

Use of Human Epidemiology Studies in Proving Causation

Epidemiology studies can be used to establish only general causation, but there are many criteria that can be employed to test those studies

By Andrew See

EPIDEMIOLOGY studies examine populations—generally smaller subsets or samples of populations—in an attempt to determine whether there is an association between exposure to a substance or factor and subsequent disease or injury. These studies are commonly used in the courts to support or refute claims that exposure to a substance or factor caused a disease or an injury in a specific plaintiff or group of plaintiffs.

The problems are (1) on what issues are epidemiological studies properly used and admitted in evidence, and (2) how a particular study was carried out and effect that may have on its admissibility.¹

USE AND ADMISSION

A. Relevance

Epidemiology studies are relevant only to general causation. To satisfy the burden of proving causation, plaintiffs must show both (1) general causation—that is, whether the exposure or substance is capable of causing the alleged disease or in-

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jury, and (2) specific causation—that is, whether the exposure or substance actually caused the disease or injury in the specific case at issue.² Results from epidemiology studies are relevant only to the issue of general causation and cannot establish whether an exposure or factor caused disease or injury in a specific individual.³ Unless general causation has been established evidence of specific causation in an individual plaintiff is not relevant and not admissible.

1. See generally Linda A. Bailey, Leon Gordis & Michael Green, *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 121-80, and David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, in *id.* 331-414 (Federal Judicial Center, 1994); B. Black & P. Lee, EXPERT EVIDENCE: A PRACTITIONER'S GUIDE TO LAW, SCIENCE AND THE FJC MANUAL 73-115 (epidemiology), 267-318 (statistics) (West 1997).

2. In re Breast Implant Litig., 11 F.Supp. 2d 1217, 1224 (D. Colo. 1998); Muzzey v. Kerr-McGee Chem. Corp., 921 F.Supp. 511, 514 (N.D. Ill. 1996); Casey v. Ohio Med. Prods., 877 F.Supp.

1380 (N.D. Cal. 1995); In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 752 (3d Cir. 1994); Wade-Greaux v. Whitehall Labs. Inc., 874 F.Supp. 1441 (D. V.I.), *aff'd*, 46 F.3d 1120 (3d Cir. 1994).

3. Berry v. CSX Transp. Inc., 709 S.2d 552, 557 (Fla.App. 1998); In re Hanford Nuclear Reservation Litig., 1998 WL 775340 (E.D. Wash. 1998); In re Fiberboard Corp., 893 F.2d 706, 712 (5th Cir. 1990); Landrigan v. Celotex Corp., 605 A.2d 1079 (N.J. 1992); Smith v. Ortho Pharm. Corp., 770 F.Supp. 1561 (N.D. Ga. 1991); Merrell Dow Pharm. Inc. v. Havner, 953 S.W.2d 706, 715 (Tex. 1997).

B. Necessity

Human epidemiology studies are a primary and generally accepted methodology to investigate the existence of a causal relationship between exposure to a factor and subsequent disease or injury. They have been held to be the most useful and conclusive type of evidence and that they must be taken into account.⁴ Depending on philosophical views and the facts of particular cases, courts have made varied pronouncements regarding the necessity of epidemiology studies in causal analysis.

Many courts have held that it is necessary to offer epidemiology evidence to prove causation.⁵

Courts have held that epidemiological studies are necessary to prove causation, but only if there is no biological evidence of a causal mechanism for the disease. For instance, in *Daubert v. Merrell Dow Pharmaceuticals Inc.* at the district court level, the court stated: "Absent a scientific understanding of the cause of [the injury or disease], causation may be shown only through reliance upon epidemiological evidence."⁶

Courts also have held that epidemiology studies are valuable but not dispositive of the causation issue. Epidemiology studies do not always prevail over non-epidemiological evidence.⁷

In inexplicable rulings that seem to beg the question of the necessity of epidemiology studies, a few courts have stated that

epidemiology evidence should be required only when they are available or if it is possible to gather the data.⁸ The far better view, and that consistent with the Supreme Court's directions in *Daubert*, is that tort cases must be decided on the basis of the best available scientific evidence at the time of trial. Dispute resolution in the tort system cannot wait or be undermined by the creation of lower standards simply because epidemiology evidence is not currently available. As the Fifth Circuit said in *Moore v. Ashland Chemical Co.*: "In sum, the law cannot wait for future scientific investigation and research. We must resolve cases in our courts on the basis of scientific knowledge that is currently available."⁹

To round out all permutations, some courts have flatly held that epidemiology evidence is not required to prove causation in an exposure case.¹⁰

CONDUCT

Epidemiology studies must be conducted properly and utilized in the legal context following the scientific method. This approach contemplates at least five steps in the reasoning process:

- Formulation of the hypothesis or research question;
- Preparation of a written protocol or study plan that provides, in advance of gathering any data, the methodology to be followed in the study;

4. *Allen v. Penn. Engr. Corp.*, 102 F.3d 194, 197 (5th Cir. 1996); *In re Paoli R.R. Yard PCB Litig.*, 706 F.Supp. 358.

