
Teratology Society Public Affairs Committee Position Paper

Causation in Teratology-Related Litigation

The Public Affairs Committee of the Teratology Society

Received 14 February 2005; Accepted 17 February 2005

INTRODUCTION

Teratology-related litigation often includes testimony by scientists on whether the exposures at issue caused a developmental abnormality. The involvement of scientists as expert witnesses in lawsuits is an important intersection between teratology and the public. The Federal Rules of Evidence (Rule 702) state, "If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case." (U.S. Congress, 2002). Not all states follow the Federal Rules, but the role of the expert is similar in all courts.

The role and responsibilities of the scientist expert witness have been discussed elsewhere (e.g., Brent, 1982). This position paper does not concern the ethics of expert witnessing, although the ethical dimensions are important. There are also legal standards concerning the qualifications of expert witnesses or the admissibility of expert testimony. These standards will not be discussed here. This paper focuses specifically on the scientific principles relevant to rendering an opinion in causation in teratology-related litigation.

CAUSATION IN THE LAW

There is no single definition of causation in the law, and different jurisdictions may use different legal criteria. Most jurisdictions use the cause-in-fact or "but-for test"; that is, causation is demonstrated between an exposure and an outcome if the outcome would not have occurred but for the exposure. The but-for test is typically modified by a substantial factor test, that is, the exposure was a substantial factor in bringing about the outcome, or by consideration of the exposure as a contributory cause.

Determining causation in a legal setting may seem unreasonable to scientists when the determination involves, as it often does, an individual plaintiff. The output of litigation is a determination that an exposure did or did not cause a specific plaintiff's injuries. Scientists, however, think about risk, which is a probabilistic term derived from observations in populations. If 1000 pregnant women are exposed to valproic acid, about 11 children can be expected to be born with neural tube defects (Lammer et al., 1987). One of the children would have a spontaneous neural tube defect and the other 10 would have a valproic acid-in-

duced neural tube defect. It could be said that valproic acid causes neural tube defects because the risk of the disorder is increased 10-fold in the population of exposed individuals. If 1 of the children with a neural tube defect comes forward in a lawsuit, however, science cannot distinguish in this individual child whether the abnormality was caused by the valproic acid exposure or whether this child might have had a neural tube defect anyway.

Scientists in court, however, are not required to determine if an individual child's abnormality was definitely caused by the exposure at issue. Absolute certainty is not required, only reasonable certainty. The criterion for reasonable certainty is defined as "more likely than not." More likely than not means that an expert witness who concludes causation believes there is a >50% likelihood that the conclusion of causation is correct for the individual plaintiff. In the valproic acid example, a scientist might determine that the chance that an individual plaintiff's neural tube defect was caused by valproic acid was 91% (10/11), >50%, and, therefore, that valproic acid caused the child's malformation to a reasonable degree of scientific certainty.

CRITERIA FOR CAUSATION

The Federal Rules of Evidence and many state rules allow expert witnesses to testify as to their "opinions," implying that an expert witness has considerable liberty in drawing conclusions. Scientists, however, use accepted methods of analysis rather than using vague impressions that a causal connection exists between an exposure and an outcome. The Principles of Teratology put forward by James Wilson (1977) (Table 1) continue to be accepted, and theories of causation should be consistent with these principles.

Most criteria for causation in teratology and other biomedical disciplines rely on features identified by Sir Austin Bradford Hill in an address to the Royal Society of Medicine (Hill, 1965). Sir Austin made it clear in his address that he was identifying factors to be considered in an evaluation and that he was not proposing rigid criteria. Criteria similar to the Bradford Hill criteria were put forward by the Surgeon General in evaluating the effects of smoking on health (U.S. Department of Health, Education, and Welfare, 1964). These criteria are viewed as being used in a

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Published online 6 May 2005 in Wiley InterScience (www.interscience.wiley.com).

DOI: 10.1002/bdra.20139

Table 1
Principles of Teratology*

1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.
2. Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.
3. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).
4. The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.
5. The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).
6. Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level.

