CLEAR AS MUD — THE ROLE OF EPIDEMIOLOGICAL DATA IN ASSESSING ADMISSIBILITY UNDER DELAWARE RULE OF EVIDENCE 702

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I. OVERVIEW

Causation is an essential element in practically every legal theory of recovery, yet it is paramount in the field of tort litigation, especially toxic or mass tort litigation. For that reason, the admissibility of expert opinions on the issue of causation has become the preeminent battleground in tort litigation, perhaps to the chagrin of Delaware courts.[1] As such, this article will discuss the general rule governing the admissibility of expert opinions by Delaware courts and will specifically examine the role epidemiology plays in assessing scientific evidence in the form of expert testimony in toxic tort cases under Delaware Rule of Evidence 702 ("Rule 702").

Ever since the Delaware Supreme Court, in *M.G. Bancorporation, Inc. v. Le Beau*,[2] adopted the rule announced by the U.S. Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*[3] and its progeny, Delaware trial courts have been obligated to act as gatekeepers to prevent irrelevant and unreliable scientific evidence from entering the courtroom. To fulfill this obligation, trial judges must look behind the "scientific curtain" to determine whether the proffered scientific evidence, in the form of expert testimony, comports with the strictures of the scientific method. This task has become particularly important in the toxic tort context where the plaintiff is required to demonstrate that her exposure to some substance or chemical was responsible for causing her to develop, or contract a specific disease. Thus a plaintiff is required to prove both general causation – *i.e.*, that the substance is capable of causing the disease in question — as well as specific causation — *i.e.*, that the particular plaintiff's exposure to that substance caused that particular plaintiff to develop the disease. To prove causation, the plaintiff must rely on scientific evidence and frequently will attempt to marshal substantial quantities of different types of scientific evidence. One such type of scientific evidence will be in the form of epidemiology. "Epidemiology is the branch of medical science that studies the distribution and determinants of health-related states and events in populations."[4]

The role epidemiological evidence plays under Rule 702 in expert opinions can be somewhat convoluted, yet in recent years it has come into clearer focus with the Delaware Superior Court opinions in *Long v. Weider Nutrition Group,*

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1. *See* Wright v. Clark, C.A. No. 09C-03-201, 2010 Del. Super. LEXIS 295, at *4 (Del. Super. July 14, 2010) (noting that the court was tempted not to consider a motion under DEL. R. EVID. 702 filed after the deadline in the scheduling order "to slow the *Daubert*-motion-cottage-industry-train").

2. 737 A.2d 513 (Del. 1999).

3. 509 U.S. 579 (1993).

4. Long v. Weider Nutrition Group, Inc., C.A. No. 00C-12-249, 2004 Del. Super. LEXIS 204, at *9 (Del. Super. June 25, 2004).

Inc.[5] and *In re Asbestos Litigation*,[6] which was remanded for clarification but not overruled, *sub nom.*, by *General Motors Corp. v. Grenier* ("*Grenier I*"),[7] clarified by the Superior Court in *In re Asbestos Litigation; Grenier v. General Motors Corp.* ("*Grenier II*"),[8] and ultimately affirmed by the Supreme Court in *General Motors Corp. v. Grenier* ("*Grenier III*").[9] Reading *In re Asbestos* and *Grenier II* together, it is clear that while epidemiological evidence is not required, as a matter of law, for an admissible expert opinion under Rule 702, where epidemiological evidence exists the parties must address that evidence in a principled, scientifically methodological and reliable manner.

Part II of this article briefly discusses the U.S. Supreme Court's decision in the so-called *Daubert* trilogy, including *Daubert* itself, *General Electric v. Joiner*[10] and *Kumho Tire Co. v. Carmichael*,[11] and Delaware's adoption of the *Daubert* test as the proper interpretation of Rule 702. Part III briefly describes the field of epidemiology as well as its limits and benefits in supporting general causation opinions. Finally, Part IV explores the role epidemiological evidence plays in the determining the admissibility of general causation opinions under Delaware law.

II. *DAUBERT* BACKGROUND

A. The *Daubert* Trilogy

The history of the landmark U.S. Supreme Court case of *Daubert* has often been repeated, but its impact, as well as that of *Joiner* and *Kumho Tire,* cannot be understated. In *Daubert*, the U.S. Supreme Court unanimously held that the enactment of the Federal Rules of Evidence, and in particular Federal Rule of Evidence 702 ("Federal Rule 702") superseded the *Frye*[12] test, which had previously been used to assess the admissibility of expert opinions in the federal courts.[13] The *Daubert* Court held that Federal Rule 702 obligated trial judges to act as gatekeepers and admit only scientifically relevant and reliable expert testimony.[14] *Daubert* marked a sea change whereby trial court judges are now under a duty to ensure that irrelevant and unreliable expert testimony is not presented to the trier of fact.

With *Daubert*, the U.S. Supreme Court established a two-prong test to determine the admissibility of expert testimony pursuant to Federal Rule 702. To assess the first prong, or the relevancy prong, the U.S. Supreme Court stated that expert testimony cannot "assist the trier of fact to understand the evidence at issue or to determine a fact in issue"[15]

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5. 2004 Del. Super. LEXIS 204.

6. 911 A.2d 1176 (Del. Super. 2006).

7. 981 A.2d 524 (Del. 2009).

8. C.A. No. 05C-11-257, 2009 Del. Super. LEXIS 548 (Del. Super. Apr. 8, 2009).

9. 981 A.2d 531 (Del. 2009).

10. 522 U.S. 136 (1997).

11. 526 U.S. 137 (1999).

12. Frye v. United States, 293 F. 1013 (D.C. Cir. 1923).

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

14. *Id.*

15. *Id.* at 591 (quoting FED. R. EVID. 702).

under the rule unless it is "sufficiently tied to the facts of the case."[16] The standard of "helpfulness" embodied in Federal Rule 702 "requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility."[17] *Daubert* characterized this relevancy prong as one of "fit." The U.S. Supreme Court warned that "[f]it is not always obvious, … scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes."[18] Rather, in order for the expert evidence to assist the trier of fact it must "fit" the facts of the case and be connected to the pertinent inquiry, otherwise, it is inadmissible. For example, while it may seem that studies done on the effect of Substance X on rats may be relevant, those studies may actually not fit the facts of addressing the effect that same substance might have on humans because rats and humans are different species that may react completely differently to that substance. Further, such a study may not fit because the amount of the substance administered to the rats in the studies may have far exceeded the amount that a human would be exposed to on a proportional basis. Thus, such evidence would be inadmissible under *Daubert* and Federal Rule 702 because it does not fit the facts at issue.

With respect to the second prong, or the reliability of the proposed expert evidence, the U.S. Supreme Court held that the trial judge must determine whether such expert evidence is "ground[ed] in the methods and procedures of science."[19] *Daubert* identified four, nonexclusive factors the trial court could use to assess whether the proposed expert evidence is the reliable product of the scientific method: (1) testing, (2) peer review, (3) error rate and standards, and (4) general acceptance.[20] The U.S. Supreme Court, however, emphasized that the "inquiry envisioned by Rule 702 is … a flexible one. Its overarching subject is the scientific validity … of the principles that underlie a proposed submission. The focus, of course, must be solely on principles and methodology, not on the conclusions that they generate."[21] Thus, the fundamental edict of *Daubert* is that in order for expert evidence to be reliable, and thus admissible, that evidence must be based on the scientific method employed by the proffered expert in arriving at his or her opinion.[22]

In *Joiner*, four years after *Daubert*, the U.S. Supreme Court further clarified how trial judges are to perform their gatekeeping role under Federal Rule 702. *Joiner* involved allegations that workplace exposure to polychlorinated biphenyls (PCBs) promoted the development of small-cell lung cancer in the plaintiff, who was a long-time smoker with a family history of lung cancer. The District Court, applying *Daubert*, excluded the plaintiff's experts' opinions and the U.S. Court of Appeals for the Eleventh Circuit reversed after applying a "particularly stringent standard of review to the trial judge's exclusion of expert testimony."[23]

The U.S. Supreme Court overruled the Court of Appeals and held the abuse of discretion is the correct standard of review to apply to appeals of admissibility determinations under Federal Rule 702.[24] The Court then proceeded to

16. *Id.* (quoting United States v. Downing, 753 F.2d 1224, 1242 (3d Cir. 1985)).