5. *E.g.*, *Richardson v. Richardson-Merrell Inc.*, 857 F.2d 823, 831 (D.C. Cir. 1988); *Wade-Greaux*, 874 F.Supp. 1441; *Casey*, 877 F.Supp. 1380; *Renaud v. Martin Marietta Corp.*, 749 F.Supp. 1545, 1554 (D. Colo. 1990); *Agent Orange*, 611 F.Supp. 1223 (E.D. N.Y. 1985); *Thomas v. Hoffman-LaRoche Inc.*, 731 F.Supp. 224, 228 (N.D. Miss. 1989); *Brock v. Merrell Dow Pharms. Inc.*, 874 F.2d 307 (5th Cir. 1989).

6. 727 F.Supp. 570, 572 (S.D. Cal. 1989), *aff'd*, 951 F.2d 1128 (9th Cir. 1991), *vacated on other grounds*, 509 U.S. 579 (1993).

7. *Lakie v. SmithKline Beecham*, 965 F.Supp.

49, 56 (D. D.C. 1997); *Pick v. Am. Med. Sys.*, 958 F.Supp. 1151, 1158 (E.D. La. 1997); *Muzzey v. Kerr-McGee Chem. Corp.*, 921 F.Supp. 511, 519 (N.D. Ill. 1996); *Kelly v. Am. Heyer-Schulte Corp.*, 957 F.Supp. 873, 882 (W.D. Tex. 1997); *Lopez v. Wyeth-Ayerst Labs.*, 1996 WL 784566 (N.D. Cal. 1996); *Raynor v. Merrell Dow Pharms. Inc.*, 104 F.3d 1371, 1375 (D.C. Cir. 1997).

8. *E.g.*, *Renaud v. Martin Marietta Corp.*, 749 F.Supp. 1545, 1554 (D. Colo. 1990); *Ambrosini v. Labarraque*, 101 F.3d 129, 138 (D.C. Cir. 1996).

9. 151 F.3d 269, 276 (5th Cir. 1998).

10. *E.g.*, *Ambrosini*, 101 F.3d at 138; *Benedi v. McNeil-PPC Inc.*, 66 F.3d 1378, 1384 (4th Cir. 1995).

- Execution of the protocol, that is, gathering data from the population specified using the methodology prescribed in the research plan;

- Analysis of the data using the statistical methodology prescribed in advance in the protocol; and

- Drawing permissible conclusions, if any, from the study results, including determining whether the study results ought to be utilized at all in forming conclusions or generalizing findings to the population at large.

These steps apply both to the critique of any specific epidemiology study and the assessment of its evidentiary value, if any, as well as to the evaluation of an expert witness's proper or improper use of study data to support a causation opinion.

A. Hypothesis

The hypothesis or research question must be set in advance of conducting the study, before the investigator knows what the data will show. These questions usually are framed in the negative—for example, that a particular form of cancer is not associated with exposure to chemical A. The investigator then attempts by the study to disprove the hypothesis by showing that the disease is, in fact, associated with A. Both as study investigators and expert witnesses, investigators are required by the scientific method to be objective in gathering data or in preparing a causation opinion—not knowing how the opinion will come out based on what the data will show.

Forming a conclusion before research is conducted is contrary to the scientific method.¹¹

B. Protocol

In advance of any data gathering, there must be a written protocol or research plan setting out the study's methodological steps. The protocol should include all information regarding the hypothesis, the selection of the study population, how and with what measuring instruments the data is to be gathered and how it is to be analyzed. All assumptions the investigator has made should be fully disclosed in the protocol and reviewed critically. If the investigator has made assumptions that are epidemiologically unsound or contrary to common sense, there is a great potential that the study results may be adversely affected.

The end points (that which is observed and measured in the course of the study) chosen by the investigator should be critically evaluated to ensure that the study is looking at symptoms that are relevant and make scientific and medical sense. For example, in *Cowen v. Mobil Oil Corp.*,¹² a study looked at only mortality rates among employees and concluded that a work place exposure resulted in no excess deaths. The court criticized the study because, among other things, it did not re-evaluate the morbidity rate, that is, the frequency of illnesses not resulting in death, of the study group.

