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Toxic Exposure and Disease: Perspectives from the Scientific, Regulatory and Legal Communities On Causation

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In the 21st century, people across the globe encounter more suspected toxins on a daily basis than any time in the history of our planet. Whether a suspected toxin increases the risk of or causes illness or disease is a central question that surfaces in very different ways in the scientific, regulatory and legal communities. There are critical differences in how scientific data is viewed, interpreted and applied when determining causation in a scientific, public health/regulatory, or legal context. Routinely, scientists form hypotheses and study whether there is a scientifically-established causal connection between exposure to a toxin and illness or disease. By contrast, while regulatory and health-based agencies/organizations are science-driven, tend to focus on broader questions on whether a toxin poses a potential health hazard to the public. In the courtroom, courts and juries consider whether exposure to a toxin is a "legal" cause of an injury. Juries are often incapable of truly understanding the differences between good and bad science, especially when well-qualified experts on both sides appear convincing. The fallout is that: (1) companies can no longer look to reliable science to dictate reasonable conduct; (2) the scientific process is diluted and replaced, at least in our court system, with a distorted misperception on what science tells us; and (3) it encourages litigation of scientifically-unsupported claims with enormous financial consequences, both in defending the claims and paying out compensation. The key to solving this problem is to educate courts on how to objectively assess the literature and only permit expert opinions that meet the high standards of truly reliable science; thus, truly fulfilling their gatekeeping role of only permitting scientifically-reliable expert opinions to support claims of toxic exposure. The scientific, regulatory, and legal fields can better support courts in their gatekeeping responsibilities by continuing this open dialogue and transparently acknowledging differing opinions, methodologies, and missions.

Keywords: Causation, Court gatekeeping, Toxic tort, Exposure, Regulation

Introduction

In the 21st century, people across the globe encounter more suspected toxins on a daily basis than any time in the history of our planet. Whether a suspected toxin increases the risk of or causes illness or disease is a central question that surfaces in very different ways in the scientific, regulatory and legal communities. Routinely, scientists form hypotheses and study whether there is a scientifically-established causal connection between exposure to a toxin and illness or disease. By contrast, regulatory and health-based agencies/organizations utilize the science to focus on broader questions on whether a toxin poses a potential health hazard to the public and incorporate multiple conservative assumptions to protect even the most sensitive communities. In the courtroom, courts and juries consider whether exposure to a toxin is a "legal" cause of an injury. There are critical differences in how scientific data is viewed, interpreted and applied in these three contexts.

In this article, we explore the methods and objectives of scientific research versus public health/regulatory initiatives. With a clear understanding of these separate approaches and goals, we then analyze how

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they should properly be considered (or not considered) by courts in fulfilling their gatekeeping role of only permitting scientifically-reliable expert opinions to support claims of toxic exposure. Herein, three authors speak to these differing perspectives:

Catie Boston, MPH, DABT and colleagues at Roux Associates discuss scientific research;

Justin DeWitt P.E., LEED AP at the Illinois Department of Public Health lends a regulatory perspective; and

Joe Welter, Esq. at Goldberg Segalla provides his observations regarding court gate-keeping.

To conclude, each author suggests role-specific recommendations and potential solutions for how to better support the court in its gatekeeping role and the importance of continuing this discussion in all communities (scientific, regulatory, and legal) to ensure just and responsible decisions are made.

How the Scientific Community Studies Causation

Catie Boston, MPH, DABT; Adam Love, PhD.; Stella Keck, MPH: Roux Associates, Inc.

Establishing general causation through scientific analysis, at the most basic level, involves demonstrating that one event (the exposure) causes another event to occur (the disease, or adverse outcome); similarly, without the exposure, the adverse outcome would not have been observed. In the area of human health, demonstrating causation is often a combination of mechanistic knowledge and strong scientific evidence supporting biologic plausibility: based on a known biological mechanism that explains how the exposure causes the disease and based on statistically significant evidence demonstrating an increase or decrease in disease rates dependent on exposure, which cannot be explained by a third variable. Additionally, understanding of causation should function as a method for explaining why certain events fail to occur as it is to explain events that do occur.

To establish causation scientifically, a variety of evidence must be utilized in tandem to demonstrate biological plausibility[1] through an evaluation of mechanistic or structural capability, dose-response assessments in animals bioassays, and epidemiological studies demonstrating elevated risk of disease post-exposure. If an effect is observed in epidemiological studies but is not observed in and/or cannot be explained by mechanistic studies, then causation cannot be proved. In contrast, if a plausible biological mechanism is observed, yet the disease is not observed in the human population that has been exposed, then a general causation claim cannot be made. In addition, the capability of an agent to produce an adverse effect should be evaluated for a dose-response relationship: where an increased exposure results in increased disease prevalence.

Scientific approaches have and will always evolve[1], and demonstrating causation using available data is no different. Countless frameworks for evaluating causation have been employed, including the Bradford Hill Criteria[2], hypothesis testing, and the weight of evidence approach (among others). While various methods for demonstrating causation have been used over time, there are several common themes that have consistently played a key role in reliable evaluations of causation:

- Reviewing the entire body of scientific evidence,
- Relying on peer-reviewed literature,
- Within each type of data utilized, recognizing and relying upon the appropriate study hierarchy strength, and
- Relying on statistically significant results and high-powered studies of high quality.

A lack of adherence to these themes often plays out in the courtroom when evidence of causation presented to a jury reflects “cherry-picking” evidence or

[1] Biological plausibility can be examined via an evaluation of mechanistic or structural capability, and in studies conducted in animal and human in vitro and in vivo settings. An assessment of a chemical’s physical properties including structure, solubility, electrophilicity, volatility and chemical reactivity is important when evaluating its potential hazards and ability to produce a biological response.

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aggrandizing weak scientific evidence. Keep in mind, these scientific themes are critical when establishing the two backbones of scientific causation: 1) identifying biological plausibility to explain how the exposure causes the outcome and 2) demonstrating statistically significant elevated rates of disease in exposed cases through epidemiological studies.