17. *Daubert*, 509 U.S. at 591-92.

18. *Id*. at 591.

19. *Id.* at 590.

20. *Id.* at 593-94.

21. *Daubert*, 509 U.S. at 594-95.

22. *Id*. at 590 (explaining that "in order to qualify as 'scientific knowledge,' [under FED. R. EVID. 702] an inference or assertion must be derived by the scientific method")

23. Joiner v. General Elec. Co., 78 F.3d 524, 529 (11th Cir. 1996).

24. *Joiner*, 522 U.S. at 143.

review, and affirm, the District Court's decision to exclude the plaintiff's expert testimony as inadmissible under *Daubert* and Federal Rule 702.[25] The plaintiff argued that his experts' causation opinions were admissible because those experts properly relied on animal studies and epidemiology. The U.S. Supreme Court, however, rejected those arguments and held that the district court did not abuse its discretion in finding that the plaintiff's experts' opinions were nothing more than speculation.[26] The Court held that the plaintiff never explained "how and why the experts could have extrapolated their opinions" from animal studies so "far-removed" from the context of the plaintiff's own alleged exposure.[27] Additionally, the Court found that the four epidemiological studies the plaintiff's experts relied on were insufficient to support the experts' opinions.[28] The Court thus reiterated its earlier holding in *Daubert* that adherence to the scientific method was a prerequisite to an admissible expert opinion. In other words, it is not enough for an expert simply to cite various studies that are loosely connected to the issue of causation. Rather the trial court, in fulfilling its gatekeeping function, must determine that the studies the expert relied upon in arriving at her opinion do, indeed, validate that opinion. The *Joiner* Court famously stated that "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."[29]

Two years later, the U.S. Supreme Court again addressed the issue of the admissibility of expert evidence under *Daubert* and Federal Rule 702. In *Kumho Tire*, the Court was called upon to determine whether a tire-failure expert's testimony was admissible and, perhaps more fundamentally, whether the *Daubert* test applied to "engineers or other experts who are not scientists."[30] The Supreme Court held that *Daubert's* "gatekeeping" obligation applies to all expert testimony, both scientific and experience based, because "the trial judge's general 'gatekeeping' obligation - applies not only to testimony based on 'scientific' knowledge, but also to testimony based on 'technical' and 'other specialized' knowledge."[31]

In *Kumho Tire*, the U.S. Supreme Court emphasized that the test enunciated in *Daubert* is a flexible one, and that there may be many cases where the four nonexclusive factors identified in *Daubert* are inapplicable.[32] The *Daubert* test depends on "the particular circumstances of the particular case at issue"[33] and, thus, the trial court has "considerable

25. *Id*. at 146-47.

26. *Id*. at 146.

27. *Id.* at 144. The animal studies plaintiff's experts relied on were done on infant mice who were directly injected with massive doses of PCBs and developed a different type of cancer than the plaintiff. Whereas, the plaintiff was an adult, exposed to a much lower dose of PCBs, who developed a completely different type of cancer. In fact the U.S. Supreme Court noted that "[n]o study demonstrated that adult mice developed cancer after being exposed to PCB's." *Id.*

28. *Joiner*, 522 U.S. at 145-46. The first study failed to support the experts' opinions because, even though the study found a higher than expected lung cancer death rate among ex-employees, the study authors refused to conclude that PCB exposure caused lung cancer. The second study was insufficient because it did not find that the somewhat higher incidence of lung cancer deaths was statistically significant. The third was insufficient because it "made no mention of PCB's," and the fourth was insufficient because it examined exposure to numerous potential cancer-causing substances in addition to PCBs. *Id.*

29. *Id.* at 146.

30. *Kumho Tire*, 526 U.S. at 137, 141.

31. *Id*. (citing Fed. R. Evid. 702).

32. *Id.* at 150.

33. *Kumho Tire*, 526 U.S. at 152.

leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable" and relevant.[34] In the end, the trial court's gatekeeping function under *Daubert* "is to ensure the reliability and relevancy of expert testimony. It is to make certain that an expert, whether basing his testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."[35]

B. Rule 702 And Delaware's Adherence To *Daubert* And Its Progeny

A mere month after the U.S. Supreme Court decided *Kumho Tire*, the Delaware Supreme Court was called upon to assess the admissibility of expert testimony under Rule 702 in *M.G. Bancorporation, Inc. v. Le Beau*.[36] In *M.G. Bancorp.*, the Delaware Supreme Court explicitly "adopt[ed] the holdings of *Daubert* and [*Kumho Tire*] as the correct interpretation of the Delaware Rule of Evidence 702"[37] because Rule 702 is "identical to its federal counterpart."[38] Thus under *Daubert* and Rule 702, Delaware trial judges must serve as "gatekeepers" and, as such, "must decide 'whether the reasoning or methodology underlying the testimony is scientifically valid and … whether that reasoning or methodology properly can be applied to the facts in issue.'"[39] The *Daubert* trilogy is the operative test for the admissibility of expert evidence pursuant to Rule 702.

Additionally, the Delaware Supreme Court has outlined five factors to consider in determining whether proffered expert testimony is admissible under Rule 702: (1) whether the witness is qualified as an expert by knowledge, skill, experience, training or education; (2) whether the evidence is relevant and reliable; (3) whether the expert's opinion is based on information reasonably relied on by experts in the particular field; (4) whether the expert testimony will assist the trier of fact to understand the evidence or to determine a fact in issue; and (5) whether the evidence will create unfair prejudice, confuse the issues or mislead the trier of fact.[40] As clearly stated in *Daubert*, pursuant to Rule 702 these five factors are not inflexible. Rather trial judges "have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable."[41]

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34. *Id.* at 150.

35. *Id*. at 152.

36. 737 A.2d 513 (Del. 1999).

37. *Id.* at 521.

38. *Id.* at 522.

39. *Grenier III*, 981 A.2d at 536 (quoting *Daubert*, 509 U.S. at 592-93).

40. Eskin v. Cardin, 842 A.2d 1222, 1227 (Del. 2004); Minner v. Am. Mortgage & Guar. Co., 791 A.2d 826, 843 (Del. Super. 2000).

41. Garden v. State, 815 A.2d 327, 338 (Del. 2003) (quoting *Kumho Tire,* 526 U.S. at 152); *see also Grenier III*, 981 A.2d at 536 (noting that "the trial court has 'broad latitude' to determine whether any or all of the *Daubert* factors are 'reasonable measures of reliability in a particular case….'" (quoting *Kumho Tire,* 526 U.S. at 153)).

III. BACKGROUND ON EPIDEMIOLOGY

A. What Epidemiology Is And What Epidemiology Can Do

"Epidemiology is the field of public health and medicine that studies the incidence, distribution and etiology of disease in human populations."[42] Epidemiology, thus, looks at patterns of a disease amongst groups of humans to attempt to determine the nonlegal cause(s) of such diseases based on risk assessments. Because epidemiology looks for patterns of diseases based on some common factor, or exposure, it assumes that those patterns are not the product of chance — that there is some other force behind the observed disease patterns.[43] For this reason, epidemiology is most frequently used in toxic or mass tort actions to support opinions that exposure to a certain product, medicine, chemical, *et cetera* is capable of causing some type of harm or disease in humans, *i.e.*, another way of defining general causation. This type of expert causation opinion will be the focus of this article. Because epidemiology focuses on the distribution and etiology of diseases in groups, its use in causation opinions "focuses on the question of general causation (*i.e.*, is the agent capable of causing disease?) rather than that of specific causation (*i.e.*, did it cause disease in a particular individual?)."[44]

It is critical to emphasize that the field of epidemiology serves primarily to identify "agents that are associated with an increased risk of disease in groups of individuals, [to] quantif[y] the amount of excess disease that is associated with an agent, and [to] provide[] a profile of the type of individual who is likely to contract a disease after being exposed to an agent."[45] Importantly, epidemiology can only identify *an association* between a substance and a particular injury or disease, which *is not the equivalent of legal causation*.[46] An epidemiological association means that the relationship between exposure and the development of a disease "occur more frequently together than one would expect by chance."[47] Such an association is clearly distinct from legal causation, that "but for" the exposure the claimant would not have developed the disease. Epidemiology can only indicate that exposure to a substance increases the risk of a particular disease within that group of individuals, and can quantify the amount of the disease that is associated with exposure above the background rate of independently occurring disease. Lastly, because epidemiology generally studies disease causation (in the nonlegal sense) and prevention it can be used to furnish "a profile of the type of individual who is likely to contract a disease after being exposed."[48]

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42. Michael D. Green et al., Reference Manual on Scientific Evidence: Reference Guide on Epidemiology 333, 335 (2d ed. 2000); *see also Joiner*, 522 U.S. at 144 n.2. ("Epidemiological studies examine the pattern of disease in human populations."); *Long*, 2004 Del. Super. LEXIS 204, at *9 ("Epidemiology is the branch of medical science that studies the distribution and determinants of health-related states and events in populations."). The section on epidemiology is intended to provide a brief overview of the science. For a more in-depth analysis, including the potential confounding factors and potential applicability under the *Daubert* framework please refer to Green et al., *supra*. Additionally, etiology is a cause or origin of a disease or abnormal condition. Webster's Seventh New Collegiate Dictionary 286 (Merriam-Webster 1965).