*Wilson (1977).

deliberative process that moves a conclusion about causation along a continuum between disproved and proved (Cole, 1997). Two commonly cited lists of criteria used in considering causation in teratology appear in Table 2. These criteria are similar to one another and can be regarded as complementary rather than contradictory.

PRINCIPLES FOR DETERMINING CAUSATION

Given the differences that exist in the quantity, quality, and types of evidence in teratology, it is not practical to endorse a checklist of criteria that must be satisfied in each and every case. There are, however, key principles that underlie all scientific determinations of causation (Table 3), and conclusions that violate these principles are not considered scientifically valid.

1. Causation determinations are made using all the scientific evidence. This evidence is derived from correctly

Table 3
Principles in Causation Determinations in Teratology-Related Litigation

1. Causation determinations are made using all the scientific evidence.
2. The determination of causation in a lawsuit is not the same as a regulatory determination of a protective level of exposure.
3. Determination of a causal relationship between a chemical and an outcome is specific to the chemical at issue.
4. Determination of a causal relationship between a chemical and an outcome is specific to the outcome at issue.
5. A single case report by itself is not evidence of a causal relationship between an exposure and an outcome.
6. Human data are required for conclusions that there is a causal relationship between an exposure and an outcome in humans.
7. Biologic plausibility is an essential element in establishing causation.
8. Evidence of exposure to the putative toxic agent is required for a conclusion of causation.

interpreted papers that have been published in the peer-reviewed literature. Unpublished data may be useful if available in sufficient detail for an evaluation and if derived from a source that is known to use reliable internal or external review standards. A National Toxicology Program report would be an example of an unpublished source that is typically reliable. All available papers are considered in a scientific deliberation; selective consideration of the literature is not a scientific procedure.

2. The determination of causation in a lawsuit is not the same as a regulatory determination of a protective level of exposure. If a government agency has determined a regulatory exposure level for a chemical, the existence of that level is not evidence that the chemical produces toxicity in humans at that level or any other level. Regulatory levels

Table 2
Two Criteria Sets for Causation in Teratology*

Brent (1995)	Shepard (2001) ^a
1. Epidemiology studies <i>consistently</i> demonstrate an increase in the frequency of congenital malformations, and especially a recognizable syndrome in the exposed population.	1. Proven exposure to agent at critical time(s) in prenatal development (prescriptions, physician's records, dates)
2. Secular trend analysis reveals that the frequency of congenital malformations is associated with the changes in population exposure, i.e., the introduction or withdrawal of environmental agents for which there has been a high population exposure.	2. Consistent findings by two or more epidemiologic studies of high quality: (a) Control of confounding factors; (b) Sufficient numbers; (c) Exclusion of positive and negative bias factors; (d) Prospective studies, if possible; and (e) Relative risk of six or more (?).
3. An animal model has been developed that is similar to the reports in the human and can be produced with pharmacokinetically equivalent exposures.	3. Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful.
4. In the appropriate animal model, the frequency and severity of the teratogenesis and embryopathology increases with a dose or exposure that is within the range of human exposures.	4. Rare environmental exposure associated with rare defect. Probably three or more cases (examples: oral anticoagulants and nasal hypoplasia, methimazole and scalp defects (?), and heart block and maternal rheumatism).
5. The teratogenic effect is consistent with the basic principles of embryology and teratology and does not contradict basic principles of biologic or common sense.	5. Teratogenicity in experimental animals important but not essential. 6. The association should make biologic sense. 7. Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention.

^aItems 1, 2, and 3 or 1, 3, and 4 are essential criteria. Items 5, 6, and 7 are helpful but not essential.

*Wording and punctuation as in the originals.

use default assumptions that are improper in lawsuits. One such assumption is that humans will be as sensitive to the toxicity of a chemical as is the most sensitive experimental animal species. This assumption may be very useful in regulation but is not evidence that exposure to that chemical caused an adverse outcome in an individual plaintiff. Regulatory levels often incorporate uncertainty factors or margins of exposure. These factors may result in a regulatory level much lower than an exposure level shown to be harmful in any organism and are an additional reason for the lack of utility of regulatory levels in causation considerations.