A. Review the entire body of evidence

A straightforward and seemingly obvious scientific pillar necessary to demonstrate causation is the need to formulate a causation opinion based on a review of all quality information – not a partial, or a subset of available evidence. Scientific causation cannot be viewed as reliable if it based only on a subset of the scientific evidence and avoids addressing the full spectrum of the scientific knowledge base. A literature review of available evidence is an integral first step in determining causation and before a court's testifying expert can form an opinion; systematic reviews should be transparent, objective, comprehensive, and reproducible[3]. After all scientific evidence is collected, study results and conclusions should be evaluated in the context of their quality, relevance, and completeness.

An expert who cherry-picks the data to utilize in their calculations or arguments, by reviewing a specific subset of the available literature, misrepresents and skews the result presented to a jury. Such misrepresentations violate the fundamental role of a testifying expert in helping the court, including judge and jury, to understand the science. Juries cannot be expected to be comprised of members who have the experience/expertise to vet the scientific method, research what studies may be missing from the expert's analysis, or understand the impacts of data omissions. Herein lies the need for, and difficulty of, scientific gatekeeping.

B. Rely on peer-reviewed literature

Another seemingly obvious step to evaluate when investigating scientific causation is the importance of relying upon peer-reviewed literature over non-peer-reviewed literature.[2] Within the scientific and academic community, technical analysis must undergo a rigorous peer-review process to validate the replicability, quality, and appropriateness of the study design. The peer review process consists of a group of experts within the appropriate field, these impartial reviewers are tasked to carefully evaluate all aspects of the study focusing on the quality, validity, accuracy, and replicability. Many times, revisions are suggested, and the process is iterative. A peer-reviewed journal will not publish an article that has failed to meet the approval of the peer review group for that specific scientific specialty.

Unfortunately, the modern scientific community now deals with a dilution of strong, peer-reviewed scientific literature. While the peer-review process has remained unaltered, the rise of journals that lack a peer-review process, or have a less rigorous review process, have allowed studies to be published that are of low quality, are low powered, and cannot be replicated by others.[4,5] It is impossible for a lay-person to distinguish which "scientific journals" are "pay to play" constructions, and realize conclusions of those studies should be weighted differently than robust, peer-reviewed scientific literature. Typically, the conclusions of one study alone do not provide sufficient basis to support causation as it would not satisfy the expectation of the replicability of such results, as similar results must be observed across multiple studies. The publishing of poor quality "junk science" leads to dilution of the true scientific evidence and muddies replicability. It takes time, energy, and scientific expertise to critically evaluate and weigh scientific evidence. Clouding the literature with junk information is a tactic to obscure true scientific evidence, a technique relied upon by certain experts

[2] There are many important examples of raw data that have been vital in determining scientific causation and public health regulatory standards that did not undergo the peer-review process. This underlying "raw," and potentially protected, human, animal, and/or cellular data may not be produced publicly or published in a journal; however, this lack of "peer-review" of the raw data does not undermine the importance of this type of data. In this context, the requirement of the peer-review process is imperative for articles that present an opinion after analysis and utilization of raw scientific data, or an opinion on a pooled analysis of multiple underlying raw studies.

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when opining in front of the court.

C. Recognize and rely upon the appropriate study hierarchy by data type

There are various types of scientific tests used to evaluate different facets of causation. A brief description of a handful of common types of tests typically conducted, and their goal, is provided below:

Cell assays: Various types of cell assays can be used to screen if a toxicant is capable of potentially causing an outcome of interest. Cell assays are inexpensive, rapid, and if conducted correctly, can provide valuable information regarding potential mode of action for toxicity. There are various assays designed to investigate different outcomes. For example, there are multiple types of genotoxicity assays that investigate a chemical's ability to damage the genetic information within a cell (micronucleus induction, in vivo chromosomal aberration, bacterial reverse mutation tests, in vitro tests for mammalian gene mutation, and in vitro tests for mammalian chromosomal abnormalities and others).

Toxicokinetic tests: Toxicokinetic studies investigate how a chemical gets into the body, and what happens once it is in the body; essentially, absorption, distribution, biotransformation, and excretion.[6] Toxicokinetic tests include various biomonitoring studies, in vitro dermal absorption tests, and a range of time course studies illustrating tissue kinetics.

Animal bioassays: Animal bioassays investigate a chemical's ability to produce the outcome of interest in an animal species, including specific types of cancer or non-cancer outcomes. Disease and/or mortality counts within the animal population can be analyzed with a variety of statistical tests including pairwise tests, trend analyses, initiation vs. promotion of carcinogenicity, etc.[7]

Epidemiological studies: Epidemiological studies investigate a chemical's ability to produce the outcome of interest in a human population, including cancer and non-cancer outcomes. Test subjects with the outcome of interest are often compared to a population of controls without the outcome of interest, to investigate the differences in exposure between the two populations. Or conversely, a group of exposed are compared to a control group of unexposed individuals and the outcome of interest is measured. Epidemiological study designs include cohort, case-control, ecological, and cross-sectional tests.[8]

Within each type of test, there is almost always a hierarchy of study design within each field. This study hierarchy, along with study quality, must guide how various studies are weighted. Each type of study will have its strengths, weaknesses, and potential biases. Ideally, the "gold" standard study design for that data type should always be relied upon; however, depending on the size of the body of scientific literature available, other study designs may need to be considered in the context of their limitations.

For example, epidemiological study design has clear consequences regarding the quality of conclusions and the potential for bias. As described above, generally epidemiological studies evaluate exposed and unexposed populations, and compare rates of adverse outcomes. Within the field of epidemiology there are many different types of study design; however, the most reliable, and most time consuming and costly is the randomized controlled trial (RCT). RCTs lack many of the biases that observational studies may have such as selection bias, recall bias, information bias, and confounding. When evaluating the full breadth of epidemiological data for a topic, it is important to consider the study design hierarchy, and the strengths and weaknesses of each study within each design category. Below is a table of the most common types of epidemiological studies, the highest quality and most robust results being found in RCTs, then cohort studies, case-control studies, and finally pooled analyses or meta-analyses.

