless, these items are not "elements" of a plaintiff's cause of action, and in some cases may not require separate proof. So long as the plaintiff introduces admissible and sufficient evidence of factual causation the burden of production is satisfied. A court in a particular case may conclude that reasonable minds cannot differ about proof of factual causation under the general test *because* reasonable minds cannot differ on whether the plaintiff was exposed to the agent, whether the agent is generally capable of causing the

disease, or whether the agent caused the plaintiff's disease in the specific case. These categories function as devices to organize a court's analysis, not as formal elements of the cause of action.

(2) Exposure to the agent. In evaluating factual causation, one issue that may arise is whether the plaintiff was exposed to the substance. Three primary means of exposure to toxic substances include inhalation, absorption, and ingestion, but others exist, such as injection or a fetus's transplacental exposure to agents in the mother's body. Often the method of exposure is critical to the type or extent of risk.

Exposure is frequently disputed in occupational-disease cases and hazardous-waste cases, while it is less often an issue in pharmaceutical cases. Proof of exposure may entail relatively straightforward historical facts, such as the presence of asbestos at the plaintiff's workplace or whether the plaintiff took a prescribed drug, or it may require complicated scientific evidence, such as dispersion modeling, to determine how and where the substance was transported. The latter form of evidence is often required in airborne- or groundwater-

pollution cases. The intensity and duration of exposure (the "dose") affects the magnitude of the risks posed and the likelihood of causation.

(3) General causation. "General causation" exists when a substance is capable of causing a given disease. The concept developed because a prominent form of scientific methodology investigates causation on a group basis and therefore addresses whether an agent causes an increased incidence of disease in the group being studied. These studies proceed by comparing the incidence of disease in a group that has been exposed to the agent with the incidence of disease in a group of unexposed persons. The latter group's disease, thus, is attributable to causes other than the agent being studied. Traumatic-injury cases, by contrast, do not require this form of evidence because other causes that might explain the injury are absent, and we have a reasonably good understanding of the causal mechanisms involved from trauma to injury.

Occasionally, biological-mechanism evidence is sufficiently developed to prove general causation. More frequently, however, the evidence consists of scientific studies comparing the

incidence of disease in groups of individuals (epidemiologic evidence) or animals (toxicologic evidence) with different levels of exposure. When a study finds a difference in the incidence of disease in the exposed and unexposed groups, an "association" exists between exposure and disease. Another type of epidemiologic study compares the extent of exposure among those with and without the disease. These studies seek to identify potentially causal substances at the aggregate population level — by finding a higher incidence of a disease in a group exposed to the substance (an "association").

Even when epidemiologic studies find an association between a substance and a disease, further analysis is necessary before a causal conclusion can be drawn. Scientists first systematically gather all of the studies that have been conducted and that are relevant to the causal question being investigated. When multiple studies exist, they are synthesized, either qualitatively in a review or quantitatively with a method known as meta-analysis. However, reasons may exist for disregarding or giving less weight to one or more of the available studies. If an association is found, epidemiologists use a number of factors (commonly known

as the “Hill guidelines”) for evaluating whether that association is causal or spurious. A spurious association may be the result of study errors — such as biases (scientists use “bias” to mean a source of error rather than as a predisposition to testify or decide a matter in an improper way) and uncorrected confounding factors (alternative causes that are responsible for the association, rather than the agent under study) — or sampling error (the result of small numbers of subjects and random chance). Similarly, a study may incorrectly fail to find an association that exists, because of study errors, especially when the disease is rare and an insufficient number of subjects exist to reveal any relationship. Epidemiologists use statistical methods to estimate the range of error that sampling error could produce; assessing the existence and impact of biases and uncorrected confounding is usually qualitative.

Whether an inference of causation based on an association is appropriate is a matter of informed judgment, not scientific methodology, as is a judgment whether a study that finds no association is exonerative or inconclusive. No algorithm exists for applying the Hill guidelines to determine whether an association truly reflects a causal relationship or is spurious. Because

the inferential process involves assessing multiple unranked factors, some of which may be more or less appropriate with regard to a specific causal assessment, judgment is required. For example, one of the Hill factors calls for an assessment of other scientific evidence that bears on the causal relationship under consideration. In some cases, there may be a substantial body of other evidence, while in other cases there may be little. The saliency of other evidence of causation often entails considerable judgment. Thus, in some cases, reasonable scientists can come to differing conclusions on whether a body of epidemiologic data justifies an inference of causation vel non. Similarly, reasonable scientists may, in some instances, disagree on whether the absence of an association is exonerative of the agent or is merely inconclusive.

Usually, other and unknown individual factors (causes) must concur with exposure to the agent for an individual to contract the disease. Group studies do not provide a basis for determining which individuals in a group suffer disease from exposure to the agent and which do not. More importantly, whenever other chemical, physical, or biological agents can produce

the disease, group studies cannot distinguish which individual's disease was caused by exposure to a particular agent and which individual's disease was caused by another agent. So long as tort law adjudicates claims on an individual basis, specific causation requires attention even when general causation is established through the use of group studies.

Occasionally, courts have suggested or implied that a plaintiff cannot meet the burden of production on causation without epidemiologic evidence. Those cases often confronted a substantial body of epidemiologic evidence introduced by the defendant that tended to exonerate the agent as causal. Circumstances in individual cases, however, are sufficiently varied that almost all courts employ a more flexible approach to proof of causation — except in those cases with a substantial body of exonerative epidemiologic evidence. Epidemiologic studies are expensive and can take considerable time to design, conduct, and publish. For disease processes with long latency periods, valid studies cannot be performed until the disease has manifested itself. As a consequence, some plaintiffs may be forced to litigate long before epidemiologic research is available. Indeed, sometimes epidemiologic evidence is

impossible to obtain, which may explain why neither the plaintiff nor the defendant is able to proffer supportive epidemiology. Thus, most courts have appropriately declined to impose a threshold requirement that a plaintiff always must prove causation with epidemiologic evidence, and, in some cases (as explained below), the evidence bearing on specific causation may be sufficient to pretermit the need to assess general causation.

(4) Specific causation. "Specific causation" exists when exposure to an agent caused a particular plaintiff's disease. Sometimes proof of specific causation is easy and collapses into proof of general causation, as when there are no alternative causal agents for a disease, and the disease is said to be a "signature" of the substance. In other cases, however, specific causation remains an issue even though general causation is established.

Scientists who conduct group studies do not examine specific causation in their research. No scientific methodology exists for assessing specific causation for an individual based on group studies. Nevertheless, courts have reasoned from the preponderance-of-the-evidence standard to determine the sufficiency of scientific evidence on

specific causation when group-based studies are involved. Properly understood and applied, this analytical framework provides a reasonable basis for determining specific causation in the absence of more particularistic evidence about the cause of plaintiff's disease.

Courts have reasoned that when a group study finds that exposure to the agent causes an incidence in the exposed group that is more than twice the incidence in the unexposed group (i.e., a relative risk greater than two) the probability that exposure to an agent caused a similarly situated individual's disease is 50 percent. Accordingly, courts generally hold when there is group-based evidence finding that exposure to an agent causes an incidence of disease in the exposed group that is more than twice the incidence in the unexposed group, the evidence is sufficient to satisfy the burden of production and permit submission of specific causation to a jury. In such a case, the factfinder may find that it is more likely than not that the substance caused the particular plaintiff's disease. The propriety of this "doubling" reasoning depends on group studies identifying a genuine causal relationship and a reasonably reliable measure of the increased risk. Courts appropriately have permitted expert witnesses to

testify to specific causation based on the logic of the effect of a doubling of the risk and other considerations explained below that modify the probability of causation for a particular individual.

Additional considerations affect the propriety of determining the probability of specific causation based on the outcome of a group-based study. Depending on the state of the evidence about these additional matters, they may bear either on the sufficiency determination by the court or be relevant to the jury's determination. Thus, the extent to which the group-study outcome reflects the increased risk to the plaintiff depends on the plaintiff's similarity to those included in the group study. Relevant differences include whether: (a) the plaintiff was exposed to a comparable dose; (b) the plaintiff was not differentially exposed to other potential causes of the disease; and (c) the plaintiff has individual characteristics that might also bear on the risk of disease, such as age, gender, or general health, comparable to those in the study group.

The likelihood that an agent caused an individual's disease may be refined when there

are independent, alternative known causes of the disease. The underlying premise is that each of these known causes is independently responsible for some proportion of the disease in a given population. Eliminating one or more of these as a possible cause for a specific plaintiff's disease increases the probability that the agent in question was responsible for that plaintiff's disease. Courts frequently refer to the elimination of other known causes for a plaintiff by employing the medical terminology of "differential diagnosis." The logic is sound, but the terminology and attribution are not. Assessing whether other causes can be ruled out (or in) as potential causes of a plaintiff's disease can provide probative evidence of specific causation. This technique is more accurately described as a "differential etiology." It is most useful when the causes of a substantial proportion of the disease are known. Then, the presence (or absence) of these causes for the specific plaintiff affects the probability that the agent in question caused the plaintiff's illness. When the causes of a disease are largely unknown, however, differential etiology is of little assistance. Evidence about biological mechanisms may also alter the likelihood that exposure to the substance caused plaintiff's

disease, either by ruling out other known causes or by explaining why the suspected agent is a more likely cause of the disease than others.

For all of these reasons, any judicial requirement that plaintiffs must show a threshold increase in risk or a doubling in incidence in a group study in order to satisfy the burden of proof of specific causation is usually inappropriate. So long as there is adequate evidence of general causation, courts should permit the parties to attempt to show, based on the sorts of evidence described above, whether the plaintiff's disease was more likely than not caused by the agent. Depending on the other factors detailed above, an increase of the incidence of disease less than a doubling may be sufficient to support a finding of causation, while in another case, even an increased incidence greater than two may not be sufficient. When the sufficiency of the evidence to meet the burden of production is at issue, courts should consider all of the evidence that bears on the matters discussed above and determine whether, in light of the general standard for sufficiency discussed in Comment *b*, the evidence would permit a reasonable jury to find that plaintiff's disease more probably than not was caused by exposure

to the agent.

In most instances, differential etiology is not an appropriate technique for proving general causation. Nevertheless, in some limited circumstances courts have found that plaintiffs met their burden of proof of agent-disease causation without separate proof of general causation. Factors such as a good biological-mechanism explanation of how the agent could have caused the plaintiff's disease, a differential etiology ruling out other known causes, a reasonable explanation for the lack of general-causation evidence (and no contrary evidence of an absence of general causation), a short latency period and acute response, and the appropriate disease response to dechallenge (removal from exposure) and rechallenge (reexposure) to the agent, if combined and consistent, provide a persuasive basis for excusing the plaintiff from providing other proof of general causation.

(5) Multiple exposures and synergistic interactions. In some cases, a person may be exposed to two or more toxic agents, each of which is known to be capable of causing (general causation) the person's disease. The two agents may operate independently, in which

case the incidence of disease in a group exposed to both will be additive — the excess incidence due to the first agent along with the excess incidence due to the second agent. Cases such as these present a relatively straightforward application of the principles set forth in Comment *c(4)*. If the toxic agents are attributable to the tortious conduct of separate actors, courts then face the question whether to apply the rule developed for multiple exposures in asbestos cases. This rule permits finding each actor's asbestos products to which the person was exposed to be a factual cause of the person's disease. See § 27, Comment *g*. Alternatively, courts might employ the traditional rule, requiring proof of which of the multiple exposures was a cause of the harm. At least where the biological mechanism by which disease develops is unknown, the asbestos rule is quite analogous and attractive as a means for adapting proof requirements to the available scientific knowledge. Apportionment of liability among those actors held liable is based on the comparative-responsibility rules in Restatement Third, Torts: Apportionment of Liability §§ 1-25. The alternative — the more traditional requirement of proof of which of the two toxic exposures was *the* cause of the disease —

would require proof that does not exist, except on a probabilistic basis, as outlined in Comment *c(4)*.

Illustrations:

1. Abby was exposed to two different solvents while working in a laboratory. Each solvent contained a toxic chemical; one contained brion, and the other contained choron. After developing a disease, myeplopia, several years later, she sues the manufacturers of each solvent, claiming that the manufacturers were negligent for including a toxic chemical in their solvents. Abby's evidence, presented by competent expert testimony based on valid scientific evidence, reveals that the increased risk of contracting myeplopia from the dose of brion to which she was exposed is insufficient to permit a finding of factual causation. Similarly, the increased risk of myeplopia from exposure to choron is insufficient to permit a finding of factual causation. However, Abby's evidence reveals that, while choron and brion operate independently (those

exposed to both are only subject to an increased risk of the additive risks of each), the combined risk of contracting myeplopia due to exposure to both is sufficient to permit a finding of factual causation. Each of the manufacturers is subject to liability. See § 26, Comment *c*. Apportionment of liability between the manufacturers is governed by Restatement Third, Torts: Apportionment of Liability.