There are two basic kinds of epidemiological studies: cohort studies and case control studies. A cohort study examines the incidence or frequency of disease in an exposed group and compares it to the frequency of disease in an unexposed control group. A case control study matches subjects who already have the disease with a control group of subjects who do not have the disease. The frequency of the exposure to the substance or factor is then compared between the groups.

In order to determine whether there is an association between the exposure or factor

11. *Clarr v. Burlington Northern R.R. Co.*, 29 F.3d 499 (9th Cir. 1994); *Flue-cured Tobacco Coop. v. Envtl. Protection Agency*, 4 F.Supp. 2d 435, 502-03 (M.D. N.C. 1998); *E.I. DuPont de Nemours & Co. v. Robinson*, 923 S.W.2d 549, 559 (Tex. 1995); *Estate of Mitchell v. GenCorp Inc.*, 968 F.Supp. 592, 600 (D. Kan. 1997); *Perry v. United States*, 755 F.2d 888, 892 (11th Cir. 1985); *Viterbo v. Dow Chem. Co.*, 646 F.Supp. 1420, 1425 (E.D. Tex. 1986), *aff'd*, 826 F. 2d 420, 423 n.2 (5th Cir. 1987).

12. 901 F.Supp. 1208, 1211 (E.D. Tex. 1995).

and subsequent disease or injury, the exposed group must be compared to an unexposed control group or population.¹³

C. Execution

1. Biases

Both the methodology and the actual execution of data gathering must be evaluated to ensure that study subjects are similar regarding their baseline characteristics and that one or more biases have not been injected into the data. There are many types of biases that routinely affect study results.

(a) Selection Bias

Selection bias occurs when the exposed group is selected in a way that makes it more or less susceptible to the disease for reasons that are independent of the exposure. In the breast implant litigation, the court stated that a valid epidemiological study requires that subjects be chosen by an unbiased sampling method from a definable population.¹⁴

(b) Recall Bias

Subjects exposed to the substance or factor are more likely to recall and relate symptoms to their exposures than are those not exposed. It is important to “blind” the questioner or survey taker—that is, make the questioner unaware of which subject is exposed or unexposed to remove the danger that the questioner will probe harder for information about symptoms among the exposed subjects. “Blinding” to the exposure status of the study subjects is an

important methodology to eliminate recall or information bias.¹⁵

(c) Ascertainment, Detection or Diagnosis Bias

Both the methodology and the execution of data gathering must be evaluated to determine whether disease is being detected or diagnosed at similar rates between comparison groups. Blinding the investigators to the exposure status of the study subjects is an important technique to avoid such bias. It also is important to ensure that uniform and consistent rules and criteria are applied to what questions are asked and how a disease is diagnosed or how a symptom is characterized to ensure that information about the presence of a disease is consistently interpreted across different investigators and different study subjects. The skill and training of the observers and appropriate quality controls to insure consistent observation and diagnosis are important. There must be uniform diagnostic criteria for the disease at issue.¹⁶

(d) Reporting Bias

Many factors influence the voluntary reporting of disease. There will be more reporting by exposed subjects than by unexposed subjects. There are varying reporting practices used by states, cities, health care institutions and individual health care professionals that will affect the number of reports and may cause observable clusters of reporting that bear no relationship to any causal association between the factor and the disease.¹⁷

13. *Ballentine v. Pioneer Chlor Alkali Co.*, 921 F.Supp. 666, 677 (D. Neb. 1996); *Cowen*, 901 F.Supp. 1208; *Breast Implant Litig.*, 11 F.Supp. 2d 1217, 1224.

14. 11 F.Supp.2d 1217, 1224 (D. Colo. 1998). *See also* *Agent Orange*, 611 F.Supp. at 1248 (self-selection bias). *But see* *In re TMI Litig. Cases Consol. II*, 922 F.Supp. 997, 1009-11 (M.D. Pa. 1996) (while individuals selected for control group should be similar to exposed population, ethnic and

geographical differences in control group subjects goes to weight of testimony regarding epidemiological study, not its admissibility).

15. *Smith*, 770 F.Supp. at 1575 n.43; *Brock*, 874 F.2d at 312.

16. *Lima v. United States*, 708 F.2d 502 (10th Cir. 1983). *Padgett v. United States*, 553 F.Supp. 794, 803 (W.D. Tex. 1982).

17. *Padgett*, 553 F.Supp. at 802-03.

