The Coming Trifecta:
Multiple Chemical Exposures with Low Dose Effects Supported by Epidemiology

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I. Introduction

There is a predictable trifecta in litigation that is comprised of 1) multiple chemical exposures, with 2) low-dose level effects, that are 3) claimed to be verified by epidemiological studies.

Most chemical litigation is chemical-by-chemical, but we know that we are exposed to many chemicals at one time. This combination-exposure scenario lends itself to suspicions about causation of adverse health outcomes. “We live in a chemical soup,” is a frequent statement.

Furthermore, recently published theories are saying that adverse effects can occur at very low exposures and in a dose-response relationship that defies long-held toxicological premises.

In addition, some epidemiological studies state that adverse effects are observed in populations with either little validation of exposure or with allusions to low dose-level effects. These three factors—multiple chemical exposure, low-dose level adverse effects, and epidemiological findings—come together in a trifecta of potential litigation.

Whereas any one of these three topics might be the central idea in a case, their unity provides significant opportunity to plaintiffs’ attorneys and calls for awareness and planning on the part of the defense attorney. This paper will cover the basics on each of the three components of the trifecta by providing for each part of the trifecta an objective rendition of the background and theory and presenting science-based perspectives. The paper will then bring all three elements together into examples of how a trifecta of litigation could present unique scientific opportunities and challenges to attorneys.

II. Multiple Exposures

A. Background and Theory

1. Our Chemical “Soup”: Realities of Many Chemicals in Our Environment

There is no single moment in our lives when we are not exposed to chemicals. Chemicals constitute both our natural environment and are part of the tens of thousands synthetic chemicals that are part of day-to-day life. Oxygen, nitrogen, carbohydrates, and sodium chloride are all chemicals that sustain life. But because they are found naturally in our environment, we pay them little attention because they are “natural.” On the other hand, synthetic chemicals engender concern because they are created by manipulation of chemistry and are thought to be different than natural chemicals. To a reasonable toxicologist, there is no distinction between “natural” and “synthetic” chemicals. Chemicals are simply molecular structures. All chemicals can be harmless or harmful, depending on the degree of exposure.

Day-to-day, moment-to-moment, we are exposed to a menagerie of chemicals, whether natural or synthetic. That much is obvious. However, human physiology has evolved to handle a wide range of natural chemicals, and only when excessive exposures occur might adverse effects develop. We are exposed daily to cyanide and arsenic, for example. But only if exposure is excessive would adverse effects occur. Likewise, oxygen is life giving, but high levels of oxygen exposure can result in injury to the lungs and eyes.

Synthetic chemical exposure is also a fact of daily life. Look around you at this very moment. Unless you are lucky enough to be reading this next to a pristine mountain lake, your immediate environment is
chock full of synthetic chemicals. Your fabrics are treated, the chair you are sitting on may be leather, but it has coatings to extend durability, the walls are painted with a combination of chemicals that give color and texture, and if you are reading this on a computer, you are in the presence of heavy metals, plastics, plasticizers, and more. More personally, the soap you used is fabricated with emollients that are petroleum based, your toothpaste probably has a synthetic color, and you may have taken pharmaceuticals. A step outside might bring you diesel exhaust or polyaromatic hydrocarbons while filling up your car with gas. The presence of synthetic chemicals in our daily life is a reality.

What is the collective effect of this chemical “soup”? How do we square the reality that any one of the synthetic chemicals we are exposed to may be toxic and, in combination, may wreak havoc with our physiology? The plaintiff may well argue that toxic effects by one chemical were exacerbated by the presence of other chemicals. Your chemical may be one or all the elements in a soup that is claimed to cause adverse effects in an individual or population.

2. Testing: Toxicity Tests Are Typically Done One Chemical at a Time

Furthermore, chemicals are tested individually. The typical testing routine is to use one chemical administered to animals at several dose levels. Studies with multiple chemicals given at one time together are rare. Some of the reasons multiple chemicals are not tested include expense, selection of which chemicals to combine, what proportion they should be mixed, and how to express the collective dose levels in understandable terms.