2. Same facts as Illustration 1, except that competent evidence shows that choron exposure increases the risk of myeplopia by 10 times, as does brion exposure. Competent evidence also reveals that the mechanism by which myeplopia develops is different for choron exposure and for brion exposure and that exposure to one or the other, but not both, is the most likely explanation for Abby's myeplopia. Abby cannot prove, however, whether choron or brion caused her myeplopia. Pursuant to § 28(b), the burden of proof on agent-disease causation is shifted to the manufacturers of choron and brion.

3. Same facts as Illustration 2, except that competent evidence reveals that

choron and brion operate in precisely the same physiologic manner in the human body; they are interchangeable in their role in causing myeplopia. Exposure to each of choron and brion is a factual cause of Abby's myeplopia. See § 27, Comment *g*.

In some cases, as, for example, asbestos workers who smoke cigarettes, the two toxic agents together have a synergistic effect. This means that the excess incidence of disease among those exposed to both agents will be greater than the sum of the excess incidences found in those exposed to each separate agent. If the synergistic effect is sufficiently large, the excess incidence of disease due to the synergistic effect will be greater than the excess incidence due to each of the agents separately. In such circumstances, factfinders may infer that the combined exposure is a cause of the plaintiff's disease. This inferential process is similar to the one permitting a jury to find specific causation based on the increase in the incidence found from a general-causation study, such as those described in Comment *c(4)*. Although the reasoning for synergistic agents differs from that for nonsynergistic agents, the

outcome is similar if the synergistic effect of the interacting agents is sufficiently large.

However, identification of both of the synergistic agents as a cause of the disease does not end the inquiry. Many causes exist for a given harm. See § 26, Comment *f*. Only those causes attributable to tortious conduct are legally relevant in determining liability and apportioning liability for plaintiff's harm. See Restatement Third, Torts: Apportionment of Liability § 26, Comment *m*. Thus, a natural condition, a genetic trait of the plaintiff, or a nonnegligent actor's conduct that are causes, in addition to a negligent actor's conduct, of the plaintiff's harm have no effect on the negligent actor's role as a cause of harm or on apportionment of liability. If more than one legally responsible agent is a cause of the plaintiff's harm, then apportionment of liability is based on comparative responsibility pursuant to Restatement Third, Torts: Apportionment of Liability §§ 1-25.

Illustrations:

4. Brett was occupationally exposed to asbestos for several decades. He also

smoked cigarettes during approximately the same time period. Brett, who has developed lung cancer, sues Rossman, Inc., the manufacturer and supplier of the asbestos to which he was exposed, claiming that Rossman failed adequately to warn of the dangers of asbestos exposure. Brett provides competent expert testimony that, based on valid scientific studies, the dose of asbestos to which he was exposed increases the risk of contracting lung cancer by a factor of five (500%). The dose of cigarette smoke to which he was exposed increases the risk of lung cancer by a factor of 12 (1200%). However, the combined exposure to both asbestos and cigarette smoke increases the risk of lung cancer by a factor of 60 (6000%). Brett's evidence is sufficient to permit the factfinder to find that exposure to both asbestos and cigarette smoke were causes of his lung cancer. Because neither Brett nor Rossman claim that the smoking implicates tortious conduct, no apportionment of liability for Brett's lung cancer would occur, if the factfinder found in Brett's favor against Rossman.

5. Same facts as Illustration 4, except that Rossman successfully persuades the

factfinder that Brett's smoking constituted negligence on his part. Neither Brett nor Rossman alleges any tortious conduct by the cigarette manufacturers. Liability for Brett's lung cancer would be apportioned between Brett and Rossman based on comparative responsibility according to Restatement Third, Torts: Apportionment of Liability § 7.

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REPORTERS' NOTE

Comment c. Toxic substances and disease. This Comment and these Reporters' Notes benefited significantly from a review of a prior draft by a panel consisting of prominent epidemiologists and a physician that was assembled by the Science, Technology, and Law Program of the National Academy of Sciences. The panelists included Dr. Steven Goodman, of Johns Hopkins University, Dr. Leon Gordis, also of Johns Hopkins University, Dr. Jerome Kassirer, of Tufts and Yale Universities, Dr. David Savitz, of the University of North Carolina, and Dr. Douglas Weed, of the National Cancer Institute, and were selected by the Science, Technology, and Law Program based on relevant expertise, familiarity with the use of scientific evidence in law, and their independence and objectivity. A meeting took place on January 21, 2003, at the National Academy of Sciences and included the Reporters for this Restatement, several others from the ALI, and the panelists. The meeting consisted of a very productive dialogue among the panelists and Institute representatives about the prior draft of this Comment and Reporters'

Notes. A transcript of the meeting is available on the website of the Science, Technology, and Law Program of the National Academies of Science at: http://www7.nationalacademies.org/stl/index.html. The Institute and the Reporters are indebted to the panelists for their valuable contributions, as well as to Professor Richard Merrill, Co-Chair of the Science, Technology, and Law Panel and Professor of Law at the University of Virginia, who understood the benefit such a meeting might have and graciously endeavored both to make it possible and oversee the necessary arrangements, and Dr. Anne-Marie Mazza, of the National Academy of Sciences staff, who cheerfully and energetically attended to the arrangements for the meeting. The Institute and Reporters also thank the Science, Technology, and Law Program for its cooperation in making this meeting possible and ALI member Patrick Malone who first suggested such a joint effort.

(1) *Introduction.* Since the mid-1970s when asbestos litigation began, there has been a steady stream of toxic-substances litigation. Some of it is large-scale, exemplified by such well-known case congregations as asbestos, Agent Orange, DES, Bendectin, silicone-gel breast implants, and fen-Phen. There are also more limited or localized cases, such as hazardous-waste cases. In addition to agents such as those identified above, an activity, such as continual use of a keyboard, may be responsible for a person's disease. These cases require courts to adapt traditional rules of proof to the greater uncertainty inherent in agent-disease causation and the specialized types of evidence that may be available. The relative absence of knowledge about the mechanisms involved in disease causation, compared to more traditional traumatic injuries, gets to the core of the adjustments required: "Scientists know very little about how, in a mechanistic sense, toxic substances cause disease such as cancer or birth defects. Nonetheless, they may know a considerable amount about whether toxic substances cause disease or injury through inferences drawn from statistical associations and other indirect means." Susan R. Poulter, *Science and Toxic Torts: Is There a Rational Solution to the Problem of Causation?*, 7

HIGH TECH. L.J. 189, 209-210 (1992) (emphasis and footnotes omitted). For thumbnail sketches of most of the major toxic-substances litigations of the 20th century and the scientific evidence of causation available in each, see Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181, 279–326 (1993). For an interesting illustration of this distinction, in which a court required expert testimony to establish the causal connection between an accident and a chronic condition but did not require such testimony for the immediate, traumatic consequence of the accident, see Dodge-Farrar v. Am. Cleaning Servs. Co., 54 P.3d 954 (Idaho Ct. App. 2002).

Toxic-substances litigation was also the genesis for substantial reform in the law governing the admissibility of expert-witness testimony. Bendectin provided the occasion for the Supreme Court's initial foray into the field in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), and a hazardous-waste case occasioned the next Supreme Court decision in the area, General Electric Co. v. Joiner, 522 U.S. 136 (1997). A considerable body of federal law now exists in which *Daubert* and its progeny have been applied to expert witnesses who propose to testify on some aspect of agent-disease causation. Many state courts have followed the approach of the federal courts in addressing these matters through the admissibility lens. See, e.g, Logerquist v. McVey, 1 P.3d 113 (Ariz. 2000); Goeb v. Thraldson, 615 N.W.2d 800 (Minn. 2000); In re Canavan, 733 N.E.2d 1042 (Mass. 2000); Schafersman v. Agland Coop., 631 N.W.2d 862 (Neb. 2001). The federal courts have not achieved perfect consistency in all aspects of their admissibility law and decisions. See, e.g., Jerome P. Kassirer & Joseph S. Cecil, *Inconsistency in Evidentiary Standards for Medical Testimony: Disorder in the Courts*, 288 JAMA 1382 (2002). State courts reveal even greater variation in this area. However, whether they formally adopt *Daubert* as the standard governing expert-witness testimony, continue to adhere to the standard provided in Frye v. United States, 293 F. 1013 (D.C.

Cir. 1923), or decide to employ some modification of these standards, state courts have been increasingly confronted with the question of adequate proof of toxic causation and the admissibility of expert-witness testimony on that subject. And regardless of the rules adopted for admitting expert testimony, the principles set forth in Comment *c* are frequently reflected in state-court decisions. See Lofgren v. Motorola, 1998 WL 299925 (Ariz. Super. Ct. June 1, 1998); U.S. Sugar Corp. v. Henson, 823 So. 2d 104 (Fla. 2002); Berry v. CSX Transp., Inc., 709 So. 2d 552 (Fla. Dist. Ct. App. 1998); Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314 (Ill. 2002); Linnen v. A.H. Robins Co., 2000 WL 16769 (Mass. Super. Ct. Dec. 14, 1999); McDonough v. Allina Health Sys., 685 N.W.2d 688 (Minn. Ct. App. 2004); Schafersman v. Agland Coop., 631 N.W.2d 862 (Neb. 2001); Valentine v. PPG Indus., Inc., 2004 WL 1908303 (Ohio Ct. App. 2004); Cutlip v. Norfolk S. Corp., 2003 WL 1861015 (Ohio Ct. App. 2003); Jennings v. Baxter Healthcare Corp., 14 P.3d 596 (Or. 2000); McDaniel v. CSX Transp., Inc., 955 S.W.2d 257 (Tenn. 1997); Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 718 (Tex. 1997); Easum v. Miller, 92 P.3d 794 (Wyo. 2004); see also Kuhn v. Sandoz Pharms. Corp., 14 P.3d 1170, 1184-1185 (Kan. 2000) (declining to require proof of general causation in a case in which there was not mass exposure and an absence of a body of epidemiologic evidence). Indeed, the federal courts, which were the first to confront these issues, are frequently cited by their state counterparts. See, e.g., John's Heating Serv. v. Lamb, 46 P.3d 1024, 1033-1037 (Alaska 2002); Kaelbel Wholesale, Inc. v. Soderstrom, 785 So. 2d 539 (Fla. Dist. Ct. App. 2001); DePyper v. Navarro, 1995 WL 788828 (Mich. Cir. Ct. Nov. 27, 1995); Allison v. Fire Ins. Exch., 98 S.W.3d 227 (Tex. Ct. App. 2002); Neal v. Dow Agrosciences LLC, 74 S.W.3d 468 (Tex. Ct. App. 2002); Easum v. Miller, 92 P.3d 794 (Wyo. 2004) (addressing the reliability of differential diagnoses to determine specific causation). For a cataloguing of the general approach to admissibility of expert testimony in the states, see *States Move to* Daubert, *Even When They Say They're Stuck on* Frye, 30 BNA PROD. SAFETY & LIAB. REP. 328 (2002); Leo H. Whinery, *Expert Testimony*

Trends in State Practice and the Uniform Rules of Evidence, in NEW DIRECTIONS IN EXPERT TESTIMONY: SCIENTIFIC, TECHNICAL, AND OTHER SPECIALIZED KNOWLEDGE EVIDENCE IN FEDERAL AND STATE COURTS 151, 176-182 (ALI-ABA Course of Study, Apr. 26, 2001); Edward J. Imwinkelried, *Evidentiary Balance*, NAT'L L.J., May 13, 2002, at B11 ("commenting that [i]t would be a mistake to overstate the differences between the jurisdictions following *Frye* and those committed to *Daubert*," and observing that the commonest explanation for a state court declining to adopt *Daubert* is because it is too liberal in permitting expert testimony to be admitted). This Comment does not address nor attempt to resolve the appropriate standard for determining the admissibility of expert testimony on agent-disease causation.