(e) Litigation/Publicity Bias

Publicity about any alleged association between the factor and the disease will tend to create more reports in exposed patients than in unexposed patients.¹⁸

2. Anecdotal Reports

Anecdotal reports, whether in the form of spontaneous reports to regulatory agencies or manufacturers or published case histories in the medical journals, are not admissible as valid scientific data on which to base an opinion about cause and effect. They report only a temporal association between the exposure and the disease and are not the type of data reasonably relied on by scientific and medical experts to form opinions about cause and effect.¹⁹ A database or registry that compiles and maintains anecdotal reports of disease likewise is not the type of data reasonably relied on to form causation opinions.²⁰

3. Data Analysis

(a) Statistical Significance

Study results must be statistically significant. Epidemiological studies usually analyze a relatively small sample of a

much larger relevant population—for example, a sample of 500 exposed individuals from tens of millions of people exposed to the substance in the general population. Analyses of such relatively small samples pose risks of misleading results owing to sampling error, which are non-representative distributions of individuals within the sample because of random chance. This risk of sampling error causes epidemiologists to draw inferences only from study results that have undergone statistical testing and which are found to be statistically significant.²¹

But there are courts that have held that results of epidemiological studies need not be statistically significant in order to be admissible on the issue of causation.²² Under the Supreme Court's *Daubert* opinion on that issue, they are clearly wrong.

(b) Confidence Interval

A way to display the amount of risk caused by sampling error is the confidence interval, which can be expressed numerically by an upper and lower limit shown parenthetically following the study result—for example, RR = 3.0 (1.5, 7.8) means a relative risk of 3.0 with a confidence interval running from 1.5 on the lower limit to 7.8 on the upper limit. If the

18. O'Gara v. United States, 560 F.Supp. 796, 789 (E.D. Pa. 1983).

19. Hagerty v. Upjohn Co., 950 F.Supp. 1160, 1164 (S.D. Fla. 1996); Muzzey, 921 F.Supp. at 519; Breast Implant Litig., 11 F.Supp. 2d at 1227; Havner, 953 S.W.2d at 720; Agent Orange, 611 F.Supp. at 1246; Wade-Greaux, 874 F.Supp. 1441; DeLuca v. Merrell Dow Pharms. Inc., 791 F.Supp. 1050-51 (D. N.J. 1992), *aff'd*, 6 F.3d 778 (3d Cir. 1993), *cert. denied*, 510 U.S. 1044 (1994); Cosgrove v. Merrell Dow Pharms. Inc., 788 P.2d 1293, 1298 (Idaho 1989); Richardson v. Richardson-Merrell Inc., 649 F.Supp. 799, 801 n.5 (D. D.C. 1986). *But see* Pick, 958 F.Supp. at 1161-62 (case studies or case series are weak evidence of causation but should be admissible as evidence having "any tendency" to prove or disprove fact).

20. Casey, 877 F.Supp. 1380; Agent Orange, 611 F.Supp. at 1248; Havner, 953 S.W.2d at 720 (Tex. 1997).

21. DeLuca, 911 F.2d at 943 (3rd Cir. 1990); Nelson v. Am. Sterilizer, 566 N.W.2d 671, 674

(Mich.App. 1997); Kelly, 957 F.Supp. at 878; Breast Implant Litig., 11 F.Supp. 2d at 1226; Flue-cured Tobacco, 4 F.Supp.2d 435; Wade-Greaux, 874 F.Supp. 1441; Whelan v. Merrell Dow Pharms. Inc., 117 F.R.D. 299 (D. D.C. 1987); Padgett, 553 F.Supp. at 800; Porter v. Whitehall Labs. Inc., 9 F.3d 607 (7th Cir. 1993); Casey, 877 F.Supp. 1380; Sorensen v. Shaklee Corp., 1993 WL 735819 (S.D. Iowa 1993), *aff'd*, 31 F.3d 638 (8th Cir. 1994); Thomas, 731 F.Supp. at 228 (N.D. Miss. 1989); Richardson, 857 F.2d at 831; Agent Orange, 611 F.Supp. 1223.

22. Allen, 588 F. Supp. at 417 (D. Utah 1984) (whether correlation between exposure and event is more likely than not is different question than whether results of epidemiological study are statistically significant); Berry v. CSX Transp. Inc., 709 So.2d 552, 570-71 (Fla.App. 1998) (statistically insignificant studies may be admitted and their insignificant status be brought out on cross-examination).

lower limit of the confidence interval is 1.0 or less, it means that there is a possible study result, given the accepted level of risk of sampling error is 1.0, which signifies no difference in risk of disease between the exposed and unexposed groups. This outcome is termed “not statistically significant,” and such a study result is not relied on by epidemiologists or any scientific person to support a conclusion that there is any association between the exposure and the disease, much less a causation association.²³