43. Green et al., *supra* note 42, at 335.

44. *Id*. at 336 (citations omitted).

45. *Id*.

46. *Id*.

47. Green et al., *supra* note 42, at 336 n.8.

48. *Id*.

B. Types Of Epidemiological Studies.

For the purposes of this article, there are two major types of epidemiological studies: (1) experimental, and (2) observational. There are, in turn, four different subtypes of observational epidemiological studies. Experimental epidemiological studies are clinical trials. Experimental epidemiological studies involve two different groups of study participants where one group is intentionally exposed to a substance while the other group is not. Both groups are then evaluated to determine the impact of the substance on the group that received it. Experimental studies are generally considered the "gold standard" for determining the relationship, if any, between an agent and a disease.[49] Experimental studies are typically used to determine the safety and efficacy of new drugs or medical treatments and are often randomized, placebo controlled and double blinded to ensure that, to the greatest extent possible, the observed result is attributable to the exposure to the substance and not some other element.[50]

Due to ethical constraints, however, experimental studies may only be used where the substance to be studied is suspected of providing a benefit, *i.e.*, a previously undiscovered pharmaceutical compound, and not where the substance is thought to be harmful, *i.e.*, a previously unknown carcinogen. If the substance to be evaluated is thought to be harmful, researchers are limited to observational studies. Observational studies, therefore, are studies where the researcher "observes" a group who has been exposed to a substance and then compares the rates of a particular disease in the exposed group to another group who has not been exposed to the same substance.[51] With observational studies researchers cannot control all aspects of the study's subjects, such as diet, weight, exercise, *et cetera* in the same manner that researchers can in experimental studies, where the researchers handpick the subjects and can closely monitor all aspects of the study's subjects, as necessary. As such, other unwanted factors may influence the result of an observational epidemiological study. Because researchers in observational studies have no control over the characteristics of the subjects who were exposed to the substance be studied, they attempt to control for these unwanted factors with various techniques, including the design of the study discussed *infra*.

As noted above, there are four different subtypes of observational epidemiological studies: (1) cohort studies, (2) case-control studies, (3) cross-sectional studies, and (4) ecological studies. Cohort studies and case-control studies are the two main types of observational studies.[52] In a cohort study, also known as a prospective study or follow-up study,[53] "the researcher identifies two groups of individuals: (1) individuals who have been exposed to a substance that is considered a possible cause of a disease and (2) individuals who have not been exposed."[54] The researcher then observes both groups

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49. *Id.* at 338.

50. *Id.* Randomization is the practice of providing the experimental substance to the study participants in a random manner. The purpose of randomization is to attempt to minimize the impact of individual differences between study participants on the study's outcome. Placebo controlling is the practice of giving the nonexposed group a placebo. And, double blinding is the process of preventing both the study participants and those conducting the study from knowing which group receives the substance and which group does not. *Id.*

51. GREEN ET AL., *supra* note 42, at 339.

52. *Id.*

53. *Id.* at 340 n.17.

54. *Id.* at 340. Additionally cohort studies can include a number of different groups with differing levels of exposure to the suspect substance. *Id.* at 340 n.18.

for a specific amount of time and compares the proportions of both groups that develop the disease in question. Thus, cohort studies "measure and compare the incidence of disease in the exposed and unexposed ('control') groups … [and] take[] the exposed status of the participants (the independent variable) and examine[] its effect on incidence of disease (the dependent variable)."[55] Because the researcher must take his, or her, study subjects as they exist in observational cohort studies, the researcher has little control over the various characteristics of the individuals in either group. As a result, there exists the potential that any observed increased risk of the specific disease studied in the exposed group could be caused by a variable other than the substance being studied.[56] Therefore, researchers must carefully design the study to identify other factors that could be responsible for any observed, increased risk. And, if the data gathered includes other possible causal factors, researchers may use statistical methods to determine whether an association truly exists between the exposure to the substance in question and the specific disease at issue.[57]

In a case-control study, or retrospective study,[58] "the researcher begins with a group of individuals who have a disease (cases) and then selects a group of individuals who do not have the disease (controls)" and compares each group in connection with their level of prior exposure to the substance at issue.[59] A case-control study, thus, measures and compares the incidence of exposure between the cases and controls and "takes the disease status as the independent variable and examines its relationship with exposure, which is the dependent variable."[60] The rates of exposure in the two groups are then compared and the odds of developing the disease when exposed to the substance at issue are compared with the odds of developing the disease without exposure. The crucial difference between the cohort and case-control studies is that "cohort studies begin with exposed people and unexposed people, while case-control studies begin with individuals who are selected based on whether they have the disease or do not have the disease and their exposure to the agent in question is measured."[61] Despite these differences, the goal of both types of studies is to determine (1) if there is an association between exposure to the substance in question and a disease, and (2) the strength of that association.

The remaining two categories, cross-sectional studies and ecological studies are less pertinent to expert opinions on general causation. In cross-sectional studies, individuals are examined and the "presence of both the exposure of interest and the disease of interest is determined in each individual at a single point in time."[62] These studies "determine the presence (prevalence) of both exposure and disease in the subjects and do not determine the development of disease or risk of disease (incidence)."[63] In ecological studies, the researcher collects data about the group as a whole rather than about individuals in the group. In ecological studies, "overall rates of disease or death for different groups are obtained

55. Green et al., *supra* note 42, at 340.

56. *Id.* at 342.

57. *Id.*

58. *Id*. at 342 n.23.

59. Green et al., *supra* note 42, at 342.

60. *Id.* at 340.

61. *Id.*

62. *Id.* at 343.

63. Green et al., *supra* note 42, at 343.

and compared" with the objective being "to identify some difference between the two groups … that might explain differences in the risk of disease observed between the two groups."[64]

C. Interpretation Of The Results Of Epidemiological Studies

To reiterate, the goal of epidemiological studies is to determine whether an association exists between exposure to a substance and the development of disease. If there is such an association, then the strength of that association must also be analyzed. Generally, such an association exists when exposure to a substance and disease occur more often than would be expected by chance alone.[65] There are three different measures to state the strength of such an association: (1) relative risk, (2) an odds ratio, and (3) attributable risk. Each of these measures the extent to which exposure to a substance impacts the risk of disease.

First, relative risk is the ratio of the incidence rate of a disease in the exposed individuals versus the incidence rate of the same disease in the unexposed individuals. The "incidence rate" is the number of individuals in the cohort that develop the disease during a specific time period divided by the number of individuals in that group. Once the relative risk is calculated, it can generally be interpreted that a relative risk of 1.0 indicates that no association exists between exposure and disease because the same number of individuals who were exposed to the substance developed the disease as those who were not. A relative risk above 1.0 indicates a positive association between exposure and disease meaning that the risk of contracting the specific disease in those exposed to the substance is higher than those who were not exposed. In contrast, a relative risk below 1.0 indicates a negative association between exposure and disease meaning that exposure to the substance could have a curative or protective effect on the risk of developing the disease.[66] The size of the relative risk indicates the strength of that association. For example, a relative risk of 3.5 means the risk of disease in those exposed to the substance is three and half times higher than the risk of disease in those who were not exposed. Thus, relative risk is a quantitative expression of the association between exposure and disease.