Expert-witness testimony is employed to prove agent-disease causation, and the admissibility of an expert's opinion may be determinative as to whether the plaintiff satisfies the burden of production on agent-disease causation. Yet the emphasis on greater scrutiny of expert-witness testimony has been with regard to the basis of the expert's opinion (in addition to the methodology and reasoning employed by the expert) thereby resulting in an examination of the scientific evidence that exists to support the expert's opinion. Courts frequently assess the state of the scientific record and only when it meets a sufficiency threshold is an expert witness permitted to testify about the existence of agent-disease causation. See, e.g., Wills v. Amerada Hess Corp., 379 F.3d 31 (2d Cir. 2004); Vargas v. Lee, 317 F.3d 498 (5th Cir. 2003) (concluding absence of scientific studies connecting trauma to fibromyalgia required ruling expert's contrary testimony inadmissible); In Re: Silicone Gel Breasts Implants Products Liability Litig., 318 F. Supp. 2d 879, 898-899 (C.D. Cal. 2004) (excluding expert's testimony about a "suggestive" connection between defendant's agent and cancer because study on which expert relied did not support such a conclusion); Newman v. Motorola, Inc., 218 F. Supp. 2d 769 (D. Md. 2002) (absence of reliable evidence of connection between cellular phones and cancer fatal to admissibility of

expert's testimony); Lindquist v. City of Jersey City Fire Dep't, 2002 NJ LEXIS 25 (N.J. 2003) (examining the scientific evidence upon which expert's opinion was based); Brookshire Brothers, Inc. v. Smith, ___ S.W.3d ___, 2004 WL 1064776 (Tex. App. 2004); Daniels v. Lyondell-Citgo Refining Co., 99 S.W.3d 722 (Tex. App. 2003) (reviewing 3 epidemiologic studies on which plaintiffs' experts relied for their opinion and concluding that none was sufficient to support a finding of causation); see also Exxon Corp. v. Makofski, 116 S.W.3d 176 (Tex. Ct. App. 2003) (examining scientific studies and evidence relied on by experts in determining the sufficiency of the evidence on causation).

Among the most useful sources explaining the various scientific fields applicable to proving causation and illustrating their application to toxic-substances litigation are FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (2d ed. 2000); DAVID L. FAIGMAN ET AL., MODERN SCIENTIFIC EVIDENCE: THE LAW AND SCIENCE OF EXPERT TESTIMONY (2d ed. 2002). For a useful summary and synthesis of the Supreme Court's decisions on the admissibility of expert testimony, see Joseph Sanders & Julie Machal-Fulks, *The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective and Substantive Law*, 64 LAW & CONTEMP. PROBS. 107, 112-119 (2001).

For explanations of some of the differences in characteristics of toxic agents that bear on the differences in proof of causation, see Daniel Farber, *Toxic Causation*, 71 MINN. L. REV. 1219, 1251-1259 (1987); Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181 (1993); Michael D. Green, *The Paradox of Statutes of Limitations in Toxic Substances Litigation*, 76 CALIF. L. REV. 965, 972-976 (1988).

For a statement of the trilogy of elements in proof of agent-disease causation —

namely, exposure, general causation, and specific causation — see Stevens v. Sec'y of HHS, 2001 WL 387418, at *35 (Fed. Cl. March 30, 2001). *Stevens* also contains an excellent explanation of the difficulties and extensive efforts required to resolve questions of agent-disease causation in the National Vaccine Injury Compensation Program. Id. at *7.

For an example of the sort of critical assessment scientists might have for specific scientific testimony in court mentioned in Comment *c(1)*, see Sander Greenland, *The Need for Critical Appraisal of Expert Witnesses in Epidemiology and Statistics*, 39 WAKE FOREST L. REV. 291 (2004).

(2) *Exposure to the agent.* In connection with proof of either specific or general causation, the extent of the victim's exposure to an agent, i.e., the dose, may play a significant role in determining causation. Dose includes both the intensity of exposure and the duration, although for different agents and diseases, one or the other may be more significant. Dosage may be important for two reasons: 1) for most agent-disease relationships, the higher the dose, the greater the risk of disease; 2) for some diseases there may be a threshold dose; exposures to the agent below the threshold dose pose no identifiable risk of causing the disease. See MICHAEL A. KAMRIN, TOXICOLOGY: A PRIMER ON TOXICOLOGY PRINCIPLES AND APPLICATIONS 36-38 (1988); Kenneth J. Rothman, *Causes*, 104 AM. J. EPIDEMIOLOGY 587 (1976) (accounting for dose-response relationships with an explanatory causal model). On dose-response relationships, see DAVID E. LILIENFELD & PAUL STOLLEY, FOUNDATIONS OF EPIDEMIOLOGY 265 (3d ed. 1994); RICHARD K. RIEGELMAN & ROBERT P. HIRSCH, STUDYING A STUDY AND TESTING A TEST: HOW TO READ THE HEALTH SCIENCE LITERATURE 45 (3d ed. 1996); Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181, 215-217 (1993). The existence of a threshold dose before an effect can occur is a controversial concept for which current scientific thinking resists any universal

answers and instead examines what is known about the pathological mechanisms of the disease. See Proposed Guidelines for Carcinogen Risk Assessment, 61 Fed. Reg. 17,960, 17,993 (E. P. A. 1996). Compare Marvin Goldman, *Cancer Risk of Low-Level Exposure*, 271 SCI. 1821 (1996) (challenging the conventional wisdom that cancer risk is not subject to a threshold dose); Bruce N. Ames, Renae Magaw & Lois Swirsky Gold, *Ranking Possible Carcinogenic Hazards*, 236 SCI. 271 (1987) (arguing that animal toxicology studies that support no threshold cannot be extrapolated to humans) with R.W. Hart & L. Fishbein, *Interspecies Extrapolation of Drug and Genetic Toxicity Data*, in 1 TOXICOLOGICAL RISK ASSESSMENT 3, 32 tbl. 19 (D.B. Clayson et al. eds., 1985) (arguing against threshold-dose theory).

For cases in which unknown dose or insufficient proof of dose played a critical role, see Mitchell v. Gencorp Inc., 175 F.3d 778, 781 (10th Cir. 1999); Christopherson v. Allied-Signal Corp., 939 F.2d 1106 (5th Cir. 1991) (occupational exposure to nickel/cadmium batteries) (applying Texas law); Martin v. Shell Oil Co., 180 F. Supp. 2d 313, 318-319 (D. Conn. 2002) (expert's explanation of how chemical migrated to plaintiff's property did not require testing where cost of test was in the range of $100,000); In re Three Mile Island Litig. Consol. Proceedings, 927 F. Supp. 834, 870 (M.D. Pa. 1996), aff'd in relevant part, 193 F.3d 613 (3d Cir. 1999); Cavallo v. Star Enter., 892 F. Supp. 756 (E.D. Va. 1995), aff'd in part and rev'd in part, 100 F.3d 1150 (4th Cir. 1996); Whiting v. Boston Edison Co., 891 F. Supp. 12 (D. Mass. 1995); Schmaltz v. Norfolk & W. Ry. Co., 878 F. Supp. 1119 (N.D. Ill. 1995); Wade-Greaux v. Whitehall Labs., 874 F. Supp. 1441 (D. V.I. 1994); Renaud v. Martin Marietta Corp., 749 F. Supp. 1545, 1555 (D. Colo. 1990) (exposure to contaminated water supply alleged to cause cancer and other diseases), aff'd, 972 F.2d 304 (10th Cir. 1992); John's Heating Serv. v. Lamb, 46 P.3d 1024 (Alaska 2002); Alder v. Bayer Corp., 61 P.3d 1068, 1085-1088 (Utah 2002) (summarizing other opinions on the precision with which plaintiffs must

prove the dosage to which they were exposed); see also Eagle-Picher v. Balbos, 578 A.2d 228, 245 (Md. Ct. App. 1990) (recognizing that dose of asbestos exposure required to cause mesothelioma is considerably lower than to cause asbestosis or lung cancer).

In cases involving occupational exposure to asbestos, many courts have fashioned a "frequency, regularity, and proximity" standard, requiring a plaintiff to prove these elements for each defendant's asbestos products in order adequately to establish exposure to a defendant's asbestos product. See Jackson v. Anchor Packing Co., 994 F.2d 1295 (8th Cir. 1993) (applying Arkansas law); Slaughter v. S. Talc Co., 949 F.2d 167 (5th Cir. 1991) (applying Texas law); Hoffman v. Allied Corp., 912 F.2d 1379 (11th Cir. 1990) (applying Florida law); Menne v. Celotex Corp., 861 F.2d 1453 (10th Cir. 1988) (applying Nebraska law); Thompson v. S. Pac. Transp. Co., 809 F.2d 1167 (5th Cir. 1987) (applying Louisiana law); Lohrmann v. Pittsburgh Corning Corp., 782 F.2d 1156, 1162-1163 (4th Cir. 1986) (applying Maryland law); Blackston v. Shook & Fletcher Insulation Co., 764 F.2d 1480 (11th Cir. 1985) (applying Georgia law); Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314 (Ill. 2002); Sholtis v. Am. Cyanamid Co., 568 A.2d 1196 (N.J. Super. Ct. App. Div. 1989); Eckenrod v. GAF Corp., 544 A.2d 50 (Pa. Super. Ct. 1988); see also James v. Bessemer Processing Co., Inc., 714 A.2d 898 (N.J. 1998) (applying "frequency, regularity, and proximity" test to chemicals alleged to cause cancer); Jobe v. W.P. Metz Refining, 664 A.2d 1015, 1020 (Pa. Super. Ct. 1995) (applying same test to occupational exposure to cadmium, alleged to have caused plaintiff's cancer).

For courts confronting the problem of exposure in a hazardous-waste case, see In re Paoli R.R. Yard PCB Litig., 916 F.2d 829 (3d Cir. 1990); In re TMI Litig., 193 F.3d 613 (3d Cir. 1997) (lengthy opinion addressing admissibility of expert witnesses testifying about dose/exposure arising out of nuclear-power-plant accident); see also Sandra A.

Geschwind et al., *Risk of Congenital Malformations Associated with Proximity to Hazardous Waste Sites*, 135 AM. J. EPIDEMIOLOGY 1197 (1992) (explaining difficulties of studying effects of hazardous-waste sites); Leon Gordis, *Epidemiologic Approaches for Studying Human Diseases in Relation to Hazardous Waste Disposal Sites*, 25 HOUS. L. REV. 837 (1988); Paul J. Lioy, *The Analysis of Total Human Exposure for Exposure Assessment: A Multi-Discipline Science for Examining Human Contact with Contaminants,* 24 ENVTL. SCI. & TECH. 938 (1990). Frequently, proof of exposure in these cases is based on modeling designed to estimate exposure. As with other types of scientific studies that may be used to demonstrate general causation, these models may be based on carefully collected and robust data and accepted or well-conceived assumptions that have some validation and therefore are of considerable evidentiary value, or they may be based on questionable assumptions not subjected to any efforts at validation and therefore of little probative value. See Susan R. Poulter, *Science and Toxic Torts: Is There a Rational Solution to the Problem of Causation?*, 7 HIGH TECH. L.J. 189, 237-240 (1992).

Infrequently, toxic agents produce a specific biomarker in those who have been exposed to the agent. Identification of the biomarker in an individual then indicates exposure to the agent and may, in some cases, permit an assessment of the dosage to which an individual was exposed. Gary E. Marchant, *Genetic Susceptibility and Biomarkers in Toxic Injury Litigation*, 41 JURIMETRICS J. 67, 68, 73-74, 95-97 (2000) (explaining concept of biomarkers, how they might be used to provide evidence of exposure or dose, discussing cases in which biomarkers were invoked in an effort to prove exposure, and concluding, "biomarkers are likely to be increasingly relied on to demonstrate exposure").

(3) *General causation.* The concepts of general causation and specific causation are widely accepted among courts confronting causation issues with toxic agents. See,

e.g., Kelley v. Am. Heyer-Schulte Corp., 957 F. Supp. 873, 875-876 (W.D. Tex. 1997) (recognizing the different concepts of general and specific causation), appeal dismissed, 139 F.3d 899 (5th Cir. 1998); Cavallo v. Star Enter., 892 F. Supp. 756, 771 n.34 (E.D. Va. 1995), aff'd in part and rev'd in part, 100 F.3d 1150 (4th Cir. 1996); Casey v. Ohio Med. Prods., 877 F. Supp. 1380, 1382 (N.D. Cal. 1995); Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 714-715 (Tex. 1996). But see Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314 (Ill. 2002) (rejecting use of "generic" and specific causation; plaintiff need only prove cause in fact).