While RCTs are of the highest quality with the most dependable results, they are extremely expensive to conduct and in many situations unethical to conduct in humans. At the other end of the spectrum, meta-analyses are low effort and low cost alternatives. Juries can easily be misled by "counting exercises" where many, low quality studies are touted above a

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handful of high-quality studies. However, it is paramount to emphasize to juries the relative weight of each of the types of studies when assessing their conclusions.

Table 1. Epidemiological Study Designs from Highest Quality to Lowest Quality.

Study Design	Description	Effect Estimate	Strengths and Sources of Bias/Confounding
Randomized Controlled	Randomly assign the subjects to a control group and an experimental group.	Odds Ratio (OR) Rate Ratio (RR) Risk Ratio (RR)	●Costly and sometimes unethical <u>Strengths</u> ●Avoids confounding ●Minimizes selection bias
Cohort	Begin with an exposed group and nonexposed group (both disease free) and follow to observe disease incidence; can be prospective or retrospective)	●Rate ratio (RR) compares incidence rate of disease in exposed and nonexposed groups based on person years (null value equal to 1); ●Risk ratio (RR) compares incidence rate of disease in exposed and nonexposed groups based on number of subjects (null value equal to 1)	<u>Strength</u> ●Avoid and/or adjust for selection bias, information bias, and confounding ●Easier to establish temporality
Case-control	Begin with diseased and non-diseased groups and look backwards in time at exposure	Odds ratio (OR) represents the odds that a disease will occur in a group of people given their exposure (null value equal to 1)	●Selection bias ●Recall bias ●Information bias: difficult to measure past exposure accurately <u>Strength</u> ●Logistically efficient

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Study Design	Description	Effect Estimate	Strengths and Sources of Bias/Confounding
Pooled Analysis/ Meta-analysis	Provides weighted average of quantitative results across multiple studies; pooled analysis uses raw data, while a meta-analysis uses summary estimates	Meta-analyses use ORs, RRs and confidence intervals from other studies	●Meta-analyses include sources of bias from original studies (potential for confounding, selection bias, recall bias) <u>Strength</u> ● Greater statistical power due to larger sample sizes

D. Rely on statistically significant results and high-powdered studies

The importance of statistical significance cannot be overstated. Modern science depends on demonstrating the difference between true association and a result that is due to bias or chance. Biostatistics are hypothetical calculations that hold no real consequence in the real world without demonstrating statistical significance.[3] For example, when a study reports a result, the author should report both the effect size and a confidence interval. The effect size is a theoretical number, such as the percentage of people who will be born with red hair. The confidence interval indicates the lower and upper confidence limits for that effect size. To interpret this result, we'd say: We are 95% confident that the percentage of people with red hair falls between X% and Y% in the true population. This means there is still a 5% chance that the true percentage of people with red hair could fall outside of that range. This effect size is then compared to the "null" result, if the effect size and its confidence interval overlaps with the null result, then it is not statistically significant.

If a result is not statistically significant then the result cannot be used to demonstrate that a relationship between the exposure and the disease exists. Statistical power is another key player in determining if the result seen in a study should be relied upon when deducing causation. Statistical power is the probability that the test correctly rejects the null hypothesis and is not a false negative. Another way of looking at statistical power is as the probability of accepting an alternative hypothesis, when that alternative hypothesis is true. Statistical power is related to the sample size of a study, generally small sample sizes result in low statistical power.

A jury may not be trained in biostatistics and may not understand the importance in demonstrating statistical significance and power, which can cause someone to allow "marginally" significant results presented to them to sway their opinion or make it seem like another expert is randomly throwing out results when they are in fact not statistically significant and should not be relied upon.

[3] Importantly, statistical significance alone does not demonstrate biological significance. For example, statistically significant results in epidemiology studies must be supported by an identified biological mechanism that can reasonably explain how a disease may arise after a specific exposure at both the cellular and animal level. Statistical significance needs to be demonstrated at each step along the biological pathway towards disease development in order to demonstrate causal association.

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These scientific pillars are the backbone in demonstrating biological plausibility and seeing a statistically significant epidemiological effects and unfortunately, are easily manipulated before a jury. Demonstrating scientific causation between an exposure and a disease outcome, requires evaluation of all available data, reference of peer-reviewed literature, recognition and utilization of the highest quality study designs within each data type, and reliance upon statistically significant and high-powered results. The scientific process in determining causation takes time, because conducting valid and sound scientific studies is time consuming.

The scientific community must recognize their responsibility as truth seekers and take a stronger stance to combat misinformation and junk science, and highlight true findings in a digestible fashion for the court, jury, and general public. This change needs to begin within the interconnected network of researchers, academics, consultants, and other professionals who create, handle, and interpret raw scientific data through refining the peer-review process, mentoring the next generation in best practices, and rewarding good, solid science, in order to prevent the full responsibility of determining specific and general causation from falling on the heads of a judge and jury.

How Regulatory and Public Health-Based Organizations Assess Risk

Justin DeWitt, PE, LEED AP: Illinois Department of Public Health (IDPH)

Public health scientists and regulators often have a different objective than establishing causation. Public health agencies and regulatory bodies, while based on the science discussed in the previous section, are tasked with identifying potential health risks and protecting the most susceptible populations—with additional margins built in for uncertainty. Regulators primarily rely on a set of standards to manage risk to public health. When levels of a known toxin are exceeded, the potential risk not the actual risk often triggers the response. Scientifically, a toxin's impact to humans varies and so individual risk assessment for exposures become too cumbersome and subjective to provide a reliable regulatory framework. Public health actions at their core are intended to protect people, and therefore, ascribe to the "precautionary principle." The precautionary principle asserts that assurance of safety is paramount, and any uncertainty must be resolved in favor of prevention of potential harm. Therefore, even in cases when causation is not yet established, precautionary measures should be taken if the potential risk could be significant.