Second, an odds ratio is similar to relative risk in that it is a quantitative expression of the association between exposure and disease; however, an odds ratio "approximates the relative risk when the disease is rare."[67] In a case-control study, the odds ratio is "the ratio of the odds that a case (one with the disease) was exposed to the odds that a control (one without the disease) was exposed."[68] Whereas in a cohort study, the odds ratio is "the ratio of the odds of developing a disease when exposed to a suspected agent to the odds of developing the disease when not exposed."[69] Because an odds ratio approximates the relative risk, the same general rules of interpretation apply, *i.e.*, an odds ratio of 1.0 indicates that there is no association between exposure and disease, whereas an odds ratio above 1.0 indicates a positive association and an odds ratio below 1.0 indicates a negative association.

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64. *Id*. at 344.

65. *Id.* at 348.

66. *Id*. at 349.

67. Green et al., *supra* note 42, at 350.

68. *Id*.

69. *Id*.

The third measurement, attributable risk, indicates the maximum amount of disease that can be "attributed" to exposure to the substance among the exposed individuals.[70] In other words, attributable risk is the proportion of a disease in the groups that can be credited to the exposure. To determine the attributable risk, the researcher would subtract the incidence rate in the unexposed group from the incidence rate in the exposed group and then divide the difference by the incidence rate in the exposed.[71] For example, if the incidence rate in the unexposed group is ten and the incidence rate in the exposed is fifty then the attributable risk is 80 percent (*i.e.*, 50-10 = 40; 40/50 = 80%). This would mean that 80 percent of the disease in the exposed group is attributable to the exposure to the suspect substance. This, however, is not the same as stating that 80 percent of the disease is caused by the exposure.

D. Types Of Errors That Could Result In An Incorrect Result

Even though a study may find a positive association, *i.e.*, a relative risk over 1.0, this alone does not necessarily mean that a true association exists. There are three reasons why a study may show a positive association where one does not truly exist: (1) chance or sampling error, (2) bias or systematic error, and (3) confounding.[72] Each of these phenomena "must be evaluated to extract a valid message from the study. Evaluation of these factors measures the 'internal validity' of an epidemiology study, that is, the extent to which the study's findings are viable and sound."[73]

1. Sampling Error

The first, significant source of a potential false positive is sampling error, *i.e.*, the risk that the study's findings may be due solely to "chance" and not a real, true association. Although there are a number of techniques, the three main techniques that are used to reduce or eliminate any sampling error are: (1) study design, (2) statistical significance, and (3) confidence intervals.[74] Study design can help alleviate the likelihood of sampling error by ensuring that the sample size is large enough to account for the possibility of chance affecting the outcome. By increasing the sample size, the researcher increases the likelihood that the results are associated with exposure to the substance being studied rather than mere happenstance. Increasing the sample size, however, cannot completely eliminate the possibility that chance has affected the study's outcome, thus epidemiologists must also use other techniques to attempt to control for sampling error.

The second key method for controlling for sampling error is to determine whether the study's results are statistically significant. In order for a study to be statistically significant, the *p*-value of that study must fall below the researcher's selected significance level. The *p*-value "represents the probability that a positive association would result from [chance] if no association were in fact present."[75] The most common significance level used is 5 percent. Therefore, in order for a

70. *Id*. at 351.

71. Green et al., *supra* note 42, at 352.

72. *Id*. at 354.

73. Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 592 (D.N.J. 2001). To put it another way, *Magistrini* explains that there are three reasons for a positive association "(1) bias (including confounding factors), (2) chance, and (3) real effect." *Id.* at 591.

74. Green et al., *supra* note 42, at 354-55.

75. *Id*. at 357.

study to be statistically significant the probability that the observed, positive association resulted from chance would need to be less than 5 percent.

The third key method for controlling for sampling error is by employing confidence intervals to provide yet another level of validity. "A confidence interval is a range of values calculated from the results of a study, within which the true value is likely to fall; the width of the interval reflects random error."[76] Confidence intervals show "the relative risk determined in the study as a point on a numerical axis [and] also display[] the boundaries of relative risk consistent with the data found in the study on one or several selected levels of … statistical significance."[77] Confidence intervals can allow the researcher to make a more sophisticated determination of the inferences to be drawn from the associations found in the study because they display the ranges of relative risk based on several levels of statistical significance.[78]

2. Bias

The second major culprit for an observed association where there truly is none is bias, or systematic error. Bias is simply anything that makes the two groups being compared different in any way other than the variable being studied, *i.e.*, exposure to the substance in question.[79] While the majority of epidemiological studies contain some bias, the sources of the bias need to be examined as bias can produce incorrect results. There are two major types of bias: (1) selection bias, and (2) information bias. "Selection bias refers to the error in an observed association that is due to the method of selection of cases and controls (in a case-controlled study) or exposed and unexposed individuals (in a cohort study)."[80] For example, studies that are based on hospital populations will most likely suffer from selection bias because the cases and controls, or exposed and unexposed, individuals will all be from a population that has some type of medical condition, which is serious enough to require hospitalization.[81] The same goes for studies based on prison populations or members of the armed forces — each group has some other factor common to all that is not necessarily the factor that is the subject of the study. Therefore, the observed association between the substance and the disease needs to be scrutinized to determine whether it is a true association, and not the result of the method of selecting the groups to be included in the study.

Information bias, on the other hand, "refers to the bias resulting from inaccurate information about the study participants regarding either their disease or exposure status."[82] Information bias, therefore, is the error in measuring the data that forms the basis of the study.[83] For example, researchers often must rely on individuals to accurately recount their level of exposure or past medical history and some individuals may be better historians than others for various reasons.[84] Therefore, the method of data collection needs to be scrutinized as well in assessing the results of a study.

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76. *Id*. at 360.

77. *Id*. at 360-61.

78. Green et al., *supra* note 42, at 360-61.

79. *Magistrini*, 180 F. Supp. 2d at 592.

80. Green et al., *supra* note 42, at 363.

81. *Id*. at 364.

82. *Id*. at 365.

83. *Id*.

84. See Green et al., *supra* note 42 at 366-68 for a more detailed explanation and discussion on informational bias.

3. Confounding

The third major, potential reason why an observed association may not be a true or real association is the problem of confounding. Confounding is where the association observed is the result of some other factor present in the studied groups other than the exposure that was to be studied.[85] It is where some other factor present in the studied groups is also a risk factor for the disease. For example, the presence of differences in residence, socioeconomic status, age or family medical history can be confounding factors in a study intended to determine whether there is an association between occupational exposure to a substance and a certain disease. To the extent the confounding factors can be identified, those confounding factors can be controlled through the study design, such as separating the groups to be studied into groups of smokers versus nonsmokers.[86] Confounding factors can be further controlled by using the statistical techniques of stratification and multivariate analysis.[87] Stratification involves the use of statistical methods to combine the results of different exposure levels (or strata) to the confounding factor to arrive at one overall estimate of risk.[88] Multivariate analysis involves using mathematical modeling to "describe the simultaneous effect of exposure and confounding factors on the increase in risk."[89]

Most importantly, confounding is inherent in observational epidemiological studies because, in observational studies, individuals are not randomly assigned to the groups being studied. Rather, the researcher must take the individuals as they find them, including all the other aspects of individuals' lives that may or may not be related to the topic being investigated. As such "[c]onfounders … do not reflect an error made by the investigators; rather they reflect the inherently 'uncontrolled' nature of observational studies."[90] Thus, practically every observational epidemiological study will be confounded in one way or another and the key is for researchers to identify and mitigate the effects of confounding.

E. Methods For Combining Multiple Studies To Produce A Single Result

When faced with numerous epidemiological studies with different findings an epidemiologist may conduct a meta-analysis of those studies. Meta-analysis is a method of combining the results of numerous different studies into a single value of the risk.[91] In a meta-analysis, studies are assigned different weights in proportion to the different attributes of the studies being combined, including, *inter alia*, the studies' population sizes. Meta-analysis, therefore, "is a way of

85. *Id*. at 369.

86. *Id*. at 372.

87. *Id*. at 373.

88. Green et al., *supra* note 42, at 373.

89. *Id*. For a more detailed discussion of stratification see *id.* For a more detailed discussion of multivariate analysis see Daniel L. Rubinfeld, et al., Reference Manual on Scientific Evidence: Reference Guide on Multiple Regression 179 (2d ed. 2000).