When the connection between an agent and disease is strong and well documented, general-causation issues fade into the background. Thus, in asbestos cases, the general-causation question does not arise with regard to mesothelioma, asbestosis, and lung cancer because the causal connection between asbestos and those diseases is quite well established. See, e.g., Karjala v. Johns-Manville Prod. Corp., 523 F.2d 155, 160 (8th Cir. 1975) (applying Minnesota law); Bertrand v. Johns-Manville Sales Corp., 529 F. Supp. 539, 544 (D. Minn. 1982) ("[I]t is clear that it is appropriate to estop litigation on the issue of whether asbestos dust can cause diseases such as asbestosis and mesothelioma. This proposition is so firmly entrenched in the medical and legal literature that it is not subject to serious dispute."); Flatt v. Johns-Manville Sales Corp., 488 F. Supp. 836, 841 (E.D. Tex. 1980) (holding that asbestos exposure causes asbestosis and mesothelioma, as a matter of law). Although general causation may not be an issue for one or several diseases caused by an agent such as asbestos, general causation may be an issue with regard to other diseases, as is the case with asbestos and colon and gastrointestinal cancers. See In re Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124 (2d Cir. 1995) (applying New York law); Landrigan v. Celotex Corp., 605 A.2d 1079 (N.J. 1992); Grassis v. Johns-Manville, 591 A.2d 671 (N.J. Super. Ct. App. Div. 1991).

Occasionally, an ailment may be so strongly associated with a specific agent and so rarely (if ever) associated with any other cause that it is called a "signature disease." Examples of signature diseases are vaginal adenocarcinoma in the daughters of mothers exposed to DES and asbestosis in those exposed to asbestos. Once a signature disease is identified, there is no need for proof of either general causation or specific causation, as the existence of the disease is tied to exposure to the signature agent. See Daniel A. Farber, *Toxic Causation*, 71 MINN. L. REV. 1219,

1251-1252 (1987); Kenneth S. Abraham & Richard A. Merrill, *Scientific Uncertainty in the Courts*, ISSUES SCI. & TECH., Winter 1986, at 93, 101.

Cases involving signature diseases are, however, rare. In cases in which group studies are employed as proof, proof of causation proceeds in two steps: general causation and specific causation. Cases accepting the proposition that relevant epidemiologic studies are acceptable evidence to support proof of general causation are legion. See, e.g., Smith v. Ortho Pharm. Corp., 770 F. Supp. 1561, 1571 (N.D. Ga. 1991) (explaining increased reliance of courts on epidemiologic evidence in toxic-substances litigation); Stevens v. Sec'y of HHS, 2001 WL 387418, at *12-13 (Fed. Cl. March 30, 2001); James v. Chevron U.S.A., Inc., 694 A.2d 270, 280 (N.J. Super. Ct. App. Div. 1997), aff'd, 714 A.2d 898 (N.J. 1998); see generally Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 335 n.2 (2d ed. 2000).

However, even when epidemiology finds an association, the observational (rather than experimental) nature of these studies requires an examination of whether the association is truly causal or spurious and due to random error or deficiencies in the study (bias). The same problems may produce a study that does not find an association when

there truly is a causal relationship between the agent and the disease in question. See Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 374-375 (2d ed. 2000); Berry v. CSX Transp., Inc., 709 So. 2d 552, 558 (Fla. Dist. Ct. App. 1998); Schafersman v. Agland Coop., 631 N.W.2d 862, 871 (Neb. 2001). Criteria for assessing whether an association is causal were proposed by Sir Austin Bradford Hill. One formulation of these criteria is:

(1) Is the temporal relationship correct? Does the "effect" follow the "cause"?
(2) Is there evidence from true experiments in humans?
(3) Is the association a strong one?
(4) Is the association consistent from study to study?
(5) Is there a dose-response gradient?
(6) Is the association specific?
(7) Does the association make biological sense?
(8) Is there an appropriate analogy to other known causal relationships?

See Austin Bradford Hill, *The Environment and Disease: Association or Causation*?, 58 PROC. ROY. SOC. MED. 295 (1965). For discussion of these criteria and their respective strengths in informing a causal inference, see 2 DAVID L. FAIGMAN ET AL., MODERN SCIENTIFIC EVIDENCE
§ 28–2.2.3 (1997); LEON GORDIS, EPIDEMIOLOGY 176-181 (1996); DAVID E. LILIENFELD & PAUL D. STOLLEY, FOUNDATIONS OF EPIDEMIOLOGY 263-266 (3d ed. 1994); Douglas L. Weed, *Epidemiologic Evidence and Causal Inference*, 14 HEMATOLOGY/ONCOLOGY CLINICS N. AM. 797 (2000). For a definition of and critical inquiry into what is meant by the seventh criterion, biologic plausibility, see Douglas L. Weed & Stephen D. Hursting, *Biologic Plausibility in Causal Inference: Current Methods and Practice*, 147 AM. J. EPIDEM. 415 (1998) (examining use of this criterion in contemporary epidemiologic research and

distinguishing between a plausible hypothesis and one supported by evidence supplied from research employing molecular biology and molecular epidemiology).

The first case to employ an epidemiologic threshold for proof of agent-disease causation was Brock v. Merrell Dow Pharms., 874 F.2d 307, 315 (5th Cir.) (applying Texas law), modified on rehearing, 884 F.2d 166 (5th Cir. 1989). The genesis for that requirement was the Bendectin litigation in which, in the face of a developing body of scientific evidence tending to exonerate Bendectin, courts sought a means to prevent submission of those cases to a jury. When a substantial body of epidemiologic evidence exists that tends to exonerate the alleged agent, other evidence of causation is far less persuasive. The Bendectin and silicone-gel breast-implant cases, the latter of which involve autoimmune diseases, teach this lesson. Earlier, in In re "Agent Orange" Products Liability Litigation, 611 F. Supp. 1267 (E.D.N.Y. 1985), Judge Weinstein had denigrated the animal studies on which plaintiffs sought to rely in the course of granting defendants summary judgment, thereby implying that epidemiologic evidence would be required. After *Brock*, several district courts in the Fifth Circuit employed it as a precedent, requiring epidemiologic evidence, and courts have used a variety of techniques to squelch Bendectin plaintiffs in the face of a substantial body of exonerative epidemiology. See JOSEPH SANDERS, BENDECTIN ON TRIAL: A STUDY OF MASS TORT LITIGATION 89 (1998) (concluding that "the substantial weight of the scientific evidence fails to support the conclusion that Bendectin causes birth defects"); Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181 (1993); Michael D. Green, *The Road Less Well Traveled (And Seen): Contemporary Lawmaking in Products Liability*, 49 DEPAUL L. REV. 377 (1999). For applications of the same principle in a non-Bendectin case, see Conde v. Velsicol Chemical Co., 24 F.3d 809 (6th Cir. 1994) ("Nineteen epidemiological studies in humans have found little evidence of long-term adverse health effects from chlordane doses

hundreds of times higher than those the [plaintiffs] were subject to under a worst-case scenario.").

A quite substantial body of case law and commentary rejects an epidemiologic threshold for sufficient proof of general causation. Many courts find that requiring proof by scientific evidence that does not exist and is not reasonably available to plaintiff when other, reasonably probative evidence exists is an overbroad method for screening cases. See Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1198 (11th Cir. 2002) ("It is well-settled that while epidemiological studies may be powerful evidence of causation, the lack thereof is not fatal to a plaintiff's case."); Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211-1212 (10th Cir. 2002) (agreeing with the proposition that plaintiffs need not, in all circumstances, provide evidence of general causation with epidemiologic studies); In re Berg Litig., 293 F.3d 1127, 1130 (9th Cir. 2002); Bonner v. ISP Tech., Inc., 259 F.3d 924, 929 (8th Cir. 2001); Kennedy v. Collagen Corp., 161 F.3d 1226, 1230 (9th Cir. 1998); Zuchowicz v. United States, 140 F.3d 381, 389-390 (2d Cir. 1998) (Connecticut law in Federal Tort Claims Act case; acute response to a drug); Ambrosini v. Labarraque, 101 F.3d 129, 138-139 (D.C. Cir. 1996) (applying District of Columbia law) (permitting plaintiff's expert to testify in the absence of epidemiological evidence); Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378 (4th Cir. 1995) (applying Virginia law); McCullock v. H.B. Fuller Co., 61 F.3d 1038 (2d Cir. 1995) (applying Vermont law); Hopkins v. Dow Corning Corp., 33 F.3d 1116 (9th Cir. 1994) (applying California law); Glaser v. Thompson Med. Co., 32 F.3d 969 (6th Cir. 1994) (applying Michigan law); Mendes-Silva v. United States, 980 F.2d 1482 (D.C. Cir. 1993) (applying District of Columbia law applicable in Federal Tort Claims Act case); Kennedy v. Collagen Corp., 974 F.2d 1342 (9th Cir. 1992); Wells v. Ortho Pharm. Corp., 788 F.2d 741, 745 (11th Cir. 1986) (applying Georgia law) (pre-*Daubert* case); In re Meridia Prods. Liab. Litig., 328 F. Supp. 2d 791 (N.D. Ohio 2004); Globetti v. Sandoz Pharms., Corp., 111 F. Supp. 2d 1174 (N.D.

Ala. 2000); Graham v. Playtex Prod., Inc., 993 F. Supp. 127, 132 (N.D.N.Y. 1998) (permitting testimony on cause of toxic-shock syndrome in the absence of epidemiological evidence); Lakie v. Smithkline Beecham, 965 F. Supp. 49, 56 (D. D.C. 1997) (acknowledging significance of epidemiology but denying its absence is dispositive); Pick v. Am. Med. Sys., Inc., 958 F. Supp. 1151, 1158 (E.D. La. 1997) (observing that while epidemiologic studies are a "most useful and conclusive type of evidence," they are not a "necessary element in all toxic tort cases"); Bowers v. N. Telecom, Inc., 905 F. Supp. 1004 (N.D. Fla. 1995); Villari v. Terminix Int'l, Inc., 692 F. Supp. 568 (E.D. Pa. 1988); Marsee v. U.S. Tobacco Co., 639 F. Supp. 466 (W.D. Okla. 1986); Althen v. Sec'y, Dep't of Health & Human Servs., 2003 WL 21439669 (Fed. Cl. 2003); Stevens v. Sec'y of HHS, 2001 WL 387418, at *8 (Fed. Cl. March 30, 2001); U.S. Sugar Corp. v. Henson, 823 So. 2d 104 (Fla. 2002); Earl v. Cryovac, 772 P.2d 725 (Idaho Ct. App. 1989); Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314 (Ill. 2002); Kuhn v. Sandoz Pharms. Corp., 14 P.3d 1170, 1184-1185 (Kan. 2000); Bloomquist v. Wapello County, 500 N.W.2d 1, 5 (Iowa 1993); Callahan v. Cardinal Glennon Hosp., 863 S.W.2d 852 (Mo. 1993); Lindquist v. City of Jersey City Fire Dep't, 789 A.2d 642 (N.J. 2003) (agent-disease causation in workers'-compensation case; supporting the idea that causation should be determined based upon the scientific evidence that is currently available); Rubanick v. Witco Chem. Corp., 593 A.2d 733 (N.J. 1991); Valentine v. PPG Indus., Inc., ___ N.E.2d ___, 2004 WL 1908303 (Ohio Ct. App. 2004); Jennings v. Baxter Healthcare Corp., 14 P.3d 596 (Or. 2001); Reese v. Stroh, 874 P.2d 200 (Wash. Ct. App. 1994); Easum v. Miller, 92 P.3d 794 (Wyo. 2004); David L. Faigman et al., *How Good Is Good Enough?: Expert Evidence Under* Daubert *and* Kumho, 50 CASE W. RES. L. REV. 645, 663 (2000) ("It is now clear that courts will not exclude causal opinions based on non-epidemiological evidence in situations where a body of such data does not exist.").

Commentators have generally been unsympathetic to the imposition of an epidemiologic threshold for proof of causation. See David L. Faigman et al., *How Good Is Good Enough?: Expert Evidence Under* Daubert *and* Kumho, 50 CASE W. RES. L. REV. 645, 663 (2000); Lucinda M. Finley, *Guarding the Gate to the Courthouse: How Trial Judges Are Using Their Evidentiary Screening Role to Remake Tort Causation Rules*, 49 DEPAUL L. REV. 335, 339 (1999); Mark Geistfeld, *Scientific Uncertainty and Causation in Tort Law*, 54 VAND. L. REV. 1011 (2001); Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of* Agent Orange *and Bendectin Litigation*, 86 NW. U. L. REV. 643 (1992); see also Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181 (1993) (arguing epidemiologic evidence should not be required in cases involving infrequent or isolated exposures but that when large numbers of people are exposed, epidemiologic evidence is and should be required). Even more antithetical to an epidemiologic threshold are commentators who advocate some form of burden shifting on agent-disease causation. See Margaret Berger, *Eliminating General Causation: Notes Towards a New Theory of Justice and Toxic Torts*, 97 COLUM. L. REV. 2117 (1997); Heidi Li Feldman, *Science and Uncertainty in Mass Exposure Litigation*, 74 TEX. L. REV. 1, 45 (1995); Ariel Porat & Alex Stein, *Liability for Uncertainty: Making Evidential Damage Actionable*, 18 CARDOZO L. REV. 1891 (1997); Wendy E. Wagner, *Choosing Ignorance in the Manufacture of Toxic Products*, 82 CORNELL L. REV. 773 (1997).