The Illinois Public Health Act specifies that "the State Department of Public Health has general supervision of the interests of the health and lives of the people of the State. It has supreme authority in matters of quarantine and isolation. . . . The Department may adopt, promulgate, repeal and amend rules and regulations and make such sanitary investigations and inspections as it may from time to time deem necessary for the preservation and improvement of the public health." (20 ILCS 2305/2).[9] Likewise, the Illinois Asbestos Abatement Act, 105 ILCS 105/2, has a stated purpose "to provide for the identification, containment or removal of those asbestos materials that constitute a significant health hazard."[10]

The Asbestos Abatement Act adopts the precautionary principle to protect public health: "precise scientific data as to the levels at which asbestos materials constitute a hazard to health in educational settings are not yet available and may not be available for many years to come because of the long period of time which elapses between the onset of exposure and the appearance of clinically detectable illness; however, mesothelioma has been found among individuals exposed to asbestos in some nonoccupational settings; and in view of the fact that the State of Illinois has compulsory attendance laws for children of school age and these children must be educated in a safe and healthy environment, the presence and condition of asbestos in the schools is of special concern to the General Assembly."

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The Asbestos Abatement Act is an example of when exposure is occurring in the general population and the scientific evidence on a topic is still in development. Conducting robust epidemiological studies and performing high quality chronic toxicological studies takes years. Therefore, regulatory agencies ascribe to the "precautionary principle" making conservative assumptions and applying conservative factors in the face of uncertainty.

This paradigm of "worst case" scenario plays out often in the regulation of public health matters. In the last 20 years asbestos-related disease cases have occupied many courtrooms across the country, perhaps none more famously than Madison County, Illinois. Though not considered a contemporary toxin by today's standards, asbestos still provides a good example of regulating to a standard of care, a standard of conduct, and the maximum levels of the regulated substance. This discussion will consider asbestos regulation in K-12 schools, the purview of the Illinois Department of Public Health. Regulated at the federal level under the Asbestos School Hazard Abatement Reauthorization Act of 1990 and in Illinois under the Asbestos Abatement Act, IDPH has worked to guide the efforts of schools in managing their asbestos.[11]

Managing asbestos in schools requires a standard of care exercised by the school administration to ensure that the installed asbestos in its building(s) is maintained and managed in accordance with the regulations. Schools inventory and assess their asbestos every six months to ensure its condition has not changed. Further, the regulations require that when asbestos is disturbed it must be handled in strict adherence to a set of rules addressing the conduct of personnel and the practices which protect workers, students and staff from exposure. Asbestos removal procedures are highly prescribed and conducted only by licensed professionals in restricted settings. Finally, asbestos abatement and the release of asbestos fibers are held to a narrow window of standards set at very low permissible levels to guard against acute or long-term exposure of building occupants. The clearance standards for asbestos in air for K-12 schools is 70 structures/mm^2 where structure size is measured in μm (10^{-6}m). Breaching these regulations comes with significant consequences as they are meant to protect school occupants from acute and long-term exposure to a known carcinogen.

A frequent occurrence in K-12 schools is the improper removal of suspect or assumed asbestos containing pipe insulation. Highly "friable" and when improperly removed, pipe insulation releases fibers contaminating large areas of school buildings. Further spread by HVAC systems, fibers can move to adjacent areas to the fiber release broadening the affected area.

When IDPH investigates such situations, it applies the "worst case" principle. It assumes that the disturbed material contains asbestos, further that its disturbance has released fibers at or above regulatory limits and that exposure of persons constitutes a real danger to public health. IDPH issues an order to stop the disturbance, seal the affected areas and require a cleanup plan to be developed. Results of regulatory samples taken during the investigation ultimately determine outcomes, but IDPH's response is immediate and protective. It is better to close a school building down for a day than allow staff and students to remain in a potentially contaminated space while awaiting lab results. The school building is reoccupied only when the clearance level is achieved.

By design, regulatory standards are designed to be protective of the most susceptible members of the population, while also assuming worst-case exposure scenarios. It is essential that scientists and the courts understand the nuances surrounding derivation of such regulatory standards, and what scenarios they truly represent. Regulatory thresholds do not represent the threshold for causation of disease, as such calculations have a fundamentally different objective than the types of calculation performed by scientists who assess causation of disease.

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When government agencies set out to develop or revise regulations, there should be consideration given to the downstream impacts. For this discussion, regulations may include statements concerning investigations and the evidence they create, making clear to a trial court the limitations of the findings and the actions of the regulator. Disclaimers in regulatory reports may be needed to ensure that findings are not inappropriately associated with disease or injury outcomes that were not part of the regulatory investigation. For example, it is often difficult to definitively match chemical or biological regulatory samples to human specimens. Further, it is often beyond the capacity of the regulator to opine on whether a health outcome was indisputably tied to an exposure to a regulated substance.

For health agencies, regulatory capacity or responsibility is generally limited to preventing immediate harm, reducing risk and permanently addressing the violative condition. Clearly spelling out, in regulation, the framework and the capabilities of the regulatory construct could reduce the inappropriate use of government actions and reports in causation cases. Providing "guardrails" in the regulations themselves must be done carefully so as not to erode the legitimate work of government regulators or their role in protecting the public and the environment. Communication and engagement between the regulated public and government at the time of revision or creation will lead to better regulations and reduced any potential misuse of the products of regulatory action.

