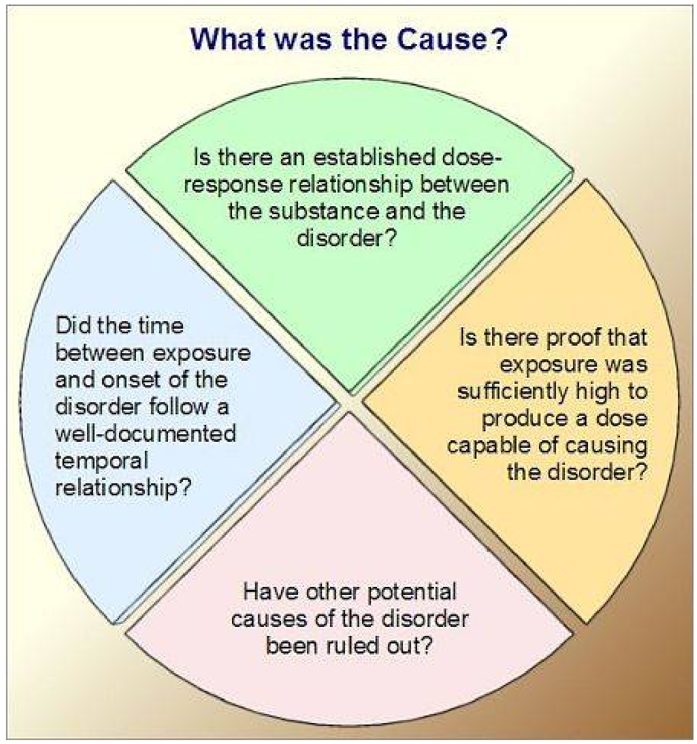
Causation Evaluation in Toxicology

Causation is at the very heart of the toxicological world. Causation in toxicology is defined as *the action of causing or producing an effect as a result of ingestion, inhalation, dermal absorption or other exposure routes to a toxic substance.* It is the process by which the expert toxicologist establishes or refutes whether a potential adverse health effect is truly caused by an exposure, dose and duration.

Establishing or refuting toxicological causation involves a highly specific and painstaking process of investigation as well as application of generally-recognized scientific, forensic and deductive principles. Toxicological causation analyses require a thorough investigation and review of all available data and case facts including generally-accepted toxicological studies, relevant deposition transcripts, medical records, police reports and (in some cases) review or inspection of the exposure or accident scene.

The expert toxicologist forms a causative opinion based on the relationship(s) between scientific information and objective evidence. Assessments must be based on sound methodologies, sometimes covering a wide range of substances. The expert must present all evidence, methods and results in an unbiased, scientifically credible and objective manner. It may also be incumbent upon the expert toxicologist to present his findings clearly and succinctly to the court, jurors and (in some cases at the client's request) the news media or other lay persons.

It is important to note that causation may or may not be established in an investigative assessment. *There is no guarantee of a conclusive outcome.* However, direct on-site investigation, exposure reconstruction supported by laboratory analyses, dose calculations and disciplined, thorough review of available (world-wide) toxicological studies in the peer-reviewed scientific literature will often lead to toxicologically-reasonable conclusions demonstrating or refuting causation.



A determination of toxicological causation must satisfy multiple investigative criteria.[a]

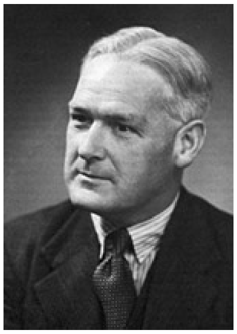
Types of Causation

Generally, the expert toxicologist must either *demonstrate* or *refute* causation. There are two types of causation which the toxicologist may be required to assess: (1) *general causation* and (2) *specific causation.*

- **General Causation** is a methodology which determines whether or not exposure to a substance or agent is *capable of producing an adverse health effect*. General causation determination can also measure the potential for impairment or death stemming from the use of (for example) pharmaceuticals, drugs-of-abuse or alcohol. Typically, an opinion of general causation requires supporting evidence in the form of peer-reviewed scientific literature identifying dose-response relationships and/or epidemiological studies describing medical conditions associated with the exposure in question. The evidence demonstrating that the exposure (chemical, drug, substance, consumer product, etc.) is capable of causing the health effect must be reliable and recognized within the generally-accepted body of scientific and/or toxicological literature.
- **Specific Causation** is a methodology which determines whether or not exposure to a substance or agent *did, in fact, cause the specific adverse health effect at issue*. There are significant and critical differences in distinguishing specific causation from general causation. It is possible that an exposure can be demonstrated to be capable of causing an adverse health effect, but this alone does not mean that it did, in fact, cause the effect. For example, radon exposure is capable of causing the same type of bronchogenic lung cancer as cigarette smoking. If both exposures have occurred, each must be appropriately quantified. This means the toxicologist must weigh the individual doses, timeframes and exposure frequencies and calculate the degree to which each exposure contributed to the adverse health effect at issue. Thus, individual exposure data must be compiled, quantified and assessed in accordance with the prevailing body of peer-reviewed toxicological literature.