In calculating the confidence interval, it is necessary to utilize the “two-tailed” test, which generates both the upper and lower boundaries of the confidence interval. A study with a more narrow confidence interval has more value than a study with a larger confidence interval because it indicates stability of the data. A larger sample size will generally produce a narrower and thus more stable confidence interval.²⁴

(c) Generally Accepted Confidence Level

A 95 percent confidence level ($p = .05$ or less) is generally accepted in the scientific, medical and epidemiology communities. This level of confidence means that the investigator is willing to tolerate a 5 percent risk that the study result does not reflect a true and valid relationship but is merely due to chance. While the 95 percent level is arbitrarily set, it is almost universally employed by scientists, most regu-

latory agencies, research institutions and almost everyone else.²⁵

The lower confidence levels used by some regulatory agencies and others for risk assessment do not apply to the cause-and-effect analysis in a tort case. These entities are engaged in prospective risk assessment, so they often accept lower levels of confidence so they can use questionable epidemiology study results to justify regulation or policy making. This practice may be perfectly appropriate for assessing future risk, but it is completely divorced from the cause-and-effect calculation required in tort cases.

The Supreme Court taught in *Daubert* that “scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes.”²⁶ There should be no confusion. Regulatory agencies are not engaged in making cause-and-effect conclusions. Their use of lower levels of confidence for their own, different purposes is irrelevant to the causal analysis in tort cases.²⁷

4. Study Conclusions

(a) Relative Risk

Relative risk (RR) is a measure of association calculated from the frequency of disease observed in the exposed and unexposed study groups. RR is expressed as a ratio; it is the incidence (frequency of occurrence) of disease in the exposed group divided by the incidence of disease in the

23. Kelly, 957 F.Supp. at 878; Brock, 874 F.2d at 312; DeLuca, 791 F.Supp. at 1057; Marder v. G.D. Searle Co., 630 F.Supp. 1087, 1092 (D. Md. 1986), *aff'd sub nom.* Wheelahan v. G.D. Searle Co., 814 F.2d 655 (4th Cir. 1987); Havner, 953 S.W.2d at 723; Smith, 770 F.Supp. at 1575 n.49; Turpin v. Merrell Dow Pharms. Inc., 959 F.2d 1349, 1353-54 n.1 (6th Cir. 1992); Wade-Greaux, 874 F.Supp. 1441.

24. DeLuca, 791 F.Supp. at 1052; Turpin, 959 F.2d at 1353-54 n.1.

25. Kelly, 957 F.Supp. at 879 n.5; Christ's Bride Ministries Inc. v. S.E. Pa. Transp. Auth., 937 F.Supp. 425, 433 n.8 (E.D. Pa. 1996), *aff'd*, 148

F.3d 242 (3d Cir. 1998); Wade-Greaux, 874 F.Supp. 1441; Whelan, 177 F.R.D. 299; DeLuca, 791 F.Supp. at 1046; Havner, 953 S.W.2d at 723-24; Flue-cured Tobacco, 4 F.Supp.2d 435; McNeil-P.P.C. Inc. v. Bristol-Meyers Corp., 755 F.Supp. 1206, 1214 n.7 (E.D. N.Y. 1990), *aff'd*, 938 F.2d 1544 (2d Cir. 1991). *But see* TMI Cases, 922 F.Supp. 997 (no specific confidence level required).

26. 509 U.S. at 591.

27. Agent Orange, 597 F.Supp. at 795; Ethyl Corp. v. Environmental Protection Agency, 541 F.2d 1, 28 n.58 (D.C. Cir. 1976); Sutera v. Perrier Group, 986 F.Supp. 655, 664-65 (D. Mass. 1997); Allen, 102 F.3d at 198.

unexposed or control group. An RR of 1.0, for example, means that there is no increased risk of disease in the exposed group. An RR of 2.0 indicates that there is double the risk for developing the disease in the exposed group as compared to the control group.

Based on the nearly universal tort causation requirement of “more likely than not,” the study result $RR = 2.0$ has become the focus of many decisions about the appropriate legal interpretation of RR values. The vast majority of courts peg admissibility on an $RR \geq 2.0$, but there are minority views. These minority views should be evaluated in the practical, scientific context in which most epidemiologists view even an $RR = 3.0$ to be a relatively weak association.

