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## Attributable Risk And Specific Causation

Law360, New York (November 10, 2008) -- The plaintiff in a pharmaceutical products liability or toxic tort case must prove by a preponderance of the evidence that the drug or other substance more likely than not caused or contributed to his alleged injury.

Proving causation in such cases typically involves a two-step process: the plaintiff first must prove that the substance is capable of causing the type of harm alleged (i.e., general causation) and then must prove that his particular exposure to it in fact caused his alleged injury (i.e., specific causation).

The complexities involved in establishing specific causation vary according to the nature of the plaintiff's alleged injury.

In cases involving 'signature injuries' - i.e., injuries, such as asbestosis, that can result only from exposure to a toxic substance - the issue typically will be whether the plaintiff was exposed to a sufficient quantity of the defendant's product to have caused his injury.

Many cases, however, involve commonplace injuries or diseases that can result from multiple possible causes. Cardiovascular events or central nervous system injuries, for example, sometimes result from exposure to drugs or chemicals.

But many people develop these problems as a result of "natural causes." For example, these health effects also can result from risk factors including, but not limited to, age, elevated cholesterol, stress, poor liver function, or genetic predisposition.

When testifying in cases involving such injuries, plaintiffs' expert witnesses may seek to prove specific causation by relying on a statistical analysis of epidemiologic data known as 'attributable risk.'

Reliance on attributable risk computations to prove specific causation is methodologically

misguided, however, and defense counsel should be ready to expose the flaws in that approach via Daubert motions, cross-examination, or other appropriate and available procedures depending on the jurisdiction.

Attributable risk refers to the statistical proportion of adverse events in an exposed study population that might be attributable to exposure to a substance as opposed to other factors.

If more than half of the adverse events in an exposed population can be attributed to exposure to a substance as opposed to other factors, an expert may seek to opine that exposure to that substance more likely than not caused or contributed to the plaintiff's injury.

Some courts have allowed experts to infer specific causation on this basis while others have not. Those that have done so oftentimes overlook the significant methodological flaws implicit in the experts' opinions.

As explained below, there are several reasons why courts should not allow experts to infer specific causation from an analysis of attributable risk.

#### *Calculating Attributable Risk*

Attributable risk sometimes is confused with relative risk. The two concepts are related but distinct.

Relative risk is the ratio of the risk of disease in the exposed population to the risk of disease in the unexposed population. It is a measure of the magnitude of association between exposure and the disease.

Attributable risk, by contrast, is a measure of the proportional increase in disease in the exposed population that might be attributable to the exposure.

Mathematically, attributable risk is calculated as follows:  $AR = E(RR - 1) / [E(RR - 1) + 1]$ , where "AR" is the attributable risk, "RR" is the relative risk, and "E" is the fraction of exposed individuals.

In a typical epidemiologic study designed to assess the impact of a single risk factor - for example, exposure to a pharmaceutical - the entire test group is exposed and "E" will equal 1.

According to this formula, when a study's relative risk is 2.0, such that exposure to the substance is associated with a doubling of the baseline risk observed in the unexposed population, the attributable risk is 0.5, or 50 percent, meaning that half of the cases of disease in the exposed population might be attributable to the exposure as opposed to other factors.

If the relative risk is greater than 2.0, the attributable risk is greater than 50 percent, meaning that more than half of the cases of disease in the exposed population might be attributable to the exposure.

Assessing attributable risk can serve an important public health function. When determining how to allocate scarce resources, public health officials may want to evaluate the potential benefit associated with eliminating a specific exposure in a particular population - for example, whether a reduction in smoking might have a greater impact on lung cancer rates than the elimination of asbestos.

Calculating attributable risk thus may provide a rational basis for future policy-making. But this public health rationale does not apply in pharmaceutical and toxic tort litigation, where the goal is not to shape policy.

Rather, the plaintiffs are seeking compensation for injuries allegedly caused by defendants' products. As explained below, reliance on attributable risk is an unacceptable substitute for proof of specific causation.

#### *Epidemiology Cannot Prove Causation*

As an initial matter, an epidemiologic study by itself cannot prove general causation - i.e., that a causal link exists between exposure to a toxic substance and an increased incidence of disease in a particular population.

While an elevated relative risk may demonstrate an association between exposure and disease, an association is not equivalent to causation. There may be no causal relationship even if the relative risk is high.

Before causal inferences may be drawn, scientists must consider a variety of additional factors beyond a study's relative risk, including but not limited to:

(1) the study's design - with randomized, double-blinded, placebo-controlled studies on one

end of the spectrum offering the most useful information and anecdotal evidence and spontaneous reports on the other offering no reliable information;

(2) the study's execution - even the best designed study must still be executed properly;

(3) whether the study's results have been reproduced by other studies;

(4) the strength of the association - any observed difference in risk must be statistically significant and of sufficient magnitude to be relevant;

(5) the presence of confounding factors;

(6) whether there are alternative explanations for the observed increase in events for the exposed group; and

(7) whether a causal connection between the exposure and the outcome is biologically plausible (i.e., mechanism of action) based on scientifically reliable evidence as opposed to mere hypotheses.