Causation and Weight-of-Evidence

A causative determination is the result of following a detailed set of procedures supported by generally-accepted methodologies. Application of a weight-of-evidence ("WOE") methodology relies in part on the list of guidelines developed by Sir Austin Bradford Hill for inferring general causation.[1] Such an approach requires review of several types of evidence relating to the effects of exposure. These types of evidence (or "modalities") include human epidemiological studies, case reports, reviews, studies assessing the commonalities between a group of epidemiological studies and studies of exposures on animals or *in vitro*.[2]



Sir Austin Bradford Hill.[(b)]

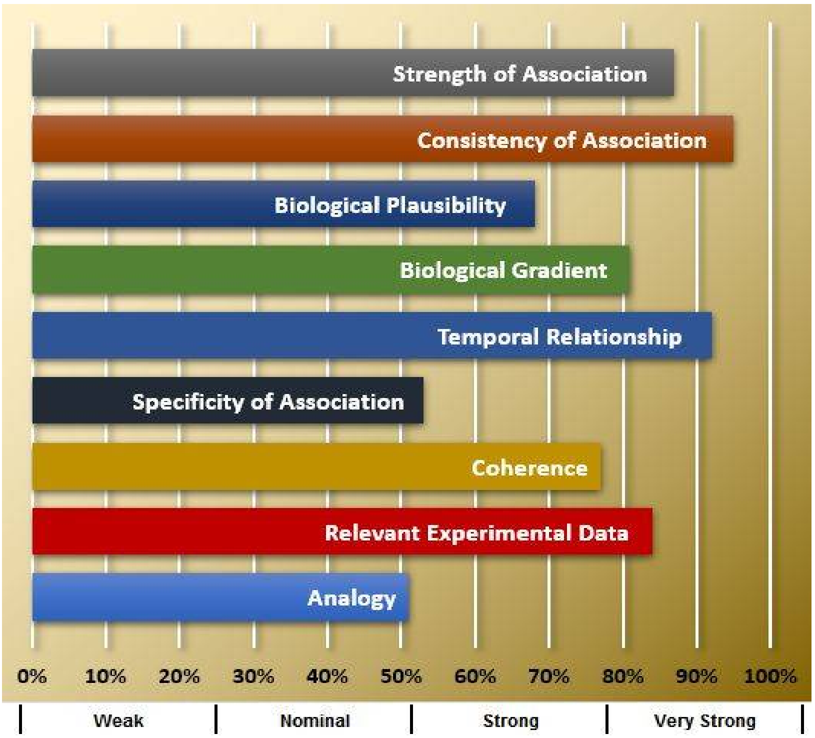
Sir Austin Bradford Hill (1897-1991) and Sir Richard Doll (1912-2005) pioneered the concept of case-control studies. Subsequently, Hill and Doll were the first to apply a scientific methodology to demonstrate the causal connection between cigarette smoking and lung cancer.[3] Hill subsequently published a groundbreaking paper in 1965 in which he formalized his approach to determining causation.[4] Today, Hill's criteria for establishing causation (the "Hill Factors") sets the toxicological standard for defining a causal relationship between an event and a consequence.

In a toxicological causation assessment the "Hill Factors" are important components in compiling weight-of-evidence. Additionally, the expert toxicologist may apply a wide variety of experimental data showing the biological mechanisms through which a substance can or may create adverse health effects with respect to the metabolic pathways of the substance in animals and humans. These and other generally-accepted methods all contribute to a scientifically-sound causation determination.

A weight-of-evidence approach should also include review of any available information regarding structure of the chemical at issue and the similarity of its structure to chemicals already known to cause certain health effects in humans. However, scrupulous care must be exercised when applying different studies to causative issues. Dr. Sheldon Krimsky, Professor of Urban and Environmental Policy and Planning at Tufts University, writes in his article entitled "The Weight of Scientific Evidence in Policy and Law" that *"Each type of study may provide some evidence, but each has its limitations."* He also writes, *"If a chemical were known to be one of the causal agents responsible for a human disease, then we would expect a series of evidentiary pathways to converge on that conclusion .. But not all of the evidence may be consistent with the result."* [5] Thus, confounding factors are almost always present in a causative investigation.