For courts that have confronted the situation in which epidemiologic studies cannot feasibly be conducted because an insufficient number of persons have been exposed, see Dawsey v. Olin, 782 F.2d 1254 (5th Cir. 1986) (workers exposed to accidental release of phosgene gas); Donaldson v. Cent. Ill. Pub. Serv. Co., 767 N.E.2d 314 (Ill. 2002) (very few cases of disease, neuroblastoma; difficulty in retrospective determinations of exposure);

Trach v. Fellin, 817 A.2d 1102 (Pa. Super. Ct. 2003) (pharmacy assistant's negligence in providing plaintiff incorrect drug resulted in his taking more than 3 times the maximum recommended dose of drug); Oukrop v. Wasserburger, 755 P.2d 233 (Wyo. 1988) (error in prescription resulted in plaintiff being exposed to dose 25 times the ordinary dose). Even when an individual is uniquely exposed to an overdose such as in the *Oukrop* case, studies of the adverse effects of the drug with normal doses may provide evidence supportive of the claim that the overdose caused plaintiff's disease. The studies may not, however, if there is a threshold dose above the therapeutic dose required before the disease can occur in humans or if the incidence of the disease occurring at therapeutic doses is so rare that studies are inadequate to reveal the effect of the agent. Another instance in which epidemiologic studies are inadequate on general causation is when the background incidence of the disease is very low and any increased risk is modest. For commentators' views that the market and legal rules provide inadequate incentives to undertake the sorts of studies that provide information about agent-disease causation, see Mary L. Lyndon, *Information Economics and Chemical Toxicity: Designing Laws to Produce and Use Data*, 87 MICH. L. REV. 1795, 1810-1825 (1989) (public-good aspect of information); Wendy E. Wagner, *Choosing Ignorance in the Manufacture of Toxic Products*, 82 CORNELL L. REV. 773, 784-796 (1997) (identifying inadequacies in market, regulatory, and common-law incentives for adequate production of evidence of toxicity). The experience of defendants in the Bendectin and silicone-gel, breast- implant cases, in which plaintiffs managed substantial success until the litigation drove the development of science that tended to exonerate the agents, may provide incentives for some manufacturers for which these commentators fail to account.

While courts have permitted proof of general causation with something less than epidemiologic evidence, case reports — reports of an instance of disease in an individual following exposure to a given agent — have been found insufficient by themselves as proof

of general causation. See Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211 (10th Cir. 2002); Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1361-1362 (N.D. Ga. 2001) (citing cases), aff'd, 295 F.3d 1194 (11th Cir. 2002); Susan R. Poulter, *Science and Toxic Torts: Is There a Rational Solution to the Problem of Causation?*, 7 HIGH TECH. L.J. 189, 216 (1992) (case reports and clusters of disease, while necessary, may only reflect coincidence due to random chance rather than a causal relationship). But see Jennings v. Baxter Healthcare Corp., 14 P.3d 596, 607 (Or. 2000) (suggesting that in an unusual case, with an especially powerful agent, case reports may be sufficient to establish causation). For a discussion of the other types of evidence bearing on general causation, see 2 DAVID L. FAIGMAN ET AL., MODERN SCIENTIFIC EVIDENCE § 27-1.0 to -1.3.2 (1997) (explaining animal toxicology, in vitro, and structure-activity studies); see also ERNEST HODGSON & PATRICIA LEVI, MODERN TOXICOLOGY (1987); MICHAEL A. KAMRIN, TOXICOLOGY: A PRIMER ON TOXICOLOGY PRINCIPLES AND APPLICATIONS (1988); Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181, 218-231 (1993); Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 401 (2d ed. 2000); Jack L. Landau & W. Hugh O'Riordan, *Of Mice and Men: The Admissibility of Animal Studies to Prove Causation in Toxic Tort Litigation*, 25 IDAHO L. REV. 521 (1988-1989); Ellen K. Silbergeld, *The Role of Toxicology in Causation: A Scientific Perspective*, 1 CTS., HEALTH SCI. & LAW 374 (1991). For sources discussing the admissibility and sufficiency of toxicologic evidence, see FAIGMAN, supra, at § 27-1.1 n.11 (concluding "[i]t is impossible to reconcile all of the cases in this area").

The point about general causation existing in a background sense in all tort cases was drawn from Joseph Sanders & Julie Machal-Fulks, *The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective*

and Substantive Law, 64 LAW & CONTEMP. PROBS. 107, 110 n.13 (2001); see also Richard W. Wright, *Causation, Responsibility, Risk, Probability, Naked Statistics, and Proof: Pruning the Bramble Bush by Clarifying the Concepts*, 73 IOWA L. REV. 1001, 1046 (1988) ("Thus, to prove that a specific condition was a cause of a particular result, one obviously must establish . . . that some credible causal generalization links conditions of that type to results of that type.").

Even when satisfactory evidence of general causation exists, such evidence generally supports proof of causation only for a specific disease. The vast majority of toxic agents cause a single disease or a series of biologically related diseases. (However, many different toxic agents may be combined in a single product, such as cigarettes.) When biological-mechanism evidence is available, it may permit an inference that a toxic agent caused a related disease. Otherwise, proof that an agent causes one disease is generally not probative of its capacity to cause other unrelated diseases. Thus, while there is substantial scientific evidence that asbestos causes lung cancer and mesothelioma, whether asbestos causes other cancers would require independent proof. Courts refusing to permit use of scientific studies that support general causation for diseases other than the one from which the plaintiff suffers unless there is evidence showing a common biological mechanism include Christophersen v. Allied-Signal Corp., 939 F.2d 1106, 1115-1116 (5th Cir. 1991) (applying Texas law) (epidemiologic connection between heavy-metal agents and lung cancer cannot be used as evidence that same agents caused colon cancer); Cavallo v. Star Enters., 892 F. Supp. 756 (E.D. Va. 1995), aff'd in part and rev'd in part, 100 F.3d 1150 (4th Cir. 1996); Boyles v. Am. Cyanamid Co., 796 F. Supp. 704 (E.D.N.Y. 1992). In Austin v. Kerr-McGee Ref. Corp., 25 S.W.3d 280, 290 (Tex. Ct. App. 2000), the plaintiff sought to rely on studies showing that benzene caused one type of leukemia to prove that benzene caused a different type of leukemia in her decedent. Quite sensibly, the court insisted that before plaintiff could do so, she would have to

submit evidence that both types of leukemia had a common biological mechanism of development.

For cases in which courts reached opposite conclusions on the value and adequacy of biological-mechanism evidence, compare Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347 (N.D. Ga. 2001) (biological-mechanism evidence of effect of Parlodel, a drug that suppresses lactation, insufficient to permit plaintiff's expert witnesses to testify to general causation), aff'd, 295 F.3d 1194 (11th Cir. 2002) with Tobin v. Astra Pharm. Prods., Inc., 993 F.2d 528 (6th Cir. 1993) (applying Kentucky law) (plaintiff's expert relied predominantly on pathogenic evidence); Globetti v. Sandoz Pharms., Corp., 111 F. Supp. 2d 1174 (N.D. Ala. 2000) (crediting expert witnesses who reasoned that because Parlodel is a vasoconstrictive agent it has the capacity to cause spasms that result in a heart attack); Stevens v. Sec'y of HHS, 2001 WL 387418, at *14 (Fed. Cl. March 30, 2001) (identifying infrequent instance when use of pathological-mechanism evidence is available and sufficiently probative to establish causation). However, scientists report that there is no methodology for assessing the strength or reliability of biological-mechanism evidence. It may vary from quite compelling to no more than hypothesis, with little supporting the latter other than some biologic knowledge and a fertile imagination. See generally Douglas L. Weed & Stephen D. Hursting, *Biologic Plausibility in Causal Inference: Current Methods and Practice*, 147 AM. J. EPIDEM. 415 (1998) (distinguishing between a plausible biological-mechanism hypothesis and biological-mechanism evidence based on research employing molecular biology and molecular epidemiology); Susan R. Poulter, *Science and Toxic Torts: Is There a Rational Solution to the Problem of Causation?*, *7* HIGH TECH. L.J. 189, 230 (1992).

One final observation about the uncertainties of group observational studies and their use in civil litigation as proof of causation may assist those who do not regularly work

in this area. The observational nature of epidemiologic studies virtually always results in concerns about the results being skewed by biases or unidentified confounders. Sampling error is also always possible in group studies, whether observational or experimental. Sometimes potential confounders can be identified and data gathered that permits analysis of whether confounding exists. Unidentified confounders, however, cannot be analyzed. Often potential biases can be identified, but assessing the extent to which they affected the study's outcome is problematical. Even sampling error, which is analyzed using quantitative statistical methods, only provides a range of outcomes (associations) that might have been produced by sampling error even if there is no association between the agent and disease. Thus, interpreting the results of epidemiologic studies requires informed judgment and is subject to uncertainty. Unfortunately, contending adversarial experts, because of the pressures of the adversarial system, rarely explore this uncertainty and provide the best, objective assessment of the scientific evidence. The extent of judgment involved in making causal assessments and range of uncertainty often involved augur for making that judgment with neutral, court-appointed experts, where feasible, whose expertise, judgment, and honest assessment of the degree of uncertainty involved can better be developed. An increasing number of judges, confronted with these issues, have chosen to employ court-appointed experts. See, e.g., Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434 (W.D. Pa. 2003); Miller v. Pfizer, Inc., 196 F. Supp.2d 1062, 1094 (D. Kan. 2002); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387 (D. Or. 1996).

Complicating appropriate assessment of uncertainty and its implications for sufficiency of the evidence is that scientists generally do not think or express their judgments in probabilistic terms. While testimony as an expert in court is sometimes an exception, when scientists are asked to make an assessment of the degree of uncertainty based on existing evidence, they often have difficulty responding. An example of this phenomenon occurred in an Institute of Medicine Committee that had been requested to

examine the evidence bearing on a causal relationship between rubella vaccine and arthritis. The Committee report stated that the "evidence is consistent" with a causal relationship. Only after further inquiries were made did the Committee clarify that it meant that the Committee "favors acceptance of" a causal relationship. The court interpreting the latter categorization interpreted it to mean more likely than not. See Snyder v. Sect'y of HHS, 2002 WL 31965742 (Fed. Cl. 2002).

(4) *Specific causation.* Applying the results of group studies to assess the probability of causation in an individual has become accepted by courts; this is especially true where, as is often the case, there is a lack of understanding about the other components of the casual chain necessary for a given disease. This acceptance has been necessitated by the legal requirement for proof of causation on an individual-plaintiff basis. Epidemiologists, however, do not seek to understand causation at the individual level and do not use incidence rates in group studies to determine the cause of an individual's disease. Epidemiologists may appreciate the conditions and caveats important to whether a study can appropriately be used to infer a probability of individual causation, but the process of doing so is not one that epidemiologists pursue outside the legal arena. See Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 381-382 (2d ed. 2000).

Although addressed to ex ante risk assessments for individuals, the observations by two leading epidemiologists are equally applicable to ex post assessments of the probability of causation:

> We cannot measure the individual risk, and assigning the average value to everyone in the category reflects nothing more than our ignorance about the determinants of lung cancer that interact with cigarette smoke. It is

> apparent from epidemiologic data that some people can engage in chain smoking for many decades without developing lung cancer. Others are or will become primed by unknown circumstances and need only to add cigarette smoke to the nearly sufficient constellation of causes to initiate lung cancer. In our ignorance of these hidden causal components, the best we can do in assessing risk is to classify
>
> people according to measured causal risk indicators and then assign the average observed within a class to persons within the class.

KENNETH J. ROTHMAN & SANDER GREENLAND, MODERN EPIDEMIOLOGY 9 (2d ed. 1998).

Caution, however, is necessary in permitting or making inferences about specific causation based on an increased incidence found in a group study. One must appreciate that an association (increased incidence of disease among those exposed to the agent) found in a group study does not necessarily mean a causal relationship exists. Observational group studies are subject to a variety of errors — sampling error, bias, and confounding — and may, as a result, find associations that are spurious and not causal. Only after an evaluative judgment, based on the Hill criteria, that the association is likely to be causal rather than spurious, is a study valid evidence of general causation and specific causation. See Michael D. Green et al., *Reference Guide on Epidemiology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 333, 383-384 (2d ed. 2000). This judgment entails employing a number of unranked factors to decide if an inference of causation is appropriate. No scientific methodology exists for this process and, hence, reasonable scientists may, in some instances, come to different judgments about whether such an inference is appropriate. See generally Douglas L. Weed, *Epidemiologic Evidence and Causal Inference*, 14 HEMATOLOGY/ONCOLOGY CLINICS N. AM. 797 (2000).