90. Green et al., *supra* note 42, at 371.

91. *See In re* Paoli Railroad Yard PCB Litigation, 916 F.2d 829, 856 (3d Cir. 1990) ("Meta-analysis involves combining the results of different epidemiological studies done by other scientists, and re-analyzing the combined data to see if the data, *in toto,* renders different results than the individual studies done with a smaller data sample."). In *Paoli,* which is a pre-*Daubert* opinion, the Third Circuit overruled the District Court's exclusion of the plaintiff's expert's meta-analysis based, in part, on an incomplete record.

systematizing the time-honored approach of reviewing the literature, which is characteristic of science, and placing it in a standardized framework with quantitative methods for estimating risk."[92] Meta-analysis is typically employed in combining the results of randomized clinical trials where the studies to be combined are carefully controlled and the studies share many important methodological attributes.[93] It is in the clinical trial context where meta-analysis is most appropriate.

When meta-analysis is employed with observational studies, however, it is fraught with problems. Such as, how does the researcher assign weights to the different studies and what is the researcher's methodology for assigning those weights? The most significant problem, however, is that the very method of conducting a meta-analysis masks "the differences among the individual studies included in the meta-analysis and the reasons for the differences."[94] These differences "are important in themselves and need to be understood" in order to properly assess the weight of the various studies' outcomes.[95] In other words, any bias and confounding can be downplayed or glossed over in a meta-analysis of observational epidemiological studies.

F. Epidemiological Association And General Causation

As noted above, an epidemiological study that demonstrates an association between exposure to a substance and an increased risk of developing an adverse health effect is not the same as a finding that exposure to a substance *caused* that adverse health effect. In other words, a well controlled and designed study that finds a statistically significant increased association between exposure and a disease to a 95 percent confidence level where the confounding factors have been analyzed does not itself indicate that exposure to that substance "causes" the observed disease. In fact, "[t]he strong consensus among epidemiologists is that conclusions about causation should not be drawn, if at all, until a number of criteria have been considered."[96] These criteria, often referred to as the Bradford Hill considerations[97] are: (1) temporal relationship; (2) strength of the association; (3) replication of findings; (4) evidence of a dose-response relationship; (5) biological plausibility; (6) consideration of alternate explanations; (7) specificity of the association; and (8) consistency of the relationship.[98]

While an entire article could be devoted to the Bradford Hill considerations this, unfortunately, is not that article. That said, a short explanation of the Bradford Hill considerations is necessary. First "temporal relationship"

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92. Green et al., *supra* note 42, at 380.

93. *Id*.

94. *Id*. at 381.

95. *Id*.

96. Merrell Dow Pharm., Inc. v. Havner, 953 S.W.2d 706, 718 (Tex. 1997).

97. These criteria or "viewpoints" are referred to as the Bradford Hill criteria because they were first developed by Sir Austin Bradford Hill in his article: *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965).

98. Green et al., *supra* note 42, at 375; *see also Magistrini*, 180 F. Supp. 2d at 592-93 (identifying the Bradford Hill criteria); *Havner*, 953 S.W.2d at 718 n.2. *See also Grenier II*, 2009 Del. Super. LEXIS 548, at *30-33 (referencing the Bradford Hill criteria and reciting the nine factors: "plausibility, coherence, strength of association, consistency of observed associations, biological gradient, experiment, analogy, specialty of the association, and temporality") (citations omitted); *In re Asbestos*, 911 A.2d at 1190 (same).

or "temporality" means that the exposure to the substance must occur before development of the disease. While there can be a true causal relationship without the presence of certain factors, temporality is not one of them; temporality is required for a finding of causation.[99] Second, "strength of the association" refers to the relative risk of the association, as that is exactly what relative risk measures. "The higher the relative risk, the stronger the association and the lower the chance that the effect" is based on any bias or confounding factor.[100] A lower relative risk, however, does not mean there is no casual relationship; it could simply mean that the possible biases or confounding factors will need to receive greater scrutiny.[101] Third, "replication of findings" means the particular study's findings are capable of being replicated in different studies under different circumstances.[102] While replication is not essential, any variances in the results between the different studies will need to explored prior to a determination of causation.[103] Fourth, "dose-response" refers to whether an increase in exposure results in an increase in the risk of disease.[104] The presence of a dose-response is a strong indicator of causation; however, some substances exhibit a "threshold phenomenon" whereby exposure to a certain dose results in disease but there is no increased risk with higher doses.[105] Fifth, "biological plausibility" refers to whether the observed association is consistent with "existing knowledge about the mechanisms by which the disease develops."[106] Biological plausibility is sometimes referred to as the "mechanism of action" and can be a difficult criterion to assess because it depends, for the most part, on the current state of scientific knowledge. Sixth, "consideration of alternate explanations" simply refers to whether potential sources of biases or confounding factors have been considered and either ruled out or reconciled with the observed results. Seventh, "specificity of the association" refers to whether exposure to the substance is associated with one disease or type of disease rather than a wide variety of diseases.[107] The common example would be asbestos and mesothelioma. While, evidence of specificity can strengthen a claim of causation, the lack of such evidence does not weaken it when there is a plausible explanation. Finally, "consistency of the relationship" refers to whether the results are consistent with other studies.

In the end, there is no special formula for using the Bradford Hill criteria to determine whether causation exists, as some factors may be missing even where a true causal relationship exists, and vice versa.[108] "Drawing causal inferences after finding an association and considering [the Bradford Hill] factors requires judgment and searching analysis … and … [thus] [w]hile the drawing of casual inferences is informed by scientific expertise, it is not a determination that is made by using scientific methodology."[109]

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99. Green et al., *supra* note 42, at 376.

100. *Id*.

101. *Id*. at 376-77.

102. *Id*. at 377.

103. Green et al., *supra* note 42, at 377-78.

104. *Id*. at 377.

105. *Id*.

106. *Id*. at 378.

107. Green et al., *supra* note 42, at 379.

108. *Id*. at 375; *see also In re Asbestos*, 911 A.2d at 1190 ("None of these criteria stand alone; they are all important when considering the issues of association and risk.").

109. Green et al., *supra* note 42, at 375.

IV. ANALYSIS

A. Epidemiological Data Is Not Required Under Rule 702 For An Admissible Expert Causation Opinion

Both the Delaware Supreme Court and Delaware Superior Court have explicitly held that epidemiological data is not required, as a matter of law, for an admissible general causation opinion.[110] The Superior Court first announced this rule in *Long v. Weider Nutrition Group* and in doing so adopted the reasoning of several federal courts that had announced a similar rule.[111] *Long* involved a *Daubert* challenge to the plaintiff's causation experts where the plaintiff claimed that the decedent's death due to cardiac hypertrophy was caused by the use of dietary supplements containing significant amounts of ephedra/ephedrine and caffeine.[112] The *Long* defendants argued that the plaintiff's experts' general causation opinions, *i.e.*, that dietary supplements containing ephedra/ephedrine and caffeine could cause cardiac hypertrophy, were unreliable because there were no epidemiological studies that established an association between the use of such products and sudden adverse cardiac side effects.[113] The plaintiff agreed that there were no such epidemiological studies. Yet the plaintiff argued that such studies were unnecessary considering the other reliable information the experts had relied on, including *inter alia*, studies finding that ephedra in nutritional supplements produces cardiovascular stimulant effects; that ephedra is similar to other substances known as sympathomimetics; studies finding that sympathomimetics can produce sudden adverse cardiac side effects; and, the fact that the FDA banned the sale of all ephedra products after finding that the risks outweighed the benefits.[114] The *Long* court agreed with the plaintiff: "As a matter of public policy, courts should not be hampered in the search for truth by the rigid proposition that no expert, however qualified, can reliably opine on the causal link between a toxic substance and injury without epidemiological studies…."[115] The holding in *Long* fits within the flexible framework of the test for admissibility under *Daubert*, *Kumho Tire* and Rule 702.[116]

The Superior Court, reiterated and reestablished the rule that epidemiological data is not required, as a matter of law, for an admissible general causation opinion in *In re Asbestos* and clarified that holding in *Grenier II*, which was

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110. *Grenier III*, 981 A.2d at 539 ("[T]here is no *a priori* requirement that an expert opinion be based on epidemiology in order to be admissible."); *Long*, 2004 Del. Super. LEXIS 204, at *21 ("Epidemiological studies are not required in every case as a threshold for the admission of an expert opinion as to the general causation relationship between and allegedly toxic substance and a plaintiff's injury or death."); *see also In re Asbestos*, 911 A.2d at 1190 (stating that "epidemiology is not required, as a matter of law, to establish general causation in every case").