The Hill factors establish a broad framework to help evaluate the various modalities of evidence relevant to the general causation question. Hill's causative modality factors include consideration of:

1. Strength of association between the exposure and a particular health effect
2. Consistency of the association
3. Biological plausibility of the causal connection
4. Biological Gradient (Dose-responsiveness)
5. Temporality (time relationships)
6. Specificity of the association
7. Coherence of the association
8. Relevant experimental data (i.e. animal studies)
9. Analogy



Example of "Hill Factor" Weighting of Causative Modalities.[(c)]

In assessing chemical causation, as many of the Hill factors should be applied as possible. However, it is not uncommon for there to be little or no information available for one or more factors. Thus, application of the Hill factors to a particular causal hypothesis (and the relative weight to assign to each) is both substance-dependent and subject to the independent judgment of the toxicologist reviewing the available body of data. *"For example, some WOE approaches give higher weight to mechanistic information over epidemiological data."*[6] Modalities beyond the Hill factors should also be considered. For example, the National Research Council states that *"the committee must rely on a combination of evidence from different sources to reach any conclusion in accordance with its mandate to estimate health effects...."* [7]

Summary of Hill Factors

The following citations originate in Dedak, et al., (2015), "Applying the Bradford Hill criteria in the 21st century: How data integration has changed causal inference in molecular epidemiology,"[6] summarizing the various prongs of the Bradford Hill causative assessment criteria.

Strength of Association

"Hill’s first criterion for causation is strength of the association. As he explained, the larger an association between exposure and disease, the more likely it is to be causal. To illustrate this point, Hill provided the classic example of Percival Pott’s examination of scrotal cancer incidence in chimney sweeps. The tremendous strength of association between that occupation and disease — nearly 200 times greater than seen in other occupations — led to a determination that the chimney soot was likely a causal factor."

Consistency of Association

"Traditionally, Hill’s consistency criterion is upheld when multiple epidemiologic studies using a variety of locations, populations, and methods show a consistent association between two variables with respect to the null hypothesis. Hill stressed the importance of repetitive findings because a single study, no matter how statistically sound, cannot be relied upon to prove causation due to ever-present threats to internal validity. This criterion is still very appropriate for determining causal relationships."

Biological Plausibility

"Plausibility has historically been judged based on the presence of existing biological or social models that explain the association of interest. Hill’s criterion of plausibility is satisfied if the relationship is consistent with the current body of knowledge regarding the etiology and mechanism of disease; though, Hill admitted that this interpretation of biological plausibility was dependent on the current state of knowledge."

Biological Gradient

"Hill wrote that “if a dose response is seen, it is more likely that the association is causal.” According to the traditional interpretation of biological gradient, the presence of a dose–response relationship supports the causal association between an exposure and an effect In traditional epidemiology, a monotonic biological gradient, wherein increased exposure resulted in increased incidence of disease, provides the clearest evidence of a causal relationship. However, Hill acknowledged that more complex dose–response relationships may exist."

Temporal Relationship

"Temporality is perhaps the only criterion which epidemiologists universally agree is essential to causal inference. Consider that Rothman and Greenland, despite finding a lack of utility or practicality in any of the other criteria, referred to temporality as “inarguable”. Hill explained that for an exposure-disease relationship to be causal, exposure must precede the onset of disease. Thus, epidemiologic study designs which ensure a temporal progression between the two measures are more persuasive in causal inference."

Specificity of Association

"Hill suggested that associations are more likely to be causal when they are specific, meaning the exposure causes only one disease. While Hill understood that some diseases had multiple causes or risk factors, he suggested that “if we knew all the answers we might get back to a single factor” responsible for causation. This view is indicative of the fact that, in Hill’s era, exposure was often defined in terms of proxies for true exposures, such as an occupational setting or a residential location. Today, we attempt to specifically define exposures not in terms of a person’s surroundings or conditions, but rather as an actual dose of a chemical, physical, or biological agent."

Coherence

"Today, coherence is another area in which molecular-based studies have been used to demonstrate a comprehensible story regarding various aspects of the exposure-to-disease paradigm. For example, lung tissue fiber analysis by scanning transmission electron microscopy (STEM) has expanded our knowledge of internal biologically effective amphibole dose relating to altered structure and function of lung tissue, supporting the conclusion that amphibole asbestos fibers induce mesothelioma."

Relevant Experimental Data

"Hill explained that evidence drawn from experimental manipulation—particularly epidemiologic studies in disease risk declines following an intervention or cessation of exposure—may lead to the strongest support for causal inference. In vitro studies that test mechanistic pathways and demonstrate the biological role of an agent in disease progression may result in knowledge that can be used to predict potential human health outcomes in a much more time-efficient manner than human studies, particularly for adverse outcomes with a long latency period."

Analogy

"Analogy has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some ways. Today, researchers have a wider range of tools by which to seek an analogy, including disease progression pattern, common risk factors and confounders, and biological mechanisms of action. Therefore, the modern value of analogy is not gained from confrming a causal inference, but rather from proposing and testing mechanistic hypotheses."