Even if an association is judged to be causal, biases in a study may result in skewing the true magnitude of the risk. In addition, differences between those persons in the study group and the plaintiff to whom the study results are being applied must be considered. In some instances the results of a study on a different population may be inapplicable to others; for example, studies of risk factors for breast cancer in women would be inapplicable to men. In other cases, more subtle differences between the study population and the plaintiff may require consideration of whether the risk found in the study is equivalent for the plaintiff or, where information permits, should be adjusted. See In re Hanford Nuclear Reservation Litig., 1998 WL 775340, at *64-70 (E.D. Wash. Aug. 21, 1998) (addressing plaintiffs' expert's efforts to adjust probability of causation for individual plaintiffs based on individual factors, including genetic susceptibility), rev'd on other grounds, 292 F.3d 1124 (9th Cir. 2002); Minn. Mining & Mfg. Co. v. Atterbury, 978 S.W.2d 183, 191 (Tex. Ct. App. 1998). See generally David A. Freedman & Philip B. Stark, *The Swine Flu Vaccine and Guillain-Barré Syndrome: A Case Study in Relative Risk and Specific Causation*, 64 L. & CONTEMP. PROBS. 49 (2001) (criticizing the use of relative risk to determine probability of causation for individuals because of the risk of spurious associations and the extent of individual variation); David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 83, 96-97 & n.38 (2d ed. 2000) (explaining the problems of employing a study outcome to determine the probability of an individual's having contracted the disease from exposure to the agent because of variations in individuals that bear on the risk of a given individual contracting the disease); Mark Parascandola, *What is Wrong with the Probability of Causation*, 39 JURIMETRICS J. 29 (1998); Joseph Sanders, *Scientific Validity, Admissibility, and Mass Torts after* Daubert, 78 MINN. L. REV. 1387, 1401-1404 (1994); see also KENNETH J. ROTHMAN & SANDER GREENLAND, MODERN EPIDEMIOLOGY 9 (2d ed. 1998) ("As knowledge expands the risk estimates assigned to people will depart from

average according to the presence or absence of other factors that affect the risk."); Gary E. Marchant, *Genetic Susceptibility and Biomarkers in Toxic Injury Litigation*, 41 JURIMETRICS J. 67, 67-68, 71-72, 90 (2000) (discussing role that knowledge about genetic contribution to disease might play in refining probability of causation based on epidemiologic studies of heterogenous populations).

The idea that a doubling of the incidence of disease in group studies is sufficient to support proof of specific causation is often accepted. Some courts have insisted on a doubling of disease as a minimum for proof of specific causation, while others have recognized that, if other known causes can be identified and eliminated, something less than a doubling would still support finding specific causation. See In re Hanford Nuclear Reservation Litig., 292 F.3d 1124, 1137 (9th Cir. 2002) (applying Washington law) (recognizing the role of individual factors that may modify the probability of causation based on the relative risk); Allison v. McGhan Med. Corp., 184 F.3d 1300, 1315 n.16 (11th Cir. 1999) (breast-implant case; relative risk of 2.0 is the threshold for an inference of specific causation; relative risk of 1.24 is insufficient); In re Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124 (2d Cir. 1995) (applying New York law) (holding that plaintiff could provide sufficient evidence of causation without proving a doubling in the incidence of disease); Daubert v. Merrell Dow Pharms., Inc., 43 F.3d 1311, 1320 (9th Cir. 1995) (applying California law) (requiring that plaintiff demonstrate a relative risk of 2); In re Joint E. & S. Dist. Asbestos Litig., 964 F.2d 92 (2d Cir. 1992) (applying New York law) (relative risk less than 2.0 may still be sufficient to prove causation); DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 958-959 (3d Cir. 1990) (applying New Jersey law) (Bendectin allegedly caused limb-reduction birth defects); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 606 (D. N.J. 2002) ("[A] relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence, among others for the court to consider in determining whether an expert has employed a sound

methodology in reaching his or her conclusion."); Miller v. Pfizer, Inc., 196 F. Supp. 2d 1062, 1079 (D. Kan. 2002) (rejecting a threshold of 2.0 for the relative risk and recognizing that even a relative risk greater than 2.0 may be insufficient); In re Breast Implant Litig., 11 F. Supp. 2d 1217 (D. Colo. 1998) (plaintiff must demonstrate more than a doubling of risk of disease by defendant's agent); Pick v. Am. Med. Sys., Inc., 958 F. Supp. 1151, 1160 (E.D. La. 1997) (stating that a relative risk of 2 implies a 50% probability of specific causation, but acknowledging that a study with a lower relative risk is admissible, if not sufficient to support a verdict on causation); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981, 1000 (C.D. Cal. 1996) (relative risk of 2 is a threshold for plaintiff to prove specific causation); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1403 (D. Or. 1996) ("plaintiffs must be able to show a relative risk of greater than 2.0"); Manko v. United States, 636 F. Supp. 1419, 1434 (W.D. Mo. 1986) (swine-flu vaccine allegedly caused Guillain-Barré syndrome), aff'd in part, 830 F.2d 831 (8th Cir. 1987); Marder v. G.D. Searle & Co., 630 F. Supp. 1087, 1092 (D. Md. 1986) (requiring a doubling of the relative risk in order to prove causation is more likely than not), aff'd without op. sub nom. Wheelahan v. G.D. Searle & Co., 814 F.2d 655 (4th Cir. 1987); In re "Agent Orange" Prod. Liab. Litig., 597 F. Supp. 740, 835–837 (E.D.N.Y. 1984) (Agent Orange allegedly caused a wide variety of diseases in Vietnam veterans and their offspring), aff'd, 818 F.2d 145 (2d Cir. 1987); Cook v. United States, 545 F. Supp. 306, 308 (N.D. Cal. 1982) (swine-flu vaccine allegedly caused Guillain-Barré syndrome); Stevens v. Sec'y of HHS, 2001 WL 387418, at *12-13 (Fed. Cl. March 30, 2001); Berry v. CSX Transp., Inc., 709 So. 2d 552, 569 n.13 (Fla. Dist. Ct. App. 1998) (suggesting that a relative risk of less than 2 might be sufficient if other risk factors can be ruled out for the plaintiff); DePyper v. Navarro, 1995 WL 788828 (Mich. Cir. Ct. Nov. 27, 1995) (suggesting a relative risk of 2 is required for adequate proof of general causation); Landrigan v. Celotex Corp., 605 A.2d 1079, 1087 (N.J. 1992) (relative risk greater than 2 "support[s] an inference that the exposure was the probable cause of the disease in a

specific member of the exposed population"); Grassis v. Johns-Manville Corp., 591 A.2d 671, 675 (N.J. Super. Ct. App. Div. 1991) ("The physician or other qualified expert may view the epidemiological studies and factor out other known risk factors such as family history, diet, alcohol consumption, smoking . . . or other factors which might enhance the remaining risks, even though the risk in the study fell short of the 2.0 correlation."); Jones v. Owens-Corning Fiberglas Corp., 672 A.2d 230 (N.J. Super. Ct. App. Div. 1996); McDaniel v. CSX Corp., 95 S.W.2d 257, 264 (Tenn. 1997) (relative risk of 2 a factor to be considered but not required as a legal matter); Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 718 (Tex. 1997) ("The use of scientifically reliable epidemiological studies and the requirement of more than a doubling of the risk strikes a balance between the needs of our legal system and the limits of science."). But cf. In re Fibreboard Corp., 893 F.2d 706, 711-712 (5th Cir. 1990) (applying Texas law) (disapproving a trial in which several representative cases would be tried and the results extrapolated to a class of some 3000 asbestos victims, without consideration of any evidence about the individual victims; general causation, which ignores any proof specific to the individual plaintiff, could not substitute under Texas law for cause in fact.). Despite the considerable disagreement on whether a relative risk of two is required or merely a taking-off point for determining the sufficiency of the evidence on specific causation, two commentators who surveyed the cases observe that "[t]here were no clear differences in outcomes as between federal and state courts." Russellyn S. Carruth & Bernard D. Goldstein, *Relative Risk Greater than Two in Proof of Causation in Toxic Tort Litigation*, 41 JURIMETRICS J. 195, 199 (2001).

The use of epidemiologic studies finding a doubling of disease in order to establish specific causation by a preponderance of the evidence rests on two important assumptions, one unarticulated. The first assumption is that the agent operates independently of other risk factors. When there is an interaction (i.e., the combined incidence of disease in those exposed to some other risk factor and to the agent is other than additive), it is not valid to

use the increased incidence of disease due to one of the agents as a measure of the probability that an individual with the disease after exposure to both agents was caused by that agent. See Comment *c(5)*; Louis A. Cox, Jr., *Probability of Causation and the Attributable Risk*, 4 RISK ANALYSIS 221 (1984).

The unarticulated assumption involves the biology of disease development. The assumption is that the agent causes disease in individuals who would otherwise never have contracted it. An alternative possibility is that the agent accelerates the onset of disease that would otherwise have occurred in those individuals, albeit at a later time. See Sander Greenland & James M. Robins, *Conceptual Problems in the Definition and Interpretation of Attributable Fractions*, 128 AM. J. EPIDEMIOLOGY 1185 (1988); Sander Greenland & James M. Robins, *Epidemiology, Justice, and the Probability of Causation*, 40 JURIMETRICS 321 (2000). If an agent accelerates the onset of disease, rather than causing it in persons who would never otherwise have suffered from it, the excess incidence of disease in a group study will understate the proportion of persons whose disease was accelerated by the agent because incidence in group studies is based on the frequency of disease in a given period of time. See Greenland & Robins, supra; see also Ofer Shpilberg et al., *The Next Stage: Molecular Epidemiology*, 50 J. CLINICAL EPIDEMIOLOGY 633, 637 (1997) ("A 1.5-fold relative risk may be composed of a 5-fold risk in 10% of the population, and a 1.1-fold risk in the remaining 90%, or a 2-fold risk in 25% and a 1.1-fold for 75%, or a 1.5-fold risk for the entire population."). For studies whose results suggest acceleration, see Brad A. Racette, *Welding-Related Parkinsonism: Clinical Features, Treatments, and Pathophysiology*, 56 NEUROLOGY 8, 12 (2001) (stating that authors "believe that welding exposure acts as an accelerant to cause [Parkinson's Disease]"); James L. Gale et al., *Risk of Serious Acute Neurological Illness After Immunization with Diphtheria- Tetanus-Pertussis Vaccine A Population-Based Case-Control Study*, 271 JAMA 37, 41 (1994) (discussing finding in another study that risk of seizures

following DPT vaccine administration were significantly higher within 6 days of administration; but, after 28 days, the incidence had dropped to normal).

Rarely will significant evidence bearing on the appropriate biological mechanism be available. If it were, permitting proof to contradict the assumption of nonacceleration would be attractive, save for one concern. If acceleration were able to be identified and proved, the measure of damages would also require reconsideration. Thus, accelerating the plaintiff's contraction of a chronic disease by two years would justify damages that are but a fraction of the damages appropriate if the agent caused a plaintiff to suffer from the disease for her remaining life. See Restatement Second, Torts § 924, Comment *e*; David A. Fischer, *Successive Causes and the Enigma of Duplicated Harm*, 66 TENN. L. REV. 1127 (1999). In addition, another impediment to employing small increases in risk as the basis for any kind of causal determination exists. Group studies of toxic agents are observational, rather than experimental. The observational nature of these studies opens them to a variety of design and methodological errors that may produce spurious results. Random error is another potential cause of invalid results, regardless of whether the study is experimental or observational. Many scientists are leery of accepting a group study that finds an increased incidence of disease below a certain magnitude as demonstrating a true causal relationship. See Gary Taubes, *Epidemiology Faces Its Limits*, 269 SCI. 164 (1995) (reporting on a wide range of epidemiologists' expressing great skepticism of studies that find modest increases in incidence of disease unless replicated consistently in a number of independent studies); see also N. E. Breslow & N. E. Day, *Statistical Methods in Cancer Research*, *in* THE ANALYSIS OF CASE-CONTROL STUDIES 36 (IARC Pub. No. 32, Lyon, France 1980) ("[r]elative risks of less than 2.0 may readily reflect some unperceived bias or confounding factor"); David A. Freedman & Philip B. Stark, *The Swine Flu Vaccine and Guillain-barré Syndrome: A Case Study in Relative Risk and Specific Causation*, 64 LAW & CONTEMP. PROBS. 49, 60 (2001) ("If the relative risk is near 2.0, problems of bias and

confounding in the underlying epidemiologic studies may be serious, perhaps intractable."); Samuel Shapiro, *Meta-analysis/Shmeta Analysis*, 140 AM. J. EPIDEM. 771, 772 (1994) (contending that meta-analysis can only minimize sampling error, leaving bias and confounding — "[r]elative risks of low magnitude (say, less than 2) are virtually beyond the resolving power of the epidemiologic microscope"). This concern is applicable to general causation rather than specific causation. The cautionary note is raised here because small relative risks are most often addressed in the specific-causation inquiry.