An RR greater than or equal to 2.0 is the lowest threshold study result to support an inference that the substance or exposure more likely than not caused the disease among the exposed group. Accordingly, epidemiology study results need to produce an RR greater than or equal to 2.0 to constitute admissible evidence to support a causal inference.²⁸

If the study results show an RR of less than 2.0, the study tends to disprove causation.²⁹ If the study produces an RR less than 2.0, the study is not admissible at all on the issue of causation.³⁰

But there is a minority view. Some courts have held that if epidemiology study results stand alone as the only evidence of causation, the study results must produce an RR greater than 2.0 to be admissible.³¹

Other courts have held that epidemiological studies producing an RR less than 2.0 in the exposed population are not sufficient to prove causation but nevertheless should be admitted for the jury’s consideration.³² If epidemiology study results with an RR of less than 2.0 are admissible, they need to be supported by other credible evidence of causation in order to make a submissible case.³³ Epidemiology study results with an RR greater than 1.0 have been considered evidence of “possible” causation.³⁴

It is worth noting again that although epidemiology study results producing RR greater than 2.0 are admissible, they do not automatically prove a cause-and-effect relationship between the exposure and a disease. Relative risk is simply a measure of association. Once a statistically significant association has been shown, it is then necessary to go through the type of general causation analysis set forth below to attempt to determine whether a causal relationship exists between the exposure and the disease.

(b) Confounding Factors

A confounding factor or “confounder” is a variable that is a risk or causal factor for the disease and also is independently associated with the exposure. The appearance of the exposure in association with the confounder may create the false appearance that the exposure is associated with the disease, when in fact it is only associated with the confounder. An inherent difficulty with epidemiology studies is that

28. *Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1315 n.16 (11th Cir. 1999); *Hanford Nuclear Litig.*, 1998 WL 775340; *Manko v. United States*, 636 F.Supp. 1419, 1434 (W.D. Mo. 1986); *Padgett*, 553 F.Supp. at 801; *Marder*, 130 F.Supp. at 1092; *Agent Orange*, 597 F.Supp. at 785; *Cook v. United States*, 545 F.Supp. 306, 308 (N.D. Cal. 1982); *Hall v. Baxter Health Care Corp.*, 947 F.Supp. 1387, 1403 (D. Or. 1996); *Havner*, 953 S.W.2d at 717; *Wade-Greaux*, 874 F. Supp. 1441.

29. *Daubert*, 43 F.3d at 1321.

30. *Breast Implant Litig.*, 11 F.Supp.2d at 1225-

26; *Raynor*, 104 F.3d at 1376; *Allen*, 102 F.3d at 197.

31. *Agent Orange*, 597 F.Supp. at 785; *DeLuca*, 911 F.2d at 958 (3d Cir. 1990).

32. *Allen*, 588 F.Supp. at 417; *Pick*, 958 F.Supp. at 1160; *Joint Asbestos Litig.*, 52 F.3d 1124 (2d Cir. 1995); *Grassis v. Johns-Manville Corp.*, 591 A.2d 671, 675-76 (N.J.Super. 1991).

33. *Bartley v. Euclid*, 158 F.3d 261, 273 (5th Cir. 1998); *Landrigan*, 605 A.2d 1079.

34. *Turpin*, 959 F.2d at 1353 n.1.

the subjects in the study population may have several factors, known or unknown, that are capable of causing the disease or injury at issue. Because epidemiology studies are based on a sample rather than an entire census of the population, there is always the chance that the other known or unknown causal factors may not be evenly distributed between the exposed and the unexposed groups. Accordingly, studies must always be evaluated for the presence of confounding factors that can skew the study results.³⁵

An observed association between exposure to a substance or factor and a disease may indicate a true cause-and-effect relationship or may indicate only a spurious finding. To distinguish between the two, it is necessary first to consider the effect of any confounding factors.³⁶

GENERAL CAUSATION ANALYSIS

A. Generalizing Results

The concept of “fit” discussed by the Supreme Court in *Daubert* also is a critical issue to the question of generalizing epidemiology study results to the general population, including the plaintiff in a particular case. It is clear that the plaintiff must be substantially similar to the population studied in all significant respects—that is, the plaintiff must qualify as a member of the exposed study group. If not, the study result cannot be generalized to the plaintiff and should not be admitted into evidence as irrelevant and misleading to the jury.³⁷

35. Brock, 874 F.2d at 311; Agent Orange, 611 F.Supp. at 1251; Joiner v. Gen. Elec. Co., 864 F.Supp. 1310 (N.D. Ga. 1994), *rev'd*, 78 F.3d 524 (11th Cir. 1996), *rev'd*, 522 U.S. 136 (1997); Wade-Greaux, 864 F.Supp. 1441.

36. Kelly, 957 F.Supp. at 878; Adams v. Ind. Bell Tele. Co., 2 F.Supp.2d 1077, 1095 (S.D. Ind. 1998); Berry, 709 So.2d at 558.