B. Science

1. What Counts

Obviously, not everything in combination causes toxicity. Otherwise, modern life in the presence of multiple chemicals and guaranteed exposure to synthetic chemicals would result in devastating effects in populations. The fact is, we are living longer, healthier lives than ever before in history (CDC, 2014). The reasons for longevity and health are many and include the availability of a variety of synthetic chemicals in combination. So, when is concern for multiple chemical exposure warranted and when is it not?

Moretto, et al (2016) gives an excellent rendition for when multiple chemical exposure may be of concern. The article refers to multiple chemical exposure as “cumulative” toxicity. In standard language, the term cumulative would refer to the accumulative dose or collective effect of a chemical over time. However, “cumulative” is a term of art in toxicological and risk assessment circles that refers to collective exposure to a group of chemicals. Hence, the title of the Moretto paper, “A framework for cumulative risk assessment in the 21st century” refers to the systematic approach to determining whether or not the combined exposure to two or more chemicals (“cumulative”) should be considered in greater depth (“cumulative risk”). Two simple criteria mark the institution of a risk assessment that would consider the possible additive toxicity of the chemicals of interest: co-exposure and a common mode of action.

a. Concomitant, Sufficient Exposure

Although obvious, an overlooked component in considering whether or not a group of chemicals may act together to cause toxicity is whether or not exposure occurred in the same time frame and if the exposure was sufficient, in combination with the other chemicals, to cause toxicity. Temporality and sufficiency of exposure are crucial first steps in determining if multiple chemicals have caused or may cause an adverse effect.

b. Common Mode of Action

For multiple chemicals to act together to cause adversity they must share a similar way of exerting their effect. How a chemical causes toxicity (or a beneficial effect) is called “mode of action.” For example, the
mode of action for carbon monoxide is by binding to hemoglobin and reducing its oxygen-carrying capacity. Other chemicals that reduce the ability for hemoglobin to bind oxygen would then share a common mode of action with carbon monoxide.

A good example of common mode of action is hypolipidemic drugs, which are taken to reduce cholesterol. A certain group of hypolipidemic drugs have a common mode of action that reduces cholesterol by inhibiting HMG CoA reductase, an enzyme that helps make cholesterol. Zocor, Lipitor, and Crestor are drugs that share that mode of action. Taken individually and at the proper dose, the beneficial effect of lower cholesterol is achieved. Imagine, though, the odd situation that a person takes Zocor, Lipitor, and Crestor together. If each are taken at the therapeutic dose, there would be a tripling of the pharmaceutical effect, perhaps exceeding the beneficial effects of the class of drugs and perhaps causing adversity. On the other hand, a person could take 1/3 of the recommended dose for each of the three and achieve a therapeutic reduction in cholesterol. That's because these drugs share a common mode of action and add together because they do the same thing. A simple way of putting it is $1 + 1 + 1 = 3$.

Common mode of action, taken in the context of dose or exposure, explains the potential for chemicals to work together to cause an adverse effect. The term used is “additivity” because the effect of each chemical adds to the collective, or “cumulative” effect of the group.

2. What Doesn’t Count

Allegations of effects from multiple chemicals with no common mode of action or concomitant, sufficient exposure cannot be supported. As the illustration in Moretto, et al (2016) shows, the only reason to progress to a risk assessment of multiple chemicals is if there is evidence for co-exposure and common toxicity.

An example is taking Zocor, ibuprofen, and caffeine together, which would not be an unusual morning ritual for many people. Individually, each chemical gives its own exclusive effect: Zocor lowers cholesterol, ibuprofen is analgesic, and caffeine is stimulatory. Together, there is no cumulative, or additive effect. Another way of putting it is $0 + 0 + 0 = 0$.

III. Low-dose and Nonmonotonic Effects

Two theories have been combined to create a toxicological concept that is very controversial. One theory, low-dose effects, is that chemicals may exhibit toxicities below the range they were tested (Vandenberg, et al, 2012; 2013). The second theory, nonmonotonicity, states that some chemicals do not follow typical monotonic dose-response curves. These two theories together suggest that toxicological testing is not accurately predicting or describing adverse reactions in humans. The implication is that there may be effects in humans either by undiscovered low-level exposures to chemicals or because the dose response curves are non-traditional—or both.