For an explanation of other assumptions necessary for the incidence rate to truly reflect the increased incidence of disease caused by exposure to the agent, see Jan Beyea & Sander Greenland, *The Importance of Specifying the Underlying Biologic Model in Estimating the Probability of Causation*, 76 HEALTH PHYSICS 269, 271-272 (1999); Sander Greenland & James M. Robins, *Epidemiology, Justice, and the Probability of Causation*, 40 JURIMETRICS 321, 332-333 (2000) (explaining assumptions that: 1) agent does not cause other diseases that might be a competing cause of death; and 2) that doses of the agent do not prevent or delay the onset of diseases among some of those exposed).

A technique sometimes available to assist in proof of specific causation is a differential diagnosis. The idea is that a cause may be identified by eliminating the possibility that other known and alternative causes were responsible for the outcome. Many courts have endorsed such use. See, e.g., Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347 (N.D. Ga. 2001), aff'd, 295 F.3d 1194 (11th Cir. 2002); Globetti v. Sandoz Pharms., Corp., 111 F. Supp. 1174 (N.D. Ala. 2000); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1413 (D. Or. 1996); John's Heating Serv. v. Lamb, 46 P.3d 1024, 1035 (Alaska 2002); U.S. Sugar Corp. v. Henson, 823 So. 2d 104 (Fla. 2002); Schafersman v. Agland Coop., 631 N.W.2d 862, 871 (Neb. 2001); Alder v. Bayer Corp., 61 P.3d 1068, 1084-1085 (Utah 2002); Easum v. Miller, 92 P.3d 794 (Wyo. 2004); see

also Martin v. Shell Oil Co., 180 F. Supp. 2d 313, 318-319 (D. Conn. 2002) (plaintiff's expert not required to perform a differential diagnosis where other evidence of specific causation is employed). For a thorough discussion of the cases and the issues posed by such evidence, see Joseph Sanders & Julie Machal-Fulks, *The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective and Substantive Law*, 64 LAW & CONTEMP. PROBS. 107 (2001).

More generally, the methodology of identifying a cause by eliminating other known causes of the outcome is widely employed in a variety of investigative fields. See, e.g., Baker Valley Lumber, Inc. v. Ingersoll Rand Co., 813 A.2d 409 (N.H. Dec. 12, 2002) (fire investigators attempting to determine the cause of a sawmill fire); Morton M. Hunt, *The Case of Flight 320*, THE NEW YORKER, Apr. 30, 1960, at 119 (explaining the method by which investigators for the predecessor to the National Transportation Safety Board attempt to determine the cause of an airplane crash). In Stubbs v. City of Rochester, 124 N.E. 137 (N.Y. 1919), one of the classic cases on proof of causation, the court sanctioned plaintiff's effort to prove that the defendant's intermingling of sanitary drinking water and unsanitary water was the cause of his typhus by eliminating many (but not all) of the other known causes of typhus.

In the medical profession, "differential diagnoses" are frequently employed to determine the patient's disease rather than its cause. When the cause of a disease, such as cancer, is not of clinical significance, physicians do not attempt to determine it. See Roach v. PPG Indus., Inc., ___ S.W.2d ___ (Ark. Ct. App. 2004) (treating physician's opinion on cause of patient's cancer held inadmissible: "[The expert] was clearly more concerned with identifying and treating the decedent's condition than he was with identifying the specific substance that caused his condition. He arrived at his opinion about benzene more as an afterthought, in an ad hoc manner."). Only when the cause may have

some continuing effect on the patient's health, as when a rash may be the result of a continuing occupational exposure, do physicians attempt to determine the cause of the patient's problems. For an explanation of the difference between the medical and legal communities in usage of the terms "differential diagnosis" and "differential etiology," see Mary Sue Henifin et al., *Reference Guide on Medical Testimony*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 439, 443-444 (2d ed. 2000); Edward J. Imwinkelreid, *The Admissibility and Legal Sufficiency of Testimony about Differential Diagnosis (Etiology): of Under — and Over — Estimations*, 56 BAYLOR L. REV. 391, 402-403 (2004); see also Turner v. Iowa Fire Equipment Co., 229 F.3d 1202, 1208 (8th Cir. 2000) (distinguishing between differential diagnosis conducted for the purpose of identifying the disease from which the patient suffers and one attempting to determine the cause of the disease); Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 807 (3d Cir. 1997) (differential diagnosis is "the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings," quoting STEDMAN'S MEDICAL DICTIONARY 428 (25th ed. 1990)); Hodgdon v. Frisbie Mem'l Hosp., 786 A.2d 859 (N.H. 2001) (employing differential diagnosis to describe the process of diagnosing patient's disease based on clinical symptoms); Yacoub v. Lehigh Valley Med. Assocs., P.C., 805 A.2d 579 (Pa. Super. Ct. 2002); MOSBY'S MEDICAL & NURSING DICTIONARY 347 (2d ed. Walter D. Glanze et al. eds., 1986) (defining differential diagnosis as "the distinguishing between two or more diseases with similar symptoms by systematically comparing their signs and symptoms"). For an example of the customary use of the phrase "differential diagnosis" in the clinical medical community, see W. Scott Richardson, *Users' Guide to the Medical Literature: XV. How to Use an Article About Disease Probability for Differential Diagnosis*, 281 JAMA 1214 (1999).

The validity of a differential diagnosis depends on a substantial proportion of the

independent causes of the disease being known. This means that each of those causes operates independently of the others and (along with background causes) causes some percentage of all cases of the disease in question. When a number of the causes are known and the plaintiff can be evaluated for the existence of such causes, the probability of an agent causing the plaintiff's disease can be evaluated. A differential diagnosis is of limited utility when a substantial portion of the incidence of a disease is of unknown etiology. See Susan R. Poulter, *Science and Toxic Torts: Is There a Rational Solution to the Problem of Causation?*, 7 HIGH TECH. L.J. 189, 233 (1992); Coastal Tankships, U.S.A., Inc. v. Anderson, 87 S.W.3d 591, 614-615 (Tex. Ct. App. 2002) (Brister, J., concurring). An example of a disease for which most of the causes are unknown is birth defects. Estimates are that some 2/3 of all birth defects are due to unknown causes. See Robert L. Brent, *The Complexities of Solving the Problem of Human Malformations*, 13 CLINICS IN PERINATOLOGY 491, 493 (1986) (citing various estimates of the proportion of birth defects due to unknown causes).

An excellent explanation for why differential diagnoses generally are inadequate without further proof of general causation was provided in Cavallo v. Star Enter., 892 F. Supp. 756 (E.D. Va. 1995), aff'd in relevant part, 100 F.3d 1150 (4th Cir. 1996):

> The process of differential diagnosis is undoubtedly important to the question of "specific causation". If other possible causes of an injury cannot be ruled out, or at least the probability of their contribution to causation minimized, then the "more likely than not" threshold for proving causation may not be met. But, it is also important to recognize that a fundamental assumption underlying this method is that the final, suspected "cause" remaining after this process of elimination must actually be capable of causing the injury. That is, the expert must "rule in" the suspected cause as well as "rule out" other possible causes. And, of course, expert opinion on

this issue of "general causation" must be derived from a scientifically valid methodology.

Id. at 771 (footnote omitted); see also Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1210-1211 (10th Cir. 2002) (district court did not abuse its discretion in excluding expert testimony based on differential diagnosis without other adequate evidence of general causation); Meister v. Med. Eng'g Corp., 267 F.3d 1123 (D.C. Cir. 2001); Lennon v. Norfolk and W. Ry. Co., 123 F. Supp. 2d 1143, 1153-1154 (N.D. Ind. 2000); Stevens v. Sec'y of HHS, 2001 WL 387418, at *20 (Fed. Cl. March 30, 2001); E.I. du Pont de Nemours & Co. v. Robinson, 923 S.W.2d 549 (Tex. 1995); Coastal Tankships, U.S.A., Inc. v. Anderson, 87 S.W.3d 591 (Tex. Ct. App. 2002); see generally Joseph Sanders & Julie Machal-Fulks, *The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective and Substantive Law*, 64 LAW & CONTEMP. PROBS. 107, 122-125 (2001) (discussing cases rejecting differential diagnoses in the absence of other proof of general causation and contrary cases).

Despite the *Cavallo* court's appropriate insistence on "ruling in" with evidence of general causation, Zuchowicz v. United States, 140 F.3d 381 (2d Cir. 1998) (Federal Tort Claims Act case adopting Connecticut law), provides the unusual circumstances for an exception. Plaintiff was exposed to a substantial overdose of a drug due to negligence by the prescribing physician and developed primary pulmonary hypertension (PPH), which resulted in her death. No studies had been conducted of doses of the magnitude taken by the deceased, and there were very few humans ever exposed to doses that high, thereby explaining why human studies did not exist. (The court did not mention the existence of, or reason for the absence of, animal toxicology studies.) Plaintiff's experts provided an apparently plausible explanation of the biological mechanism by which the overdose caused PPH, backed at least with regard to some aspects by a variety of studies. Plaintiff's

experts also ruled out, through a differential diagnosis, some of the other causes of PPH, including other drugs. The decedent exhibited symptoms of drug-induced PPH shortly after her overdose and the disease progressed consistently with other drug-induced cases of PPH. Based on this evidence, the court of appeals affirmed the district court's decision admitting the expert testimony and refused to disturb the finding of causation by the court, sitting as factfinder. See also Westberry v. Gislaved Gummi AB, 178 F.2d 257 (4th Cir. 1999) (acute response, differential diagnosis ruled out other known causes of disease, dechallenge, rechallenge tests by expert that were consistent with exposure to defendant's agent causing disease, and absence of epidemiologic or toxicologic studies; holding that expert's testimony on causation was properly admitted). As a prominent medical clinician and former editor of the New England Journal of Medicine observed, "Unfortunately no set formula or algorithm exists for deciding whether a human illness or condition is the consequence of a given exposure to a drug, chemical or some other agent." Jerome P. Kassirer, Joint Discussion of Science, Technology, and Law Panel and American Law Institute: Restatement of Torts 12 (Jan. 21, 2003), at http://www7.nationalacademies.org/stl/index.html. This comment could encompass the variety of circumstances that may exist in a toxic-substances case affecting the available and appropriate proof, the lack of any methodology on employing the Hill criteria to determine whether an inference of causation is appropriate based on a group study that finds an association, the absence of any scientific methodology or guidelines for determining specific causation from group studies, or the lack of any established methodology for clinical judgments of causality.

(5) *Multiple exposures and synergistic interactions*. The discussion of multiple exposures and synergistic interactions in this Comment assumes a disease for which the severity of the disease is not dose dependent. Asbestosis is an example of a disease whose severity *is* dose dependent: the severity of the disease in an individual is a function

of that individual's exposure level. For such diseases, each additional unit of exposure causes some marginal additional harm. By contrast, the severity of many cancers is assumed not to be dependent on the dose to which the individual was exposed. For these non-dose-dependent diseases, each exposure is a cause of the disease. See § 27, Comment *g*. It is the latter class of diseases (or ones that are treated as such) that is addressed in this Comment.

In this multiple-exposure situation, courts have adopted a rule that each nontrivial exposure to a toxic agent may be found by the trier of fact to be a factual cause of plaintiff's disease. See § 27, Comment *g*, and Reporters' Note thereto. Alternatively, especially when plaintiff has been exposed to the toxic agent of multiple defendants, as is frequently the case with asbestos, plaintiffs would be presented with proving which exposure initiated the disease. If a court adopted the latter requirement, it would then be confronted with the propriety and application of alternative liability, see § 28(b), and shifting the burden of proof to defendants on the question of factual causation. See Rutherford v. Owens-Ill., Inc., 941 P.2d 1203, 1215-1220 (Cal. 1997).