37. Agent Orange, 611 F.Supp. at 1273-74.

38. *Id.* at 1241; Wade-Greaux, 874 F.Supp. 1441; Havner, 953 S.W.2d at 720; Schudel v. Gen. Elec. Co., 120 F.3d 991, 997 (11th Cir. 1997).

39. Joint Asbestos Litig., 758 F.Supp. at 203, 774 F.Supp. at 114; Sutera, 986 F.Supp. at 662; Wade-Greaux, 874 F.Supp. 1441; Schudel, 120 F.3d at 997.

1. Level of Exposure or Dose

The epidemiology study must be conducted in a population that received a dosage or exposure level of the substance or factor which is the same, or at least is not significantly different from that received by the plaintiff.³⁸

2. Duration of Exposure

The plaintiff must have received the same or substantially similar duration of exposure if study results are to be generalized to a larger population including the plaintiff.³⁹

3. Route of Administration

If relevant, the route of administration must not be significantly different between the plaintiff and members of the exposed group.⁴⁰

4. Timing of Exposure

The timing of exposure must not be significantly different.⁴¹

5. Identity of Substance

The plaintiff must have been exposed to the same substance or factor evaluated in the epidemiological study.⁴²

6. Identity of Disease and Subtype

The epidemiology study must look at the same disease from which it is alleged that the plaintiff suffers.⁴³

40. Wade-Greaux, 874 F.Supp. 1441.

41. *Id.*; Sutera, 986 F.Supp. at 662; Cadarian v. Merrell Dow Pharms. Inc., 745 F.Supp. 409 (E.D. Mich. 1989); Dodd-Anderson v. Stevens, 1994 WL 26922 (D. Kan.).

42. Joiner, 864 F.Supp. 1310; Marder, 130 F.Supp. 1087, 1089; Chikovsky v. Ortho Pharm. Corp., 832 F.Supp. 341, 346 (S.D. Fla. 1993).

43. Christophersen v. Allied-Signal Corp., 939 F.2d 1106 (5th Cir. 1991); Peterson v. Sealed Air Corp., 1991 WL 66370 (N.D. Ill. 1991); Paoli PCB Litig., 35 F.3d 717; Estate of Mitchell v. GenCorp Inc., 968 F.Supp. 592, 600 (D. Kan. 1997); Casey, 877 F.Supp. 1380; Whiting v. Boston Edison Co., 891 F.Supp. 12 (D. Mass. 1995).

7. Extrapolation of Animal Data

Results of animal studies cannot be extrapolated to human beings without a valid scientific basis, taking into account species differences and the magnitude of exposure in most animal studies.⁴⁴

B. Contrary Usage

It has become commonplace for expert witnesses to announce that they have relied on raw data presented in published epidemiology studies but that they reject the authors' analyses and conclusions. Courts, including the U.S. Supreme Court in *General Electric Co. v. Joiner*, have condemned that practice.⁴⁵

Another common practice of expert witnesses who reject the interpretation and conclusions of epidemiological study authors is to recalculate study data using different statistical methodology. This practice is contrary to the scientific method. It violates the study protocol and is by definition a post hoc analysis after the data has already been collected. This practice, so obviously result oriented, would not be tolerated in the scientific world and deserves no better treatment in the courts.⁴⁶

C. Association and Causal Inference

Epidemiology study results indicate only whether there is a positive, statistically significant association between an exposure and a subsequent disease or injury. Once a positive, statistically significant association is observed, it is necessary

to consider and eliminate the effect of any confounding factors. When that has been done, the observed association must be judged against established causation criteria to determine whether it is scientifically valid to draw a causal inference.

These criteria are known as the Koch-Henle postulates or the Austin Bradford Hill criteria and include

- strength of the association,
- consistency of the association,
- specificity of the association,
- temporality,
- dose response relationship,
- biological plausibility and
- consideration of alternative explanations.

1. Strength Of Association

A higher relative risk may be less likely to be the result of bias or sampling error and therefore more likely to reflect a causal relationship.⁴⁷

2. Temporal Relationship

If exposure to a substance has caused the disease, that exposure must have occurred before disease symptoms appeared. In addition, it is necessary to consider any possible latency period of the disease to determine whether the exposure occurred in the appropriate temporal relationship. For example, all types of cancer have a specific latency period; one does not develop cancer the day after exposure to a particular substance.⁴⁸

44. Allen, 102 F.3d at 197; Agent Orange, 611 F.Supp. at 1273; Paoli PCB Litig., 35 F.3d at 743 (3rd Cir. 1994).

45. 522 U.S. 136 (1997). See also Moore v. Ashland Chemical, 151 F.3d 269, 227 n.8, 278 (5th Cir. 1998); Kelly, 957 F.Supp. at 878; Cadarian, 745 F.Supp. at 411-12; Rutigliano v. Valley Business Forms, 929 F.Supp. 779 (D. N.J. 1996), *aff'd sub nom.* Valley Business Forms v. Graphic Fine Color Inc., 118 F.3d 1577 (3d Cir. 1997).