111. *Long*, 2004 Del. Super. LEXIS 2004, at *19 n.20 (collecting cases).

112. *Id*. at *2-4.

113. *Id.* at *16.

114. *Id*. at *16-18.

115. *Long*, 2004 Del. Super. LEXIS 2004, at *18.

116. *See*, *infra*, Parts II.A and B discussing the *Daubert* trilogy and the Delaware Supreme Court's adoption of *Daubert* as the operative interpretation of Del. R. Evid. 702. The *Long* opinion also addresses the admissibility of expert opinions based on the process of differential diagnosis. The differential diagnosis aspects of *Long* are not addressed in this article, which focuses on the narrow issue of epidemiology in the admission of expert causation opinions under *Daubert* and Del. R. Evid. 702. The issues surrounding the admission of opinions based on differential diagnoses is left for another day and another article.

ultimately affirmed in *Grenier III*. In *In re Asbestos*, the Superior Court was faced with a *Daubert* challenge to the plaintiff's expert causation opinion that exposure to asbestos-containing automotive friction products, *i.e.*, clutches and brakes, can cause asbestos related diseases.[117] The defendants claimed that the plaintiff's expert opinion was inadmissible, *inter alia*, because it contradicted all the available occupation-specific epidemiological studies that found no association (or even a negative association) between exposure to automotive friction products and asbestos-related diseases.[118] "Stated differently, when considering the link between toxic exposure and human disease, does epidemiological evidence, when it exists, trump all other science for purposes of testing the reliability of a scientific hypothesis and assessing the reliability of a scientific conclusion?"[119] The Superior Court answered that question in the negative stating that parties "need not support their general causation case with epidemiological evidence as a matter of law. Other scientific evidence, if sufficiently relevant and reliable, may suffice."[120] The Supreme Court ultimately affirmed this aspect of the opinion stating that "there is no *a priori* requirement that an expert opinion be based on epidemiology in order to be admissible."[121]

In the end, because epidemiology does not "trump" all other scientific data in the context of general causation[122] it also cannot form the sole basis of an admissible general causation opinion. The flexible framework of *Daubert* and Rule 702 does not allow for such a formulaic approach either for or against admission of general causation opinions. Therefore, it is simply insufficient to a party to rely exclusively on epidemiology to support an expert general causation opinion, or as the grounds to exclude an expert general causation opinion.

B. The High Level Of Other Scientific Data Required In The Absence Of Epidemiological Data To Demonstrate An Admissible Expert Opinion

Even though epidemiology has its flaws and is not required by Delaware law, well designed and controlled epidemiological studies are generally regarded as the best evidence for demonstrating general causation.[123] Therefore, the lack of such evidence sets a high threshold for a plaintiff to overcome in proffering an admissible general causation opinion

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117. *In re Asbestos*, 911 A.2d at 1178.

118. *Id.* at 1179. *In re Asbestos* and the *Grenier* line of cases address numerous issues pertinent to the admissibility of expert opinions and asbestos litigation in general. This article, however, will not address those points. This article addresses only the narrow issue of the use of epidemiological evidence in assessing admissibility under DEL. R. EVID. 702 and the holding that such evidence is not required, as a matter of law.

119. *In re Asbestos*, 911 A.2d at 1181.

120. *Id.* at 1209.

121. *Grenier III*, 981 A.2d at 539.

122. *In re Asbestos*, 911 A.2d at 1210.

123. Norris v. Baxter Healthcare Corp., 397 F.3d 878, 882 (10th Cir. 2005) (holding "that epidemiology is the best evidence of general causation in a toxic tort case…. While the presence of epidemiology does not necessarily end the inquiry, where epidemiology is available, it cannot be ignored. As the best evidence of general causation, it must be addressed.") (citations omitted); *see also* Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1198 (11th Cir. 2002) ("Epidemiology … is generally considered to be the best evidence of causation in toxic tort actions."); Soldo v. Sandoz Pharm. Corp., 244 F. Supp. 2d 434, 532 (W.D. Pa. 2003) ("Epidemiology is the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease.") (citation and internal quotations omitted).

under Rule 702. As such, the level of other scientific data the plaintiff must marshal is substantial, as evidenced by the amount and type of scientific evidence present in both *Long* and *In re Asbestos*.

In *Long* the other scientific evidence plaintiff's experts relied on was substantial enough to meet this high threshold.[124] The plaintiff's expert was able to rely on the fact that the FDA banned the sale of all ephedra products after finding that the risks outweighed the benefits and that numerous national organizations, including, the American Medical Association, the American Heart Association, the U.S. Navy and the National Football League had accepted the connection between ephedra and sudden adverse events, including significant cardiac problems.[125] The expert in *Long* also cited several studies finding that ephedrine and other sympathomimetics could lead to cardiac issues and even death.[126] Moreover, the *Long* expert testified that there was "no scientific basis to presume that ephedrine taken as a dietary supplement would have different clinical effects that [sic] ephedra in prescription drug form."[127] Thus, while the expert in *Long* was not able to point to epidemiology as support for his general causation opinion, he was able to point to the findings of at least twelve different government agencies and private organizations that had come to the same conclusion as well as other scientific evidence demonstrating the same causal relationship with the same substance, albeit in a pharmaceutical product rather than in a dietary supplement product. *Long*, therefore, demonstrates the high threshold of data that an expert's proponent would have to marshal to meet the requirements of Rule 702 in the absence of reliable epidemiological data.

The *In re Asbestos* and *Grenier* line of opinions reiterate this point, but for different reasons. In *Grenier II*, the Superior Court clarified its holding in *In re Asbestos* and ultimately arrived at the same conclusion — admitting the general causation opinions. In *Grenier II*, the experts started from the scientifically accepted premise that chrysotile asbestos can cause asbestos related diseases, which is supported by available epidemiological data. The experts then "conducted research to determine that friction products contain a significant amount of chrysotile asbestos, and conducted further research to conclude that working with friction products … can release respirable chrysotile fibers in amounts sufficient to cause disease."[128] Additionally, the experts testified that they were not aware of any credible evidence to support the defendants' hypothesis that the process used to manufacture friction products somehow changed the chrysotile asbestos fibers such that they were no longer capable of causing disease.[129] The plaintiff's experts admitted that none of the occupation-specific epidemiological studies supported a positive association between asbestos-related disease and exposure to friction products.[130] However, plaintiff's experts pointed out the numerous confounders and structural defects in the occupation-specific epidemiological studies the defendants claimed demonstrated a negative association between exposure to friction products and asbestos-related diseases.[131] Based on this, the Superior Court found that the occupation-specific epidemiological studies

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124. *Long*, 2004 Del. Super. LEXIS 204, at *16-20.

125. *Id.* at *17-18.

126. *Id.* at *17.

127. *Id.*

128. *Grenier II*, 2009 Del. Super. LEXIS 548, at *31-32.

129. *Id.* at *22-23, 39-40.

130. *Id.* at *34.

131. *In re Asbestos*, 911 A.2d at 1210.

were equivocal.[132] Perhaps more importantly, the Superior Court stated that epidemiology serves a less significant role in the asbestos context because the background rate for asbestos-related diseases is so low and those diseases are "signature" diseases.[133] Therefore, in the *Grenier* line of opinions, the experts overcame the fact that the occupation-specific epidemiology did not support a positive association (and in defendants' opinion, demonstrated a negative association between exposure to friction products and asbestos-related diseases) by relying on other scientific data as well as "the abundant epidemiological evidence of a positive association between exposure to chrysotile and asbestos disease."[134] Outside of the asbestos context, where epidemiological evidence would not have such a limited role, the fact that the occupation-specific epidemiology did not demonstrate a positive association between exposure and disease would, no doubt, receive more weight than it did in *Grenier II* and *In re Asbestos*.

Despite the fact that epidemiological data is not required as a matter of law, the typical case, toxic tort or otherwise, will not fall into the mold of *Long* and *Grenier*. Thus a plaintiff whose opinion is not supported with reliable epidemiological studies will need a substantial amount of otherwise reliable scientific evidence to demonstrate an admissible opinion under Rule 702.