The difference between these two proof requirements results from different assumptions about the biology of disease development. The asbestos rule (a "threshold rule") rests on an assumption that each dose of asbestos contributes to a threshold dose above which disease is caused in the individual exposed. See Eagle-Picher Indus., Inc. v. Balbos, 604 A.2d 445 (Md. Ct. App. 1992) (expert testifying to belief in an "undefined 'threshold' of asbestos exposure" required before disease would occur). Alternatively, each dose of a carcinogen may pose an independent and distinct, albeit small, risk of causing cancer in the exposed individual. Indeed, the "one-hit" model of carcinogenesis is consistent with this no-threshold hypothesis. See COMMITTEE ON RISK ASSESSMENT OF HAZARDOUS AIR POLLUTANTS, NATIONAL RESEARCH COUNCIL, SCIENCE AND JUDGMENT IN RISK

ASSESSMENT 123-124 (1994); COMMITTEE ON THE INSTITUTIONAL MEANS FOR ASSESSMENT OF RISKS TO PUBLIC HEALTH, NATIONAL RESEARCH COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS 19-20 (1983); 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, 23-24 (1997).

The court in Rutherford v. Owens-Illinois, Inc., 941 P.2d 1203, 1218 (Cal. 1997), recognized these two different causal models to explain the role of asbestos in causing asbestotic malignancies. Because of the impossibility of proof that would be posed if the second model were assumed, the court adhered to a threshold rule model, only requiring that plaintiff's exposure to defendant's asbestos was a "substantial factor in contributing to the aggregate dose of asbestos" to which the plaintiff was exposed. Id.

In Manguno v. Babcock & Wilcox, 961 F.2d 533 (5th Cir. 1992) (applying Louisiana law), plaintiffs were smokers who were occupationally exposed to asbestos and suffered from lung cancer. They sued several asbestos manufacturers who argued that plaintiffs could not recover without proving that their lung cancer would not have occurred but for the exposure to asbestos. None of plaintiffs' experts testified to that, instead characterizing the asbestos exposure as a significant contributing factor, while recognizing the causal role of smoking as well. The trial court instructed the jury as requested by defendants, and the court of appeals reversed. Initially, the court of appeals was confronted with the plaintiffs' argument that but-for causation is not required in a multiple sufficient causal case. See § 27. Defendants countered that the case did not present a multiple sufficient causal situation and therefore but-for cause was appropriate. The court of appeals recognized (or assumed) that the case did not present multiple sufficient causes. Nevertheless, the court denied that multiple sufficient causes was the only situation

in which but-for cause was relaxed. The court cited multiple asbestos-exposure cases, see § 27, Comment *g*, and held that the but-for causal instruction was erroneous. Thus, the court of appeals adapted the threshold rule to the case of multiple exposures to different toxic agents, each of which is a risk factor for plaintiff's disease.

When synergies exist, the question of how to allocate the probability attributable to the synergistic (supra-additive) effect of the combined agents (in addition to the probability due to each agent alone) requires normative judgment and cannot be calculated simply by mathematical technique. See Grahn v. Dillingham Constr., Inc., 2004 WL 2075570 (Cal. Ct. App. Sept. 17, 2004) (affirming exclusion of expert witness's testimony that plaintiff's cancer was more probably due to smoking than exposure to asbestos and that probability could be readily determined with "just math."). The expert's testimony in *Grahn* not only ignored the question of how to allocate the probability due to the synergistic effect, it also assumed that cigarette smoking and asbestos exposure operate independently of each other in causing cancer. See Illustrations 2-3.

The discussion of synergy and Illustrations 4 and 5 are based on a number of cases in which plaintiffs were exposed to both asbestos and cigarette smoke. In Dafler v. Raymark Indus., Inc., 611 A.2d 136 (N.J. Super. Ct. App. Div. 1992), aff'd, 622 A.2d 1305 (N.J. 1993), the court permitted apportionment of liability without a determination that the plaintiff's smoking constituted contributory negligence (or that the manufacturer of the cigarettes was liable for the plaintiff's harm). The *Dafler* court relied on § 433A, Comment *a*, of the Second Restatement of Torts, which provides for causal apportionment. That reliance may not be justified, however. Comment *a* states that its provisions "apply also where one of the causes in question is the conduct of the plaintiff himself, whether it be negligent or innocent." That statement is best read as inapplicable to a harm, the entirety of which was caused by both innocent-plaintiff conduct and tortious conduct by a

defendant. Only when the innocent conduct and the tortious conduct each cause less than the entirety of the harm is causal apportionment appropriate. While Subsection (1)(b) of § 433A suggests that causal apportionment might be appropriate even when the innocent conduct, along with the tortious conduct, was a cause of the entirety of the harm, if "a reasonable basis for determining the contribution of each cause to a single harm" exists, all of the innocent-cause discussion and Illustrations are consistent with the innocent cause causing less than the entirety of damages. Apportionment is then based on what harm was caused by each of the defendants and the innocent plaintiff. Any contrary reading would run afoul of long-time and well-established rules of causation, which merely require that tortious conduct be *a* cause of harm for liability, regardless of any other causes that may exist. Indeed, the Second Restatement recognizes these principles and evidences inconsistency in Subsection (2) of § 433A and Comment *i*, which observes that some harms cannot be apportioned and includes as examples death, a broken limb, destruction of real property, and an Illustration involving the death of cattle. Comment *i* also recognizes that the existence of other innocent causes in the causal chain producing these outcomes does not change the result. The inconsistency between Subsection (1)(b) of § 433A and Comment *i* is best demonstrated by two Illustrations, virtually identical, that involve two defendants, each of whom pollutes a stream with oil. Illustration 5 permits apportionment in a nuisance case based on the proportion of oil provided (70/30) by each of the defendants. Illustration 15 bars apportionment for the death of plaintiff's cattle, poisoned by drinking oil, without any mention of evidence of the respective contribution of oil by defendants. Apportionment based on causation appears more justified in Illustration 15, as the oil of each defendant could have caused the discrete deaths of some of the plaintiff's cattle, although that evidence is unlikely to be available. The exception for "exceptional cases" in Comment *h*, including instances when one defendant is insolvent, is also inconsistent with Subsection (1) of
§ 433A. See Gerald W. Boston, *Toxic Apportionment: A Causation and Risk Contribution*

Model, 25 ENVTL. L. 549, 568-572 (1995) (criticizing some "problems" with § 433A of the Second Restatement).

At the time the Second Restatement was drafted and approved, there was no apportionment based on comparative responsibility between a plaintiff and defendant; multiple defendants who were liable for a single harm were jointly and severally liable; and apportionment among them was pro rata. The widespread adoption of comparative responsibility and modification of joint and several liability have changed those rules. Section 433A has been superseded by Restatement Third, Torts: Apportionment of Liability § 26.

The apportionment sanctioned by *Dafler* was based roughly on the ratio of increased risks posed by plaintiff's exposure to asbestos and to cigarette smoke. This evidence was provided by plaintiff's expert witnesses, one of whom testified that it was impossible to apportion plaintiff's disease based on causation, and the other of whom testified he could not apportion based on "responsibility." Defendant's expert provided no basis for apportioning, opining that plaintiff's disease was due solely to smoking. Nevertheless, the court found that a reasonable basis for apportioning liability existed and affirmed the trial court's decision to submit this question to the jury. Other courts have held that similar evidence is insufficient to permit apportionment based on causation. See Borman v. Raymark Indus., Inc., 960 F.2d 327, 334-335 (3d Cir. 1992) (applying Pennsylvania law) (denying apportionment based on § 433A of the Restatement Second of Torts despite relative-risk evidence similar to that presented in *Dafler*); Martin v. Owens-Corning Fiberglas Corp., 528 A.2d 947, 949 (Pa. 1987). The *Dafler* court's reliance on an earlier New Jersey decision holding that a plaintiff's emotional distress due to an abortion could be causally apportioned among her physician, who was negligent in an earlier sterilization procedure, a negligent driver, who caused an accident that resulted

in the plaintiff who did not know she was pregnant at the time, being x-rayed, and the treating physician, who x-rayed her, reveals that the New Jersey courts do not make the same sharp distinction between apportionment on the basis of comparative responsibility and on the basis of causation provided by the Apportionment of Liability Restatement. See Bendar v. Rosen, 588 A.2d 1264 (N.J. Super. Ct. App. Div. 1991) (invoking apportionment based on comparative responsibility and causation without acknowledging the difference).

The overwhelming number of courts that permit apportionment between smoking and asbestos exposure base it on comparative-responsibility principles, rather than causation, and therefore require a finding of contributory negligence by the plaintiff in smoking (liability of a person who manufactured or sold the cigarettes). See Ingram v. ACandS, Inc., 977 F.2d 1332, 1340-1341, 1342 (9th Cir. 1992) (applying Oregon law) (rejecting apportionment based on causation but upholding comparative-responsibility apportionment both among asbestos defendants and between defendants and plaintiff who smoked); Zarow-Smith v. N. J. Transit Rail Operations, 953 F. Supp. 581 (D. N.J. 1997) (upholding comparative-responsibility apportionment to plaintiff based on smoking in FELA case); Fulgium v. Armstrong World Indus., Inc., 645 F. Supp. 761, 763 (W.D. La. 1986) (evidence of plaintiff's smoking admissible for purposes of comparative-responsibility apportionment); Richards v. Owens-Ill., Inc., 928 P.2d 1181 (Cal. 1997) (statutory immunity of tobacco suppliers prevented apportionment of comparative responsibility to them); Champagne v. Raybestos-Manhattan, Inc., 562 A.2d 1100, 1118 (Conn. 1989) (permitting plaintiff's smoking to be the basis for comparative-responsibility apportionment, citing Brisboy v. Fibreboard Corp., infra); In re Asbestos Litig. Pusey Trial Group, 669 A.2d 109, 111-113 (Del. 1995) (trial court erred in permitting apportionment without instructing on and requiring jury to find that plaintiff's smoking constituted comparative fault); Hao v. Owens-Ill., Inc., 738 P.2d 416 (Haw. 1987) (same); Owens Corning

Fiberglas Corp. v. Parrish, 58 S.W.3d 467 (Ky. 2001) (upholding comparative-responsibility assignment to plaintiffs based on their smoking); Brisboy v. Fibreboard Corp., 418 N.W.2d 650, 655-656 (Mich. 1988); cf. Jones v. Owens-Corning Fiberglas Corp., 69 F.3d 712 (4th Cir. 1995) (applying North Carolina law) (contributory fault by plaintiff in smoking cigarettes can be asserted by asbestos defendants); Gideon v. Johns-Manville Sales Corp., 761 F.2d 1129, 1138-1140 (5th Cir. 1985) (applying Texas law) (evidence of asbestosis victim's smoking admissible for purposes of defendant's claim of mitigation of damages and for jury to decide if future risk of cancer was caused by smoking, asbestos exposure, or both).

Professor Boston, in a thorough and careful article, advocates apportionment based on risk contribution similar to *Dafler*. Gerald W. Boston, *Toxic Apportionment: A Causation and Risk Contribution Model*, 25 ENVTL. L. 549, 572-591 (1995). He does so in apportioning liability among multiple defendants because of his concern about the unfairness of holding a defendant jointly and severally liable when there are other defendants who contributed to the risk of disease who are insolvent. Yet apportionment can be on the basis of comparative responsibility, rather than risk apportionment, and joint and several liability can be modified if a jurisdiction wishes. See Restatement Third, Torts: Apportionment of Liability § 17, Reporters' Note to Comment *a* (detailing jurisdictions that have modified joint and several liability). Professor Boston favors risk-contribution apportionment when a plaintiff's smoking concurs with asbestos exposure in order to further incentives for persons to assume responsibility for safer lifestyles. Yet tort law does not impose liability (or reduce recovery) to provide deterrence unless the person has engaged in tortious conduct. Absent a finding of contributory negligence by the plaintiff, there is no basis for apportioning liability on the basis of causation to the plaintiff. Taken to its logical extreme, Professor Boston's risk-contribution apportionment approach would permit apportionment of liability to a plaintiff whose genotype contributed to the risk, once

that information is available, or even to exposure to sunlight or other environmental factors that also are risk factors for disease. Well-settled law does not permit apportionment of liability or causal contribution to a preexisting condition. See U. S. Fid. & Guar. Co. v. United States, 152 F.2d 46, 49 (2d Cir. 1945); Buchalski v. Universal Marine Corp., 393 F. Supp. 246, 248 (W.D. Wash. 1975).

Another basis for apportioning liability in cases like those discussed above is on the basis of damages. Thus, an asbestos manufacturer might claim that, although plaintiff's lung cancer was caused by exposure to asbestos, plaintiff's smoking would have caused death at an early age, and therefore the damages should be reduced. See Restatement Second, Torts § 924, Comment *e*. Because questions of damages are beyond the scope of this Restatement and because of the absence of any cases addressing this matter, this Restatement does not address this means of apportionment.

For a study of asbestos workers that finds increased risks relating to asbestos exposure, smoking, and relative risks similar in magnitude to those in Illustrations 4 and 5, see Piero Mustacchi, *Lung Cancer Latency and Asbestos Liability*, 17 J. LEGAL MED. 277 (1996).

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