A. Low-dose Effects

As a common sense principle, low dose seems obvious: very small amounts. But the theory and implications of Vandenberg, et al (2012) is different and is called the “low dose paradigm.” The authors postulate that endocrine active chemicals could affect humans at environmentally relevant doses that had been thought to be safe. They cite a report by the National Toxicology Program (Melnick, 2002) that defined low dose effects as “…biologic changes that occur in the range of human exposures or at doses lower than those typically used in the standard testing paradigm of the US EPA for evaluating reproductive and developmental toxicity.”

The implications of this theory create significant concern. What they are implying is that current USEPA testing protocols might be missing effects that occur below doses in animals that show no effects and upon which
B. Nonmonotonic Effects—Background and Theory

In typical toxicological testing, a chemical is given to groups of test animals at several dose levels and the magnitude of an effect is measured at each dose level. This is the dose-response curve. The most common dose-response curve is “monotonic”. A monotonic function simply means that the direction of the curve does not change: what’s going up, keeps going up; what’s going down, keeps going down. This is demonstrated in the first two example graphs in Figure 1.1. The vast majority of pharmacological and toxicological dose-response curves look like this. Take, for example, alcohol. One shot of bourbon is relaxing, two makes you tipsy, four and you’re probably not standing, and at eight you’re flirting with death. Two aspirin alleviates pain, six upsets the stomach, and ten may put you in the hospital. Dose. Response.

A “non-monotonic” dose-response (NMDR) curve is one that changes direction at least once and is known as a “U-shaped” or “bell-shaped” dose-response curve. You can see what they look like in the second two examples in Figure 1.1. Perhaps the best example of a U-shaped dose-response curve is with the effect of vitamins. At low, insufficient levels, there is adversity, and at high, excessive levels there is toxicity. In the middle, at the recommended daily intake, there is neither adversity from lack of the vitamin nor toxicity from too much.

More recently, several investigators are finding evidence that the classic monotonic toxicological dose-response curve does not always occur and nonmonotonicity is more common than originally thought. Effects on endocrine regulation, also known as “endocrine disruption” or ED, appear to be a focus for demonstrating nonmonotonicity (Vandenberg, et al, 2013). For example, Lagarde, et al (2015) looked at 51 ED experimental studies and found 148 examples of nonmonotonicity, of which they concluded that 82 were “moderately” to “highly” plausible. At least for ED, there seems to be a growing literature that indicates such non-traditional, nonmonotonic dose-response curves exist.

Practical considerations of nonmonotonicity can be challenging. For most chemicals, imagining a change in direction for the dose response curve is puzzling. For example, two bourbons would relax, one shot might have a minor effect, and a fourth (1/4th) of a shot would have no effect. Would then a tenth of a shot, in a demonstration of nonmonotonicity suddenly cause inebriation? No. The reason has to do with the mode of action for the chemical. In the case of ED chemicals, the effects are caused by a complex combination of receptors and biological control points, each of which has biochemical characteristics that can vary with dose. Molecular targets and feedback loops are dose dependent and may turn on or off other biochemical processes. Thus, at high doses, the chemical may degrade a receptor or its cellular environment, giving a bell-shaped dose-response curve: the receptor works fine at lower doses, but degrades and is no longer operative at high doses.
What this means is that traditional monotonic dose-response curves that are central to toxicological theory and practice and were formulated by Paracelsus in the 16th century may not always predict what a chemical might do.

C. Science

The toxicological area of low-dose, nonmonotonicity is far from settled. While there is a continued effort on the part of those who subscribe to the theory to promote and research the concept, there is also a significant degree of skepticism (Rhomberg and Goodman, 2012) that such a dose-response scenario is real or, if real, a typical or useful concept in human health.