C. The Role Of Epidemiological Data Under Rule 702

1. Epidemiological Evidence, Where It Exists, Must Be Addressed

As noted by the U.S. Court of Appeals for the Tenth Circuit in *Norris v. Baxter Healthcare Corp.*, "[w]hile the presence of epidemiology does not necessarily end the inquiry, where epidemiology is available, it cannot be ignored. As the best evidence of general causation, it must be addressed."[135] While not formally adopted by any Delaware court, the *Norris* rule succinctly articulates the rule applied by *Long* and the *Grenier* line of opinions — where epidemiological evidence exists it must be addressed. In *Long*, the Superior Court was faced with a situation where there were no "stud[ies], using generally-recognized epidemiological methodology, that show[] what percentage of the population has any adverse reaction after using a dietary supplement containing ephedra and caffeine."[136] Thus, in such a situation where there are no epidemiological studies to rely on, then the lack of such data alone would not be grounds for exclusion of the expert opinion under *Daubert* and Rule 702.[137] The other scientific evidence relied upon to support the expert's general causation opinion, however, must still be reliable under *Daubert* and Rule 702.

Where epidemiological evidence does exist, either in support of or in opposition to the proffered expert opinion, the proponent of that opinion will have to "at least address it with evidence that is based on medically reliable and sci-

132. *Grenier II*, 2009 Del. Super. LEXIS 548, at *36.

133. *Id.* at *35.

134. *Id.*

135. *Norris,* 397 F.3d at 882.

136. *Long*, 2004 Del. Super. LEXIS, at *11-12.

137. *See also Norris,* 397 F.3d at 882, which expands the rule from there simply being no studies available to where there are no studies that contradict the expert's opinion. The *Norris* court held that "[i]n cases where there is no epidemiology challenging causation available, epidemiological evidence would not necessarily be required." *Id.* This holding is somewhat obvious. Yet, if there were no studies contradicting the expert's opinion, it would reasonable to believe that the expert would include that fact in his opinion.

entifically valid methodology."[138] In *Norris*, the plaintiff's experts opined that silicone breast implants caused plaintiff's systemic autoimmune disease, despite the fact that there existed a mountain of reliable epidemiological studies that found no reliable association between silicone breast implants and systemic autoimmune disease.[139] The Court of Appeals affirmed the District Court's exclusion of plaintiff's experts' opinions because both had ignored or discounted the extensive epidemiological evidence to the contrary without any explanation. Instead both proffered experts relied, almost entirely, upon their own personal observations to support their conclusions; observations that contradicted the epidemiological evidence.[140]

The *Norris* rule is also consistent with the holdings of *In re Asbestos* and later clarified and reiterated in *Grenier II*. In *In re Asbestos*, plaintiffs' experts did not ignore and dismiss without explanation the defendants' occupation-specific epidemiological evidence. Rather, plaintiffs' experts disagreed with the defendants' characterization of the occupation-specific epidemiological data, critiqued defendants' occupation-specific epidemiological studies, and cited to the well-accepted epidemiological evidence that general exposure to chrysotile asbestos can cause asbestos-related diseases.[141] The Superior Court, thus, determined that the occupation-specific epidemiological data was "equivocal" and based on the

> disagreement between two "well-credentialed camps of scientists" with respect to the meaning and importance of the occupation-specific epidemiology, … determined that it would not decide who was right and who was wrong … but would instead allow the parties to present their scientifically sound methodologies and conclusions to the jury for resolution.[142]

As such, where epidemiological data exists, the proponent of the expert general causation opinion must address that data in order to comply with *Daubert* and Rule 702.

Therefore, where epidemiological studies do exist, in order for those studies to support the proffered general causation opinion those studies must be properly controlled, designed and reliable. As the U.S. Supreme Court held in *Joiner*, epidemiological studies that do not report a statistically significant association between exposure to the substance in question and the disease, that lack proper controls and that examine substances other than the substance in question (*i.e.*, do not fit the facts of case) cannot be used to support an admissible expert general causation opinion that exposure to the substance can cause disease.[143]

2. Methods For Assessing Epidemiological Evidence To Ensure It Is Reliable

Thus, under *Daubert* and Rule 702, the trial court must analyze epidemiological studies to determine whether they can provide a reliable foundation for the expert's general causation opinion in keeping with the scientific method. In fulfilling its gatekeeping role the trial court must thoroughly evaluate the studies to determine whether the expert was

138. *Id*.

139. *Id*. at 886.

140. *Id*. at 884-86.

141. *In re Asbestos*, 911 A.2d at 1209-10; *Grenier II*, 2009 Del. Super. LEXIS 548, at *34-36.

142. *Grenier II*, 2009 Del. Super. LEXIS 548, at *36 (quoting *In re Asbestos*, 911 A.2d at 1210).

143. *Joiner*, 522 U.S. at 145-46.

justified in relying on those studies.[144] Put another way, the trial court must ensure that "the expert's opinion is based upon information reasonably relied upon by experts in the particular field."[145] In doing so, the trial court must evaluate the studies with respect to at least four different areas.[146] First, the trial court would need to identify whether the study found an association, *i.e.*, was the relative risk higher than 1.0, and then determine whether the relative risk is sufficiently high to support a causation opinion. For example, a study could result in a relative risk of 1.1, which equates to only a 10 percent increase in risk in the exposed group versus the nonexposed group. Such a relative risk would signify a positive association between exposure and disease; albeit a weak association that arguably would not support an admissible general causation opinion.[147]

Other courts have held that an association of less than a 2.0 relative risk cannot support a reliable, admissible general causation opinion. "A relative risk of 2.0 thus implies a [50 percent] likelihood that the agent caused the disease. Risks greater than 2.0 permit an inference that the plaintiff's disease was more likely than not caused by the agent."[148] In other words because "the threshold for concluding that an agent was more likely than not the cause of an individual's disease is a relative risk greater than 2.0,"[149] any relative risk below 2.0 cannot meet the proponents burden of proof on causation. That is, the proponent of the causation opinion would not be able to demonstrate that the plaintiff's disease was more likely than not caused by the exposure to the substance where the relative risk was less that 2.0, *i.e.*, less than 50 percent. Additionally, at least one court has suggested that a relative risk of less than 3.0 denotes only a weak association.[150]

Second, the trial court would need to assess whether the study adequately controlled for the possibility that the association was caused by chance, or sampling error, rather than a true association. To that end the trial court, acting as the gatekeeper, would need to closely look at the study's design to determine, *inter alia*, whether the sample size was large enough to address the possibility that the results were caused by chance. The trial court would also need to ensure that the results were statistically significant to a 95 percent confidence level.

Third, the trial court would need to assess whether the study was affected by any bias — or systemic error — that would lead to an incorrect, unreliable result. As such, the trial court would need to assess the likelihood of any possible

144. *Daubert*, 509 U.S. at 589; *see generally Joiner*, 522 U.S. at 144-47 (analyzing the studies plaintiff's expert relied on to hold that the district court did not abuse its discretion in excluding the expert's opinion as unreliable).

145. *Eskin*, 842 A.2d at 1227 (citations and internal quotation marks omitted).

146. *See* Parts II.C and D of this article, *supra*, generally outlining the methods for interpreting epidemiological studies and identifying the possible sources of and solutions to errors in epidemiological studies.

147. Allison v. McGhan Med. Corp., 184 F.3d 1300, 1315 (11th Cir. 1999) (affirming the District Court's exclusion of an epidemiological study that only reported "a relative risk of only 1:24, a finding so significantly close to 1.0 that the court thought the study was not worth serious consideration for proving causation").

148. *Id.* at 1315 n.16. The *Allison* court also held that "the threshold for concluding that an agent more likely than not caused a disease is 2.0. A relative risk of 1.0 means that the agent has no causative effect on incidence. A relative risk of 2.0 thus implies a 50% likelihood that the agent caused the disease. Risks greater than 2.0 permit an inference that the plaintiff's disease was more likely than not caused by the agent." *Id.* at 1315 n.16. This 2.0 threshold has been adopted by various other courts including *Magistrini*, 180 F. Supp. 2d at 591, and *Siharath v. Sandoz Pharmaceuticals Corp.*, 131 F. Supp. 2d 1347, 1356 (N.D. Ga. 2001).