Other factors might be relevant or even dispositive in a given case. Because epidemiology alone cannot prove causation on a population-wide basis, it follows necessarily that it cannot prove causation on an individual basis.

Invoking attributable risk does not change this fundamental limitation of epidemiology. In statistics, the term 'attributable' does not mean 'caused by.'

Instead, attributable risk refers to the proportion of disease in an exposed population that might be caused by the exposure, assuming that the observed association is causal.

Further, even if the association is causal, the attributable risk does not allow differentiation between those individuals whose injuries resulted from exposure to the substance and those whose injuries resulted from other factors.

Either the exposure contributed to a study participant's injury or it did not. The attributable risk, no matter how high, never can provide the answer for any given individual.

As a leading commentator notes, "employing the results of group-based studies of risk to make a causal determination for an individual plaintiff is beyond the limits of epidemiology."<sup>[1]</sup>

### *The 'Everybody Wins' Problem*

When experts rely on attributable risk to infer specific causation, they engage in an erroneous methodology.

If a study shows that exposure to a substance is associated with a doubling of the risk for developing an injury, only half of the injuries in the exposed group can be attributed to the exposure.

This is because individuals in the unexposed group have a pre-existing baseline risk.

If a study shows that exposure to a substance is associated with slightly more than a doubling of that baseline risk, it still follows that almost half of the injuries in exposed individuals can be attributed to factors other than the exposure.

In this latter circumstance, it would be wrong to presume that exposure to the substance more likely than not caused the injury of each individual in the exposed group.

Yet that is the implicit reasoning process employed by experts who infer specific causation from attributable risk.

Consider the hypothetical study in which exposure to a substance is associated with slightly more than a doubling of the baseline risk in the unexposed population. The attributable risk for the exposed population in such a study would be over 50 percent, say 51 percent.

It would be wrong to conclude that a particular plaintiff's injury more likely than not resulted from exposure to a substance merely because the attributable risk of such injuries in the exposed population is more than 50 percent.

If we allowed that reasoning, a defendant could be held liable for the injury of every exposed individual even though some injuries in the exposed population - in this example, nearly half of them - were not statistically attributable to exposure to the substance in question.

Such reasoning self-evidently results in unfair overcompensation. Unless experts reliably can distinguish those injuries caused by exposure to a substance from those caused by other factors, they ultimately engage in nothing more than guesswork when relying on attributable risk to infer specific causation.

### *Additional Complicating Factors*

Experts who rely on attributable risk to infer specific causation are potentially subject to challenge on other grounds as well. One such ground might arise based on the uncertainty surrounding a study's relative risk.

Relative risk typically is reported as a point estimate within a 95 percent confidence interval. The confidence interval represents the range of values within which the true relative risk would fall in 95 percent of similar studies.

Consider a study with a relative risk of 2.05 and a 95 percent-confidence interval of 1.01-2.50. Based on this confidence interval, the relative risk could be as low as 1.01 or as high as 2.50, which means that the attributable risk could be as low as 1 percent or as high as 60 percent.

An expert may overlook the inherent uncertainty in this data and conclude that exposure to the substance more likely than not caused the plaintiff's injury because the relative risk point estimate of 2.05 yields an attributable risk of 51 percent.

But such reasoning ignores the fact that up to 99 percent of the injuries in the exposed group may be attributable to factors other than the exposure (i.e., based on a relative risk of 1.01 and a corresponding attributable risk of 1 percent).

Another ground for challenging an expert can arise when the plaintiff is insufficiently similar to the participants in a study on which the expert relies.

The plaintiff, for example, may have been exposed to a lower dose of the substance than the study participants or may have a variety of physiologic conditions that make it less likely that his particular exposure caused his injury.

Experts who purport to infer causation from epidemiologic data must address such dissimilarities.

Oftentimes, however, they neglect to do so and instead simply assume that a study's results are applicable to individuals in the general population. When experts engage in such casual analysis, defendants can challenge the reliability of their opinions.

### *How Can An Expert Establish Specific Causation?*

Finally, plaintiffs are not without a remedy when courts preclude their experts from relying on attributable risk to infer specific causation.

In such cases, plaintiffs still can satisfy their burden of proof by proffering experts who engage in rigorous causal analyses similar to the differential diagnoses that doctors conduct when diagnosing their patients' conditions.

As part of this process, the expert first rules in potential causes of a plaintiff's injury and then rules out causes until the most likely cause remains. The expert's testimony, of course, must conform to the strictures of Daubert, Joiner, and similar cases.

While this process may be complex and subject to some uncertainty, it can provide a more reliable basis for a specific causation opinion than attributable risk.

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[1] See Saks et al., Federal Judicial Center, Annotated Reference Manual on Scientific Evidence (2d ed. 2005) ("Reference Manual on Scientific Evidence") at 481.