The Vandenberg, et al (2013) paper in particular spurred a high degree of interest by European and United States agencies and scientific groups in understanding the veracity and applicability of LDNM theories that contest the traditional “dose makes the poison” approach to assessing the potential effects of chemicals on human health. Subsequent to the Vandenberg paper, the USEPA embarked on an investigation of nonmonotonic dose-response (USEPA, 2013) that was reviewed by the National Research Council (NRC, 2014), and is still in progress (USEPA, 2014). The USEPA analysis and workplan are summarized here. The first part summarizes public presentations by Dr. L. Earl Gray and is followed by the NRC review and the ongoing program of work by EPA.

1. Analysis by L. Earl Gray, USEPA, Office of Research and Development

Dr. Gray is a highly-respected expert in endocrinology, particularly as it applies to ecology. He and his colleagues examined a wide range of endocrine active substances, including estrogen and testosterone, in an attempt to shed unbiased light on the scientific support for low-dose effects and nonmonotonic dose-response curves. His colorful presentations were declared to be his own opinion, not that of the USEPA, and were very helpful in understanding NMDR. He concluded that NMDR is...

- Biologically plausible. Meaning that for complex biological systems (such as the endocrine system), changes in the dose-response curve is possible because of multiple receptors, binding affinities, and enzymatic reactions that are related to each other with feedback and control mechanisms that fluctuate according to cellular need.

Think of what happens when you step down on the gas pedal in your car (dose) that results in the speed of the car (response). Although the gas pedal pressure and car speed are monotonic, lots of things happen that are not strictly related to the pressure of your foot. Everything from fuel injectors, pumps, and spark plugs are responding in feedback loops and control mechanisms to ultimately produce desired speed. Any one of those elements may be up- or down-regulated (nonmonotonicity). Thus, cellular systems have plausible, believable, and testable control points that may respond in a nonmonotonic way.
• Seen in vitro, but rarely in vivo. Meaning that if you take any one part of the cell and study its reaction to various dose levels of a chemical, you might see changes in the direction of the dose-response curve. But those detailed events are not seen in the overall response of the test animal. Again, think of your car's engine: if you study only the fuel injectors, you would see that they are reacting moment to moment to how much oxygen and how much fuel should be mixed to optimize performance. Sensors monitor and alter that mix in a nonmonotonic way. But that does not mean your car is jerking ahead with each minor adjustment in the air/fuel blend. In this analogy, the fuel injector is an in vitro, isolated event in a pathway between your foot pressure and the speed of your car (the in vivo, whole animal, whole car perspective). Insofar as changes in one or more detailed parts of the pathway may be nonmonotonic, the overall effect on the whole animal is likely to be monotonic.

2. USEPA Analysis and Workplan

As part of Dr. Gray's work with USEPA colleagues, the Agency described a workplan and issued a report on its analysis of NMDR curves (NMDRC). The analysis was built around answering three key scientific questions. Those questions and a summary of their answers are:

• “Do non-monotonic dose response curves (NMDRC) exist for chemicals and if so under what conditions do they occur?”
  As in Dr. Gray's presentations, the conclusion is yes, but typically in in vitro studies that look at one step in a multistep process and rarely in in vivo studies.

• “Do NMDRCs capture adverse effects that are not captured using our current chemical testing strategies?”
  No. “…current testing strategies are unlikely to mischaracterize, as a consequence of NMDR, a chemical that has the potential for [endocrine] adverse perturbations….”

• “Do NMDRCs provide key information that would alter EPA's current weight of evidence conclusions and risk assessment determinations, either qualitatively or quantitatively?”
  No. “There is currently no reproducible evidence that the early key events involved in the expression of NMDRs that are identified at low dose are predictive of adverse outcomes that may be seen in humans or wildlife populations for [endocrine effects].”

Overall, the scientific perspective from the USEPA is that there is little concern that current toxicological testing misses effects that would be relevant in either preventing or explaining chemical toxicity in humans or populations. They regard NMDR as an interesting phenomenon when studying individual steps in the pathway from exposure to effect, but do not see such information altering their judgement in establishing safe levels of exposure to chemicals.

3. National Research Council (National Academy of Sciences) Review of the USEPA’s Analysis

The USEPA review was reviewed by a panel of scientific experts convened by the NRC (NRC, 2014). The NRC looked at the answers to each question and offered critique and recommendations. With regard to the first question (do NMDR curves exist) the most salient point by the panel is that they agreed in general with the USEPA, but insisted that epidemiological and other human studies be included. This recommendation will be particularly important when considering the next section of the trifecta: epidemiology.