Standards of Admissibility

In view of Professor Hill's epidemiological background, it is not surprising that several of his factors focus on consideration of epidemiological evidence. However, such evidence addresses only one aspect among the several modalities of evidence that should be considered in assessing causation. *"The term WOE has come to mean not only a determination of the statistical and explanatory power of any individual study (or the combined power of all the studies) but the extent to which different types of studies converge on the hypothesis."* [8]

The expert toxicologist's testimony must be responsive to answering the questions at issue and rest on a sound, reliable scientific foundation (Rule 702, Federal Rules of Evidence).[9] In particular, toxicological testimony cannot be considered admissible if the evidence is based upon a "novel" scientific technique or methodology. Expert testimony must have its basis in reliable scientific techniques that are generally accepted by the relevant scientific community. Thus, although personal observations and professional experience may play a role in formulating an opinion, they do not, in themselves, constitute an admissible basis for a conclusion. The expert toxicologist must pragmatically assess the list of contributing factors, weigh them appropriately and communicate findings in a scientifically-sound and objective manner.

Accordingly, causation cannot be based solely on professional judgment that is difficult to trace to a well-established scientific methodology. It cannot be vague, formulaic or ignore the complexity and case-specificity of scientific interpretation. Although a causative determination can have statistical support, the statistics merely support the reliable outcome of applying a generally-accepted scientific method. Thus, a scientifically credible causative opinion cannot be reached solely through statistics or extrapolation of numbers. For example, so-called "evidence-based medicine" has not achieved general acceptance in causation due to its very nature which reduces the role of expert judgment in favor of data compiled in computer programs.

Interpretation of Toxicological Evidence

A scientifically credible weight-of-evidence approach to demonstrating or refuting causation must do more than merely comply with the Daubert standard. In some cases (particularly in toxic tort matters), the toxicologist's expert testimony may be required to satisfy a "preponderance of evidence" criteria. This can be seen in cases where a judge applies the Daubert standard not only to expert testimony but also to each study upon which the expert relies. This interpretation of Daubert requires each study to stand on its own merits. In his *Proposal for Linking Culpability and Causation to Ensure Corporate Accountability for Toxic Risks,* McGarity writes:[10]

> "If the plaintiff fails to establish the relevance and scientific reliability of a sufficient number of individual studies, the trial judge may exclude the expert's testimony and (in the absence of other relevant and reliable expert testimony on causation) grant the defendant's motion for summary judgment before the jury ever enters the picture."
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> T.O. McGarity "Proposal for Linking Culpability and Causation to Ensure Corporate Accountability for Toxic Risks."
> William and Mary Environmental Law and Policy Review, Fall 2001.

This reminds us that there are both judicial and regulatory approaches to interpreting toxicological evidence. In regulation, the strands of evidence are not assumed to stand by themselves but are seen as pieces of a larger puzzle. Scientific interpretation of the puzzle forms the basis of the peer-review process in which each piece is assessed on its merits by professionals with good education, experience and reputation.

The expert toxicologist must also be mindful of the fact that good communication is paramount and judges and juries are not toxicologists. Toxicological assessments can be extremely complex and findings must be presented such that the court can understand them. A judicial interpretation may apply different weights to different pieces of evidence based on comprehension of the evidence *as presented.* Thus, whether submitting a report or offering testimony in deposition, being "right" and being concise are equally important. Conscientious application of brevity and meticulous attention to detail can go a long way toward avoiding misunderstandings in forensic matters.

To that end, it is helpful to remember that the "weighing instrument" for "weighing evidence" is always *human cognition.* Forensic toxicological testimony can be complex and the more simplistically it can be presented, the greater the likelihood that it will be understood by a judge and jury. By sticking strictly to the science and presenting each piece of information in its most understandable form, the expert toxicologist assists the court by assembling the puzzle pieces into a comprehensive picture that either demonstrates or refutes causation.

Concordantly, causation is based on weight-of-evidence which must always be based on good science. Ideally, WOE turns subjective perceptions in a forensic matter into a purely rational, objective experience. Since interpretation is involved, criticism must not only be expected, it must be anticipated. The expert toxicologist must be fully prepared to defend both his opinions and the data upon which his opinions are based — with concise professionalism, integrity and objective evidence.

Summary

In forensic causation matters, the expert toxicologist proceeds in the direction in which the evidence leads. The goal of any toxicological analysis of causation is to establish the true cause to *reasonable toxicological certainty.* Since toxicological expert testimony has the potential to significantly impact the outcome of a case, accurate compilation of evidence, thorough collation of Hill factors and conscientious application of weight-of-evidence, are all central to an accurate toxicological causation assessment.

Notes and References

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A Message from Dr. William R. Sawyer
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