3. Determination of a causal relationship between a chemical and an outcome is specific to the chemical at issue. If an expert witness believes that Chemical A causes congenital anomalies in humans, that belief does not establish that Chemical B causes congenital anomalies in humans unless there is reason to believe that Chemical A and B are metabolites of one another, even if Chemicals A and B have structural or physical features in common. Note that regulatory action on Chemical B based on characteristics of Chemical A might be reasonable, but conclusions about causation are not.

4. Determination of a causal relationship between a chemical and an outcome is specific to the outcome at issue. If an expert witness believes that a chemical causes malformation A, this belief is not evidence that the chemical causes malformation B, unless malformation B can be shown to result from malformation A. In the same sense, causation of one kind of reproductive adverse effect, such as infertility or miscarriage, is not proof of causation of a different kind of adverse effect, such as malformation.

5. A single case report by itself is not evidence of a causal relationship between an exposure and an outcome. Combinations of both exposures and adverse developmental outcomes frequently occur by chance. Common exposures and developmental abnormalities often occur together when there is no causal link at all. Multiple case reports may be appropriate as evidence of causation if the exposures and outcomes are both well-defined and low in incidence in the general population. The use of multiple case reports as evidence of causation is analogous to the use of historical population controls: the co-occurrence of thalidomide ingestion in pregnancy and phocomelia in the offspring was evidence of causation because both thalidomide use and phocomelia were highly unusual in the population prior to the period of interest. Given how common exposures may be, and how common adverse pregnancy outcome is, reliance on multiple case reports as the sole evidence for causation is unsatisfactory.

6. Human data are required for conclusions that there is a causal relationship between an exposure and an outcome in humans. Experimental animal data are commonly and appropriately used in establishing regulatory exposure limits and are useful in addressing biologic plausibility and mechanism questions, but are not by themselves sufficient to establish causation in a lawsuit. In vitro data may be helpful in exploring mechanisms of toxicity but are not by themselves evidence of causation.

7. Biologic plausibility is an essential element in establishing causation. There are different elements that can demonstrate the biologic plausibility of a putative association. Experimental animal studies may model the human exposure-outcome relationship or they may provide mechanistic information that adds to the plausibility of a causal

relationship. Biologic plausibility includes a consideration of alternative explanations for the outcome in an individual plaintiff. For example, if a plaintiff has a birth defect syndrome caused by a known genetic disorder, chemical exposure becomes implausible as a cause of the abnormality in that particular individual. The consideration of alternative explanations is sometimes misused by expert witnesses to mean that failure to find an alternative explanation for an outcome is proof that the exposure at issue must have caused the outcome. A conclusion that an exposure caused an outcome is, however, based on positive evidence rather than on lack of an alternative explanation.

8. Evidence of exposure to the putative toxic agent is required for a conclusion on causation. Exposure involves both exposure level and appropriate timing. Wilson's second and sixth principles address these elements. It is not appropriate to conclude causation from exposure to a chemical characterized as "a teratogen" independent of the exposure level and timing of the exposure. If a chemical has been shown to cause a malformation when exposure occurs at a particular time in gestation and at a particular dose, it does not follow that the chemical will cause the malformation when exposure occurs at different times or at lower doses.

SUMMARY

The Teratology Society Public Affairs Committee recognizes that scientists are asked to render opinions in court on the causal relationship between exposures and developmental outcomes. The determination of whether an exposure caused a specific developmental outcome is different from determinations of regulatory exposure limits performed by governmental agencies. Scientifically valid opinions on causation in litigation are consistent with accepted principles of teratology and with criteria such as those put forward by the Surgeon General in 1964 and by Sir Austin Bradford Hill in 1965. The specific principles required for a conclusion of causation in teratology-related litigation to be scientifically valid are set forward in Table 3. The Public Affairs Committee recognizes that additional principles may be appropriate for specific data sets; therefore, the principles in Table 3 are considered minimum requirements.

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