When Science, Regulatory/Public Health Pronouncements and the Law Collide

Joseph Welter, Esq.: Goldberg Segalla

The importance of true, unbiased scientific research resulting in reliable scientific conclusions is the cornerstone of general and specific causation analysis. Yet, when the concept of "reliable science" is raised in our adversarial legal system, it leads to manipulation, dilution and mischaracterization of these core principles. Claims are often pursued despite the lack of any scientifically-established causal connection between the claimed exposure and injury or disease. This is precisely why the courts are tasked with the critical role of scrutinizing the science and rejecting expert opinions that are untethered to sound scientific methodology and analysis. While the legal standard for the admissibility of expert causation opinions varies by jurisdiction, the goal is the same, namely to only permit juries to consider scientifically-supported opinions offered by experts.

In fulfilling this gatekeeping role, Courts are required to view the proposed expert opinion through the prism of scientific analysis discussed in the first section of this article. In other words, the Court conducts its own independent "peer review" of the scientific literature to ensure the expert is actually following those principles. Is the expert relying on the type of scientific testing that people in the scientific community rely on? Is the literature on which the expert relies the type from which causation conclusions can be reached? Does the literature actually support the expert's hypothesis and conclusions? Did the expert consider all the available literature in reaching their conclusion? These are the fundamental questions that should be asked. Courts that ask these questions and scrutinize the offered opinions as scientists invariably fulfill their gatekeeping role of only allowing juries to consider scientifically-reliable evidence.

A. Legal Standards for Admissibility of Scientific Evidence

In the seminal case of Frye v. U.S., 293 F. 1013 (D.C. Cir. 1923), the Court set the standard for admissibility of expert opinions in court:

> Just when a scientific principle or discovery crosses the line between the experimental and demonstrable stages is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized, and

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> while courts will go a long way in admitting expert testimony deduced from a well-recognized scientific principle or discovery, the thing from which the deduction is made **must be sufficiently established to have gained general acceptance in the particular field in which it belongs**.

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

In 1975, Federal Rule of Evidence §702 was enacted, which set the following standard for admissibility of expert testimony:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evidence 702. Under this new rule, sections (c) and (d) have become the standard for assessing the scientific reliability and admissibility of expert causation opinions. In Daubert v. Merrill Dow. Pharms., Inc., 509 U.S. 579 (1993), the Supreme Court establish additional factors for admissibility of expert opinions:

> The specific factors explicated by the Daubert Court are (1) whether the expert's technique or theory can be or has been tested—that is, whether the expert's theory can be challenged in some objective sense, or whether it is instead simply a subjective, conclusory approach that cannot reasonably be assessed for reliability; (2) whether the technique or theory has been subject to peer review and publication; (3) the known or potential rate of error of the technique or theory when applied; (4) the existence and maintenance of standards and controls; and (5) whether the technique or theory has been generally accepted in the scientific community.

Fed. R. Evidence 702 (commentaries).

Historically, different states have adhered to the Frye "general acceptance" theory while other states have adopted the Rule 702 and Daubert standard. Some Frye jurisdictions, such as New York, have not adopted Daubert, but have gravitated in that direction for toxic exposure cases. For example, in toxic exposure cases, New York's Court of Appeals has adopted the following standard:

> [A]n opinion on causation should set forth a plaintiff's exposure to a toxin, that the toxin is capable of causing the particular illness (general causation) and that plaintiff was exposed to sufficient levels of the toxin to cause the illness (specific causation) (see e.g. McClain v Metabolife Intl., Inc., 401 F3d 1233, 1241 [11th Cir 2005]; Wright v Willamette Indus., Inc., 91 F3d 1105, 1106 [8th Cir 1996]).

Parker v. Mobil Oil Corp., 7 N.Y.3d 434 (2006). In this context, New York requires that the expert either quantify the exposure or rely on analogous exposure evidence known to be capable of causing the claimed illness.

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Whether a scientist can draw conclusions on causation from the body of scientific literature is distinct from any legal proceeding. Nevertheless, the nuances of the legal standards in different states may render the same expert opinions admissible in one state but not another.

B. The Reference Manual on Scientific Evidence

In an effort to bridge the gap between the scientific and legal communities, the Federal Judicial Center and National Research Council of the National Academies published the "Reference Manual on Scientific Evidence," which purpose is described as follows:

> First published in 1994 by the Federal Judicial Center, the Reference Manual on Scientific Evidence has been relied upon in the legal and academic communities and is often cited by various courts and others. Judges faced with disputes over the admissibility of scientific and technical evidence refer to the manual to help them better understand and evaluate the relevance, reliability and usefulness of the evidence being proffered. The manual is not intended to tell judges what is good science and what is not. Instead, it serves to help judges identify issues on which experts are likely to differ and to guide the inquiry of the court in seeking an informed resolution of the conflict.[12]

Over the years, courts refer to this manual and, in some cases, use it as the foundation under which it assesses the reliability of an expert's opinion. The manual is a compilation of articles published by experts in various fields of expertise. While some of the comments do not reflect traditional scientific methodology, it is nevertheless an important reference guide to encourage courts to consider scientific questions in the proper context.

C. Proper Scientific Analysis Should Trump Legal Admissibility Standard

Regardless of which legal standard is applied, when Courts properly scrutinize the scientific evidence as scientists do, in most cases the conclusion should be the same. Here is a prime example.

In Chapman v. Procter & Gamble Distrib. LLC, 766 F.3d 1296 (11th Circuit 2014), the Court examined under the Daubert standard opinions offered by four plaintiff experts as to whether zinc in denture adhesive was capable of causing injury. The district court considered these expert's opinions based on "reliable methodologies, including dose-response relationship, epidemiological evidence, background risk of the disease, physiological processes involved, and clinical studies." After thoroughly scrutinizing the body of scientific literature, the Court concluded that these experts did not satisfy any of these recognized methodologies. On appeal, the 11th Circuit affirmed that the district court opinion.

Similarly, the same types of claims were brought in Pennsylvania state court, which applies the Frye standard for admissibility of expert testimony. Jacoby v. Rite Aid Corp., 2013 Pa. Super. Unpub. LEXIS 433 (Superior Ct 2013). Despite the different legal standard, the Court considered the expert opinions as scientists would. Initially, the Court rejected the expert's attempt to proffered "methodologies" such as weight of the evidence in the abstract that had no acceptance in the scientific community. The Court then proceeded to scrutinize the literature relied on by plaintiff's experts, concluding that it simply did not support the conclusions reached by the experts.