The USEPA's second and third questions (testing and risk) were taken together. The panel did not disagree with EPA's analysis that NMDR doesn't alter the Agency's testing methods for toxicity or assessment
of human health risk; however, they asked for greater clarification concerning the types of tests EPA uses. Overall, the NRC review did not refute the EPA’s analysis.

IV. Epidemiology

A. Background

In its early stages, epidemiology played a key role in clearly connecting disease to causative agent, for example cholera and contaminated water, understanding the adverse effects of coal mining as a profession, and establishing the role of tobacco smoke in lung cancer. In parallel, clinical epidemiology has been pivotal in establishing the efficacy (or lack thereof) of pharmaceuticals. However, the current world of multiple risk factors, low and background exposure possibilities, and the complexities of a mobile society have stressed the methodological and, indeed, the philosophical approaches to designing, interpreting, and applying epidemiological studies to decision about causality.

In addition, there is an ever-growing desire by the public to identify those activities and agents that are either good for us or not. Aerobic exercise and cardiovascular health, vitamin C for colds, or higher dietary magnesium are questions that are on the minds of a well informed and health conscience modern society. Perhaps the most controversial arena for epidemiology is chemical exposures to populations, known as environmental epidemiology. What’s in my water? Will that harm me or my family? To answer those questions, epidemiologists must consider appropriate study design, acquisition of medical information, and collection of exposure data and conflict of interest (perceived or real) of the investigators.

The field of environmental epidemiology is at a crossroads. Addressing a symposium entitled, “Trends in 21st Century Epidemiology: From Scientific Discoveries to Population Health Impact,” Dr. Harold Varmus, US National Cancer Institute Director stated: “I expect to see a pretty dramatic revolution in epidemiology…” (NCI, 2012). He went on to explain the many factors that complicate obtaining clear conclusions, while still stressing the importance of epidemiology to human health policy development. Broadbent (2015), following discussions during the 2014 World Congress on Epidemiology, described an epidemiologic “methodological revolution” in response to challenges of established methods for causal inference.

B. Causal Inference

Causal inference, the process of connecting the dots between an exposure and an effect, that “X” causes “Y”, is at the heart of environmental epidemiology. To make a causal inference depends on evidence and evidence, in turn, depends on several key factors that drive the reliability of epidemiological conclusions.

Pai (Figure 2) captures the many stages to making conclusions about causation. Unless each stage is carefully considered, inappropriate or inaccurate conclusions of causality may be drawn.

Missing from Pai’s depiction are two additional characteristics of environmental epidemiology studies that can render causal conclusions to be suspect:

![Figure 2: Pai, M Lecture Notes—McGill University](image-url)
exposure and quality. To reliably conclude that agent “X” causes disease “Y”, one needs a credible quantification of exposure to “X”. Quality of epidemiology studies is frequently discussed in both scholarly and non-scholarly literature. Development of an agreed set of standards for quality is, however, more elusive.

In summary, although scholarly articles on epidemiology have noted methodological shortcomings such as bias, confounding, and chance, a broader view leads to questions about reliability, reproducibility, exposure data, and metrics of quality.

C. Approaches to Evaluating Environmental Epidemiology Studies

Various attempts have been made to enhance the value and validity of epidemiological studies. The purpose has been to add some sense of standards into the field even though there are no agreed set of guidelines or firmly held rules that govern statements of causality in and from an environmental epidemiology study. The following is a short list of principles, criteria, and suggestions that may help when testing the claims in an epidemiology study.

The Hill Criteria. Sir Austin Bradford Hill’s presidential address to the Section of Occupational Medicine of the Royal Society of Medicine (Hill, 1965) is perhaps the most cited and perhaps misinterpreted attempt to set forth criteria to judge the merits of a causal inference. His nine criteria became a foundation for evidence-based decisions that transcend the field of epidemiology. The sometimes-slavish adherence to his criteria have led to publications (Phillips and Goodman, 2004) that have helped clarify the appropriate interpretation of Hill’s intent and the application of his philosophy. However, the Hill guidance does not account for bias or confounding.