46. Kelly, 957 F.Supp. at 879 n.5; Lynch v. Merrell Nat'l Labs., 646 F.Supp. 856, 865 (D.

Mass. 1986); Brock, 874 F.2d 307; Marder, 630 F.Supp. 1087; Lee v. Richardson-Merrell Inc., 772 F.Supp. 1027 (W.D. Tenn. 1991), *aff'd*, 961 F.2d 1577 (6th Cir. 1992), *cert. denied*, 506 U.S. 868 (1992); Turpin, 736 F.Supp. 737; Hall, 947 F.Supp. 1387; Daubert, 43 F.3d 1311 (9th Cir. 1995).

47. Christ's Bride, 937 F.Supp. at 434; Berry, 709 So.2d at 559; Cook, 545 F.Supp. at 308; Landrigan, 605 A.2d 1079.

48. Nat'l Bank of Commerce v. Associate Milk Producers, 22 F.Supp.2d 942, 974 (E.D. Ark. 1998); Whiting, 891 F.Supp. 12 (D. Mass. 1995).

By itself, a temporal relationship between exposure and subsequent disease is not sufficient to establish a cause and effect relationship.⁴⁹ Evidence of a temporal relationship between exposure and disease, standing alone, is inadmissible.⁵⁰ Likewise, if there is no evidence of general causation, evidence of a temporal relationship between the exposure and the disease is inadmissible.⁵¹

3. Replication and Consistency

Replication—that is, the repeated performance of the same or similar study design—is a cardinal scientific principle. In the scientific world, if results cannot be replicated by a different investigator, they have virtually no credibility. To enable the drawing of a general causation conclusion, there should be repeated human epidemiology studies showing consistent results. Studies with inconsistent results are not weighed in a scientific balance to prove one or the other side of a question. The only scientifically valid conclusion in that circumstance is that the studies are inconclusive and cannot be used as affirmative evidence on either side of the issue.⁵²

4. Biological Plausibility

An assessment should be made as to whether the study results are consistent with existing knowledge. The importance of this factor depends on the level of scientific knowledge regarding the physiological mechanism by which the disease process works.⁵³

D. Occam's Razor

Finally, any general causal inference should be tested against the principle of Occam's razor, named after William of Occam and also known as the rule of parsimony. It holds generally that if there is a simple and obvious explanation, that explanation probably is correct and is to be preferred over a complex and unfamiliar explanation. Illustration: "When you hear hoofbeats in Texas, it is probably a horse and not a zebra." When the disease or injury occurs in the absence of the exposure, it may be unscientific to assume that the same disease or symptom occurring in an exposed individual was caused by the substance or factor, at least in the absence of convincing epidemiological or direct evidence of causation.⁵⁴

49. *Baker v. Danek Medical*, 35 F.Supp.2d 875, 880-81 (N.D. Fla. 1998); *Moore*, 151 F.3d at 278; *Porter*, 93 F.3d 607; *Saari v. Merck & Co.*, 961 F.Supp. 387, 396 (N.D. N.Y. 1997); *Sanderson v. Int'l Flavors & Fragrances Inc.*, 950 F.Supp. 981, 988-89 (C.D. Cal. 1996); *Hall*, 947 F.Supp. 1387;.

50. *Breast Implant Litig.*, 11 F.Supp.2d at 1232; *Cuevas v. E.I. DuPont de Nemours & Co.*, 956 F.Supp. 1306, 1311 (D. Mass. 1997).

51. *Hall*, 947 F.Supp. 1387; *Kelly*, 957 F.Supp. 873.

52. *Joint Asbestos Litig.*, 827 F.Supp. at 1037 n.18, 1038; *Christ's Bride*, 937 F.Supp. at 432; *Breast Implant Litig.*, 11 F.Supp.2d at 1228; *Berry*, 709 So.2d at 559; *Kehm v. Proctor & Gamble Co.*, 580 F.Supp. 890, 901 (N.D. Iowa 1982), *aff'd*, 724 F.2d 613 (8th Cir. 1983); *Raynor*, 104 F.3d at 1375; *Wade-Greaux*, 874 F.Supp. 1441; *Agent Orange*, 611 F. Supp. at 1273-74; *Havner*, 953 S.W.2d at 727.

53. *Berry*, 709 So.2d at 559.

54. *Kelly*, 957 F.Supp. at 882 n.12.