D. True Scientific Debates in Our Legal System

Even when courts faithfully and diligently fulfill their gatekeeping role and objectively assess the scientific literature, there is still room for legitimate and reasonable disagreement among scientists. There is also the potential for courts to subjectively emphasize certain aspects of the scientific methodology to reach a conclusion. In this setting, the questions include who has the burden of proof, should juries be tasked with deciding scientific disagreements, or should expert opinions be precluded until there is a consensus from the scientific community on causation? It is in this

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setting where courts are challenged with deciding these issues.

An interesting example of courts applying objective scientific assessment, but reaching different conclusions, can be found in the Carl v. Johnson & Johnson case out of New Jersey. In

Carl v. Johnson & Johnson, the scientific issue was whether exposure to pure talcum powder (not contaminated with asbestos) was capable of causing ovarian cancer. The Court conducted an extensive *Kemp* hearing (akin to a *Daubert* hearing in New Jersey) to assess the reliability of plaintiffs' experts Dr. Graham Colditz and Dr. Daniel Kramer. In its decision, the court discussed the intersection between science and the courtroom and defined its role as follows:

> What follows are the "building blocks" of the scientific method which the court must consider in evaluating Plaintiffs' experts' methodologies in arriving at their conclusions and opinions, and whether the same are "reliable." The key is consistent adherence to the scientific method. In addressing the issues to be resolved, the court has endeavored to faithfully apply the principles and tools of science to the issues at hand.

Id. at *22. After a comprehensive sophisticated scientific discussion of the literature, including the court's own independent assessment of the Bradford Hill criteria, the Court concluded that the plaintiff's experts did not follow the scientific method, but instead focused only on favorable studies: "As these proceedings drew to a close, two words reverberated in the court's thinking: 'narrow and shallow.' It was almost as if counsel and the expert witnesses were saying, Look at this, and forget everything else science has to teach us."

With respect to Dr. Colditz, the court examined the literature and concluded that it did not support the expert's opinion. Ultimately, the Court concluded:

> there are significant gaps in his methodology and analysis. He has committed the very error which Hill warned scientists against, namely, that the results of their research "...does not confer upon us a freedom to ignore the knowledge we already have." Dr. Colditz has overlooked the knowledge to be learned from laboratory research regarding the biology of cancer.

Id. at *52. Similarly, the Court rejected Dr. Kramer's opinions because his "methodology appears to be litigation driven rather than objectively and scientifically grounded." The Court cited Dr. Kramer's reliance on retrospective cohort studies rather than stronger prospective cohort studies, his dismissal of the importance of doing a meta-analysis of the studies, and his reliance on epidemiology to support his specific causation opinion, which is strongly is discouraged by the Reference Manual on Scientific Evidence published by the Federal Judicial Center and National Research Council of the National Academies (reflective of what the scientific community deem reasonable). The court precluded both experts.

On appeal, the New Jersey Superior Court issued an equally comprehensive opinion with a noticeable different angle. Carl v. Johnson & Johnson, 464 N.J. Super. 446 (Superior. Ct. 2020). After a general discussion of the literature, the Court laid out in detail what Drs. Kramer and Colditz did to form their respective opinions, concluding:

> We have provided exhaustive details of the reports to support our conclusion that plaintiffs' experts provided admissible opinions meeting the Manual and Hill protocols. They relied upon significant studies that the relevant scientific field accepted as suitable for such reliance. The reasons that Cramer and Colditz gave for finding certain epidemiological studies more pertinent than others did not conflict with the scientific community's principles for interpreting and relying

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> upon studies. They neither misread or misrepresented study results, nor relied on studies that represented less than a substantial portion of the available scientific literature. They anchored their opinions on the studies regarding biologically plausible mechanisms that even governmental and agency resources recognized as plausible.

Id. at 497. Finally, the appellate court pointed out what it believed to be errors in the lower court's application of scientific principles.

While this case is currently on appeal to the New Jersey Supreme Court, it demonstrates two things. First, these are precisely the types of scientific discussions the courts should be having in fulfilling its gatekeeping role. Second, even when the conversation is correctly framed, reasonable judges can still disagree on its application.

E. Public Health Pronouncements Do Not Answer the Causation Question

The role of regulatory and public health organizations is critical for many reasons in our society as discussed in the prior section. However, the question is whether these types of studies in the abstract can be relied on in litigation by experts as "evidence" of whether exposure to a toxin at certain levels is capable of causing a particular condition or disease.

In In Re Roundup Product Liability Litigation, 390 F. Supp. 3d 1102 (N.D. Cal. 2018), the Court framed the question as to "whether a reasonable jury could conclude that glyphosate, a commonly used herbicide, can cause Non-Hodgkin's Lymphoma ("NHL") at exposure levels people realistically may have experienced." By way of background, in 2017 IARC found that glyphosate was an animal carcinogen and probably a human carcinogen, which prompted California's Office of Environmental Health Hazard Assessment to add glyphosate to the Proposition 65 list, which likely influenced the pursuit of cases in California. While the Court engaged in an extensive analysis of the literature,[4] it did not support IARC's classification of glyphosate as a Stage 2A carcinogen, (i.e. where there is limited evidence of exposure causing cancer in humans and sufficient evidence that it causes cancer in animal studies) as sufficient evidence on its own to establish general causation. The Court recognized that IARC's approach is hazard and risk assessment at a much more general level, which is a type of scientific study, but does not address the issue of medical causation:

> [E]xpert opinions that simply parrot IARC's analysis and conclusions are somewhat off topic and are unduly limited, rendering them insufficient to satisfy the plaintiffs' burden at the general causation phase. A "hazard assessment," as IARC and other public health bodies define that inquiry, is not what the jury needs to conduct when deciding whether **glyphosate** actually causes NHL in people at past or current exposure levels. An expert who recites IARC's conclusions and analysis therefore may be offering a sound scientific opinion, but not an opinion that speaks squarely to the issue the jury must decide. And in addition to the fact that such opinions are not enough to get the plaintiffs past the general causation hurdle, there is a significant possibility that, if there ever is a jury trial (that is, if any plaintiff can get past summary judgment on the issue of specific causation), expert opinions that go no further than IARC's analysis will be excluded. An expert opinion of this sort may not "fit" the general causation inquiry closely enough to be helpful to the jury in the way Rule 702 requires; it may serve primarily to confuse the jury, causing

[4] The Court's analysis suffers from some of the other fundamental departures from truly scientific causation analysis. However, it did correctly recognize that regulatory and health organizations pronouncements are irrelevant to causation analysis.

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> the trial to devolve into an abstract discussion about the differences between what public health organizations do and what juries do. In any event, for current purposes, the point is that to the extent the plaintiffs have offered opinions from experts who merely reiterate the IARC analysis, those opinions do not allow the plaintiffs to avoid summary judgment.

By contrast, in In Re Johnson & Johnson Talcum Powder Prods. Mktg. Sales Practices & Products Litig., 2020 U.S. Dist. LEXIS 76533 *; __ F. Supp. 3d __; 2020 WL 8968851 (D.N.J. 2020), the Court was faced, in part, with the question of whether heavy metals in talcum powder were capable of causing ovarian cancer. Under this general causation analysis, plaintiffs offered Dr. Arch Carson who opined that exposure to heavy metals was capable of causing ovarian cancer, despite the fact that there were no scientific studies linking specific metals to ovarian cancer. Instead, Dr. Carson substituted IARC's analysis for scientific causation analysis:

> Defendants argue that Dr. Carson's testimony—that the heavy metals contained in **talc**, i.e., cobalt, chromium, and nickel, may also cause **ovarian cancer**—is unreliable, because these metals have not been proven to be specifically carcinogenic to the ovary. (See Defs.' Post-Hr'g Br., at 43-45.) At the outset, for the purposes these **Daubert** motions, Defendants do not dispute that **talc** powder may contain these heavy metals. (See id.) Dr. Carson explained that while there are no studies linking these specific metals to **ovarian cancer**, they have been identified by the International Agency for Research on **Cancer** ("IARC") as carcinogens, and these metals have been linked to specific types of cancer. (See Carson **Daubert** Hr'g Tr., at 1308.) However, importantly, the IARC, in its 2012 Monograph explains that while it may identify certain carcinogens as having specific target organs or tissues where an increased risk of cancer has been shown, it further states that "identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites." Int'l Agency for Research on Cancer, 100C Monographs on the Evaluation of Carcinogenic Risks to Humans: Arsenic, Metals, Fibres, and Dusts, at 29 (2012) (emphasis added). As such, in conducting this analysis, Dr. Carson relied, inter alia, on the IARC's conclusions and, consistent with that conclusion, opined that similar to asbestos, the carcinogenic heavy metals found in **talc** may plausibly cause other types of **cancer**, such as **ovarian cancer**. In that regard, because Dr. Carson's opinion is based on biological plausibility, the Court will permit him to testify that it is plausible that, as carcinogens, these heavy metals may cause **ovarian cancer** with respect to his Bradford Hill analysis only. To the extent Defendants take issue with that opinion, they may cross-examine Dr. Carson on that basis.

This is a classic failure of the Court's gatekeeping role. Dr. Carter's opinions are not based on what scientists consider to determine whether there is a causal connection. In fact, he admitted there were no scientific studies. That should have been the end of the inquiry. Instead, the jury is now burdened with having to decipher the meaning of a public health agency pronouncement in the abstract and whether there is a true causal connection between exposure to heavy metals in talcum powder and ovarian cancer.

F. The "Subjective Interpretation" Fallacy

Assessing the body of literature to determine whether it

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supports a scientifically reliable causal connection requires careful scrutiny. It is not uncommon to have different types of studies in different contexts where the scientists reach different conclusions. The focus, however, is whether the literature as a whole **objectively** supports an established causal connection. Nevertheless, experts in litigation, inappropriately acting as advocates for their clients, subjectively inflate the significance of favorable studies and dismiss anything that does not support the expert's conclusion. This is precisely why the Courts, in fulfilling their gatekeeping role, must look closely at the science behind the opinion. Unfortunately, some Courts allow experts to substitute their subjective "interpretation" of the literature for objective scientific analysis.

For example, in Pistone v. American Biltrite, 2021 N.Y. App. Div. LEXIS 3409 *; 2021 NY Slip Op 03341 ** (2nd Dep't May 26, 2021), the defendant flooring manufacturers moved for summary judgment on the grounds that the scientific evidence does not support the hypothesis that chrysotile asbestos from flooring tile is capable of causing peritoneal mesothelioma. In support of the motion, the moving defendants met their *prima facie* burden on the motion through submission of expert affidavits showing that plaintiff's exposure to asbestos from work around those products was below a safe threshold. While the lower court agreed, the appellate division reversed because it concluded plaintiff had created an issue of fact because experts relied on studies and it presented a battle over "interpretation" of the literature:

> However, in opposition, the plaintiffs submitted expert affidavits raising triable issues of fact as to both general and specific causation (see Dominick v Charles Millar & Son Co., 149 AD3d 1554, 1555-1556; Penn v Amchem Prods., 85 AD3d 475, 476). The conclusions of the plaintiffs' experts were sufficiently supported by studies and medical literature, and demonstrated specific causation through a scientific method (see Parker v Mobil Oil Corp., 7 NY3d at 449). The experts' conflicting interpretations of the underlying studies and literature presented a credibility battle between the parties' experts, which is properly left to a jury for its resolution.