The STROBE Initiative. In 2007, a collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors developed a checklist of 22 items that are critical for proper reporting of observational epidemiology studies (von Elm, 2007). STROBE points out that the checklist is not intended to evaluate the quality of the research. Instead, it is intended to be a transparent way of assuring the consistent representation of studies to allow evaluation and comparison of data.

Cochrane Reviews. The Cochrane Collaborative was founded in 1993 to develop up-to-date systematic reviews of randomized controlled studies in health care. Their motto: “Trusted evidence. Informed decisions. Better Health.” is based on their statement, “As access to health evidence increases, so do the risks of misinterpreting complex content; meanwhile the likelihood of any one person getting a complete and balanced picture decreases. Our mission to provide accessible, credible information to support informed decision-making has never been more important or useful for improving global health.”

LaKind, et al. (2014). Whereas the Cochrane Reviews provide carefully thought out criteria for evaluation of epidemiological studies in health research, LaKind et al. contend that, “For the field of environmental epidemiology, no parallel mechanisms have been developed and no analogous processes are in place.” LaKind, et al. propose a three-part path forward “…toward more concordant, transparent, and readily accessible environmental epidemiology evidence that parallels ongoing efforts in medical research…” that includes:

1. High-Quality and Readily Accessible Systematic Reviews (needed for identifying knowledge gaps and quality studies in need of replication; ensure that new study builds on previous study (i.e. increased harmonization) to aid in WOE; aid in hypothesis generation and study design),

2. Improved Access to Information on Ongoing and Completed Studies (reduces unnecessary replication, increases harmonization of study design to improve WOE; reduces potential publication bias), and

3. Clearly Articulated Principles for Reporting (aids in consistent and transparent reporting).
**ECETOC (2009) and Adami, et al. (2011):** These two publications address the issue of biological plausibility by linking adverse effects in animals (toxicology) with epidemiology. In both papers, quality assessment and weight of evidence is systematically considered to achieve a unified description of a causal relationship. In Adami, et al. the process results in a highly visual causal representation as Likely, Unlikely, or Uncertain. Key critical features are captured in the schematic that have been echoed in several papers, including collection of ALL available data, sorting studies on the basis of quality, and a weight-of-evidence analysis with the higher quality studies to come to a qualitative view on the legitimate contributions of both toxicological and epidemiological evidence. Unfortunately, neither of these schemes have been routinely or consistently applied to highly important reviews. Nonetheless, they serve a valuable role in setting the stepping stones toward better systematic reviews.

In summary, there are several carefully considered methodologies that would provide a high-quality and, to the extent possible, objective systematic reviews. There are additional papers and perspectives in this area, but each trend towards similar objectives. The challenge is to find a way to synthesize these approaches into a methodology that will thoroughly examine the reliability of causal claims made in environmental epidemiological studies.

### V. Example(s) of How the Trifecta Comes Together

Each aspect of the trifecta, multiple chemical exposure, low-dose/nonmonotonic response, and epidemiology, could create substantial challenges in litigation. Together they are a powerful argument in supporting a claim.

**A. Endocrine Disruptors**

Endocrine disruption seems to be at the epicenter of allegations of adverse effects. Bis-phenol-A (BPA), is a plasticizing agent with weak estrogenic activity as well as widespread human exposure. Vandenberg (2013) makes the case for BPA's "undisputed evidence for low-dose effects" on the mammary gland and states that BPA works in concert with other estrogenic compounds. Furthermore, the authors link the cited animal studies to epidemiology: “…epidemiologists must collect information about prenatal and neonatal exposures and relate them to adult breast cancer incidence. These types of studies would take decades to conduct … and should take into consideration the effects of other estrogens, because their effects can be additive or even synergistic.”