149. *Magistrini*, 180 F. Supp. 2d at 591 (*quoting* GREEN ET AL., *supra* note 42, at 384).

150. *See Havner*, 953 S.W.2d at 719 (noting "that some of the literature indicates that epidemiologists consider a relative risk of less than three to indicate a weak association" and citing to various statements made by influential scientists corroborating that sentiment).

selection bias and the effect such selection bias would have on the outcome. The trial court would also need to assess whether any information bias could have impacted the study's results by scrutinizing the method of data collection in the study.

Fourth, and finally, the trial court would need to identify whether the study's result was affected by any confounding factor(s) and whether those confounding factors were properly controlled for by the researcher through the study's design and/or the use of stratification and multivariate analysis. The trial court would also need to assess whether any of those confounders, if uncontrollable, could have a negative impact on the study's results. If after thoroughly scrutinizing the epidemiological data, the trial court is satisfied that the study can form the basis of the expert's opinion then that general causation opinion can be submitted to the jury under *Daubert* and Rule 702.

It is along this line that it appears the *Long* opinion may have deviated from the teachings of *Daubert* and *Joiner*. In holding that epidemiology is not required as a matter of law for an admissible expert general causation opinion under Rule 702, the Superior Court stated:

> As a matter of public policy, courts should not be hampered in the search for truth by the rigid proposition that no expert, however qualified, can reliably opine on the causal link between a toxic substance and injury without epidemiological studies *conducted according to strict guidelines*.[151]

The addition of the phrase "*conducted according to strict guidelines*" would appear to indicate that the *Long* court is dispensing with the requirement that in order for epidemiological studies to form the basis of an admissible opinion those studies need to be well-controlled and report a statistically significant positive association. The U.S. Supreme Court was clear in *Daubert* and *Joiner* that in order for epidemiological studies to be admissible, those studies must be conducted according to the scientific method, including proper epidemiological protocols.[152] And those opinions were explicitly adopted by the Delaware Supreme Court as the correct interpretation of Rule 702 in *M.G. Bancorp*.[153] Quite simply, inconclusive or sloppily-done science can never be reliable under *Daubert*. Thus, in order for epidemiological, or any scientific, evidence to be admissible it must be *conducted according to strict guidelines*, which are necessary to comply with the scientific method.

3. Epidemiology's Role In The Bradford Hill Considerations

Epidemiology is a key component in assessing the Bradford Hill considerations. As noted above, a finding of a positive association is not the same as a determination of causation. For that reason, before arriving at a potentially admissible general causation opinion, an expert must assess the Bradford Hill considerations.

Without epidemiological data, it is practically impossible to assess the "strength of the association" let alone demonstrate that an association even exists.[154] Relative risk, by definition, measures the strength of the association. Yet,

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151. *Long,* 2004 Del. Super. LEXIS 204, at *18 (emphasis added).

152. *Daubert*, 509 U.S. at 590 (holding that "in order to qualify as 'scientific knowledge,' [pursuant to FED. R. EVID. 702] an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation — *i.e.*, 'good grounds,' based on what is known"); *Joiner*, 136 U.S. at 146-47 (holding that because the epidemiological studies relied upon by the experts were not sufficient due to various scientific shortcoming to support the experts conclusions and thus were properly excluded).

153. *M.G. Bancorp.*, 737 A.2d at 521-22.

154. GREEN ET AL., *supra* note 42, at 376.

even where there is a statistically significant positive association between exposure to a substance and a disease, courts have rejected such studies under *Daubert* where the relative risk is only somewhat elevated.[155] Moreover, at least one court has suggested that a relative risk of less than 3.0 times denotes only a weak association.[156]

Epidemiology is also essential when considering alternate explanations. As described above, the process of identifying potential biases and confounding factors seeks to ferret out and address other alternate explanations for a positive association. This is necessary to ensure that the observed increased incidence of disease is associated with exposure to the substance in question and not some other phenomenon. Thus, despite the fact that epidemiology is not required as a matter of law, epidemiology is germane to the determination of admissibility under *Daubert* and Rule 702, and the failure of a general causation expert to address the available epidemiological evidence will, in most instances, result in the exclusion of that opinion.

D. The Role of Meta-Analysis under Rule 702

The admissibility of general causation opinions based on meta-analysis — the process of combining numerous epidemiological studies to arrive at a single risk assessment — has yet to be thoroughly analyzed by Delaware courts. In fact, this author's research has only revealed two opinions in Delaware that address meta-analysis and those opinions were *In re Asbestos* and *Grenier II*. In both *In re Asbestos* and *Grenier II*, the Superior Court noted the plaintiff's expert's disagreement with and challenges to the defendants' expert's meta-analysis.[157] The Superior Court, however, did not analyze the methodology employed by the defendants' expert in conducting the meta-analysis. Rather, the experts' disagreement formed the basis for the Superior Court's conclusion that the occupation-specific epidemiological evidence was equivocal.[158]

Considering the inherent limitations of meta-analysis, Delaware courts should carefully scrutinize any expert opinion that relies on meta-analysis to support a general causation conclusion. Particularly because meta-analysis can downplay or eliminate the legitimate impact of bias and confounding factors in each of the underlying studies. Meta-analysis can be reliable if properly conducted pursuant to the scientific method; however, *Daubert* and Rule 702 require the court to delve into that methodology to determine whether it is both relevant and reliable. One commentator has stated:

> meta-analysis begins with scientific studies, usually performed by academics or government agencies, and sometimes incomplete or disputed. The data from the studies are then run through computer models of bewildering complexity, which produce results of implausible precisions…. Pursuant to *Daubert*, a court must look behind this "bewildering complexity" and require the expert to establish the reliability and relevance of both the different pieces of information going into the meta-analysis and the calculations used to combine the information into a single result.[159]

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155. *See Allison*, 184 F.3d at 1315 (affirming the District Court's exclusion of an epidemiological study that only reported "a relative risk of only 1:24, a finding so significantly close to 1.0 that the court thought the study was not worth serious consideration for proving causation").

156. *Havner*, 953 S.W.2d at 719.

157. *In re Asbestos*, 911 A.2d at 1192; *Grenier II*, 2009 Del. Super. LEXIS 548, at *35 n.52.

158. *Grenier II*, 2009 Del. Super. LEXIS 548, at *36.

159. Joe G. Hollingsworth and Eric G. Lasker, *The Case Against Differential Diagnosis: Daubert, Medical Causation Testimony, and the Scientific Method*, 37 J. Health L. 85, 92 (2004) (*quoting* Samuel Shapiro, *Meta-Analysis/Shmeta-Analysis*, 140 Am. J. Epidemiology 771, 771 (1994)).

This approach fits the general framework of *Daubert* and Rule 702 to admit scientific testimony so long as that testimony is relevant, reliable and faithful to the scientific method.

V. CONCLUSION

Delaware courts have emphatically rejected the notion that epidemiological data is required as a matter of law in order to proffer an admissible general causation opinion under *Daubert* and Rule 702. Rather, Delaware has adopted the flexible approach, consistent with the U.S. Supreme Court's guidance in *Daubert* that an admissible general causation opinion may be based on "other" scientific evidence so long as that evidence is reliable and true to the scientific method. This rule, however, leaves a large swathe of grey area surrounding the role epidemiological data plays in determining admissibility under Rule 702. To that end, considering the holdings in both *Long* and *In re Asbestos/Grenier* as well as the U.S. Supreme Court's holdings in *Daubert* and *Joiner*, where epidemiological evidence on general causation exists it must be addressed by the proponent of the expert opinion, especially because epidemiological data is considered the best evidence of general causation. Faithful adherence to the scientific method requires the expert to consider and address such evidence.

Practitioners on both sides of the "v" need to be cognizant of the major role epidemiological evidence plays in the admissibility of general causation opinions. Where epidemiological evidence exists, it will be in only the rarest of circumstances that expert testimony that fails to address or contradict such epidemiological evidence will be admissible under Rule 702. Proponents of general causation opinions, therefore, need to be prepared to demonstrate to the trial court, as the gatekeeper, why the opinion is reliable in the face of, or in conjunction with, the existing epidemiological data. Similarly, opponents of general causation opinions must be able to effectively identify and attack the flaws in such studies, and efficiently and easily demonstrate to the trial court why the expert's opinion is unreliable.