Id. at *4. The appellate division fundamentally failed in its gatekeeping role in two respects. First, the court framed the issue as to whether the plaintiff's expert's conclusions were supported by "studies and medical literature" and some unidentified "scientific method." The correct question is whether the scientific literature, objectively assessed as a whole, supports the hypothesis that asbestos from flooring products is capable of causing disease. Second, and more relevant to this section, the court without any analysis concluded that the plaintiff's expert's subjective interpretation of the literature was enough to create an issue of fact.

Savvy experts will always be able to "distinguish" literature that does not support the opinion, which is why it is critical for the court to look past subjective interpretation and independently assess the scientific literature as a whole (a scientific methodology) to determine whether it objectively supports a causal connection. The court in Pistone never engaged in that assessment.

G. Other Misplaced Scientific Discussions

While of lesser importance, some courts either miss the mark when it comes to certain aspects of proper scientific analysis or simply do not feel comfortable critically assessing experts in different fields and passing judgment on the reliability of their opinions. In fairness, precluding a plaintiff expert may effectively result in dismissal of a claim. This consequence tends to influence judges to stray from proper scientific analysis and accept some of these other arguments.

First, courts sometimes struggle with reconciling medical and legal causation nomenclature. In the scientific community, the operative terms are association and causal connection. In this context, an association is not an established causation connection, but simply the threshold for engaging in a further causation analysis, which includes whether the association is statistically significant. Nevertheless,

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experts and courts use phrases such as "causal association," "substantially contributes" and a "substantial factor." These terms are legal, not truly scientific terms that have no place in assessing the reliability of expert opinions in the first instance. If and when the expert is permitted to testify at trial, that is when the legal causation standards become relevant for the jury's consideration. Blending medical and legal causation terms in a Daubert or Frye analysis is a plaintiff strategy to cloak otherwise scientifically unreliable opinions.

Second, in a similar vein, a plaintiff in litigation has the burden to establish that it is "more likely than not" that exposure to a toxin caused his/her illness/disease. This does not mean that preponderance of the evidence standard can be applied to an objective assessment of the scientific literature. Scientists examining causation issues simply do not apply this legal standard. It is only if the science establishes that exposure to a toxin is capable of causing illness/disease and that a plaintiff was exposed to sufficient levels known to cause the disease that a jury would determine whether it was more likely than not that the factual exposure and disease support such a theory.

Finally, some courts simply do not appreciate that some scientific literature is hypothesis generating, but not any evidence of causation. Often, experts will cite to case reports or case series as "support" for their opinions. Unless aggressively challenged, courts may simply accept this as "some" evidence of causation. From a defense perspective, it is imperative to educate the courts on what is acceptable scientific evidence.

H. What Can We Do To Ensure True Science Determines the Outcome?

While there are no easy answers, the solutions start with litigants doing a better job educating courts on the nature of science, the role of regulatory pronouncements and how to critically assess the scientific literature. Parties are starting to more routinely retain science counsel to work with experts and provide that education to courts. The "Reference Manual on Scientific Evidence" is a prime example of the types of educational tools available to courts. Courts are more routinely scheduling "science days" to allow parties and experts to educate the court.

Another way courts and litigants have been able to address these issues is to agree to an independent science panel to make determinations. For example, in a class action litigation against DuPont for claims of exposure to PFAS and alleged injuries, the Court, with the parties' consent, appointed the "C-8 Science Panel" to conduct an epidemiological study on PFAS and disease. The challenge was that there was not enough scientific study on PFAS to assess causality. The solution was to have an unbiased panel of scientists identify the diseases that were associated with PFAS exposure, which the parties agreed to accept for purposes of the litigation.

From a legislative perspective, some states have established medical criteria for some types of claims with the requirement that a plaintiff meet certain medical criteria, supported by medical proof.

Finally, in some countries, such as Scotland, experts on both sides are required to confer on these issues and submit joint reports to the courts for consideration. While such joint approaches have not gained traction in the United States, there is value to requiring expert to speak directly as scientists without interference of lawyers.

Conclusion

Science and causation are at the core of toxic exposure claims. Juries are often incapable of truly understanding the differences between good and bad science, especially when well-qualified experts on both sides appear convincing. This is precisely why it is paramount that courts vigilantly fulfill their gatekeeping role. Courts' willingness to allow juries to consider bad science heavily favors plaintiffs and typically results in exorbitant compensation for injuries that are simply not causally connected to the toxic exposure. The fallout is that: (1) companies can no longer look to reliable science to dictate reasonable conduct; (2) the scientific process is diluted and replaced, at least in our court system, with a distorted misperception on what science tells us; and (3) it

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encourages litigation of scientifically-unsupported claims with enormous financial consequences, both in defending the claims and paying out compensation.

The key to solving this problem is to educate courts on how to objectively assess the literature and only permit expert opinions that meet the high standards of truly reliable science. The goal of this publication was to explain the differences in how scientific data is viewed, interpreted and applied when determining causation in a scientific, public health/regulatory, or legal context. Each of the three communities/perspectives discussed in the article can better support courts in their gatekeeping responsibilities by continuing this open dialogue and transparently acknowledging differing opinions, methodologies, and missions. Suggestions include:

Scientific Community: Approach their position as truth seekers—combating misinformation and highlighting true findings in a digestible fashion.

Regulatory Community: Clear communication and engagement between the regulated public and government at the time of revision or creation of regulations to clarify limitations and risk reduction goals, reducing potential misuse of the products of regulatory action.

Legal Community: Educate the courts on the science including creating educational tools, scheduling "science days," relying on independent science panels, and/or encouraging collaboration between experts on both sides.

A combined effort from all communities can reduce the amount of noise introduced into a courtroom, limit the unnecessary financial burdens on both parties currently required to counteract junk science, and increase the confidence of judges in their role as gatekeepers. When only solid, reliable science is allowed inside a courtroom and there is a clear understanding of all perspectives, just and equitable decisions can be made.

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