In 2012, the International Agency for Research on Cancer (IARC) convened two workshops to consider the mechanisms by which agents identified as human carcinogens produce cancer. The participants concluded that these carcinogens frequently exhibit one or more of 10 key characteristics called the Hallmarks of Cancer (Smith, et al, 2016).
Also in 2012, the non-profit organization “Getting to Know Cancer” created the “The Halifax Project” to use the Hallmarks of Cancer as a way of assessing the likelihood of a long list of chemicals to be contributing to cancer incidence (Goodson, et al, 2015). The list is considered to be, “…biologically disruptive chemicals (i.e. chemicals that are known to have the ability to act in an adverse manner on important cancer-related mechanisms, but not deemed to be carcinogenic to humans) that might be acting in concert with other seemingly innocuous chemicals and contributing to various aspects of carcinogenesis (i.e. at levels of exposure that have been deemed to be safe via the traditional risk assessment process).”

Quite clearly, the Halifax Project is combining the trifecta of multiple chemical exposures with low-dose effects that will seek the support of epidemiological evidence.

VI. Recommendations

A. Consider Daubert/Frye

I am not an attorney nor an expert in the kinds of scientific evidence that may be admissible in a court. However, I am familiar with the general concepts of Daubert and Frye and refer you to Surprenant and Surprenant (2012) for a thorough evaluation of how the courts might treat evidence on low-dose and nonmonotonic dose-response. In brief, the review suggests that Daubert and Frye courts should reject such theories because the science is unsettled. However, since 2012, there have been additional scientific publications regarding theories of low-dose effects and nonmonotonic dose-response that may be adding to the credibility of such claims. Combined with multiple chemical exposures and with provocative epidemiological evidence, the LDNM concept may provide substantial challenges.

B. Address Each Area

Plaintiffs are likely to use the trifecta as a collective argument for cause and effect. Each element will have its evidence with attendant strengths and weaknesses, but together may provide a strong case. Thus, each element should be singled out and addressed. In brief, the following general strategy in each area should be fleshed out with supportive evidence:

1. Multiple Chemical Exposure Does Not Lead to Multiples of Toxicity

Unless a group of chemicals shares a common mode of action, they will not work together to create greater toxicity. We are, indeed, a healthy population, with life-span and life-quality increasing, not decreasing, in the presence of many, many chemicals.

2. Low-dose Effects, WithoutHigher-Dose Effects, Is at Best Unsettled

The gold standard for toxicity testing is still the whole animal and examples of surprise effects at doses lower than previously tested are rare at best. What happens in the whole animal when given a chemical is the integration of many biochemical steps that regulate normal biology. Remember that individual steps in a pathway of events to toxicity may be affected at doses lower than doses that affect the whole animal. Any one of those steps may be necessary, but is not in and of itself sufficient to cause an adverse effect in the whole animal. “The Dose Makes the Poison” still holds, as it did for Paracelsus in the 16th century.

3. Nonmonotonic Dose-response Is Very Rare

Along with being rare, such responses are typically only seen in in vitro studies. As with claims of low-dose effects, speculation cannot take the place of evidence. If a chemical has been properly tested with multiple dose levels and a clear indication of a no-effect dose level, the burden of proof for allegations of lower
dose effects would logically fall to the plaintiff. Hopefully, common sense and an understanding of what happens with more (or less) shots of bourbon or aspirin will guide judgement.

4. Epidemiology Challenges Are Nothing New

Support or challenges to an epidemiology study typically center on the quality of the evidence to support causality. Systematic review, the Hill criteria, STROBE guidance, and other publications and concepts are well established methods in establishing and challenging claims of causality.

C. Exposure Quantification Is the Truth Serum

High quality exposure analysis will be of great value in addressing all aspects of the trifecta. For multiple chemical exposure, the questions should be: how much and when? Quantification of exposure is crucial to establishing if any one chemical is present in sufficient quantity. Knowing when the exposure occurred provides the temporal knowledge that, together with common mode of action, fits into the paradigm proposed by Moretto, et al (2016). Without co-exposure and a common mode of action, additive toxicity is not going to happen.

For purported claims of low-dose exposure, quantitation will answer the question of how low is low and allow a comparison to known dose levels that can cause effects in whole animals.

The Achilles heel in many environmental epidemiology studies is quantitation of time-related exposure. Urinary metabolites, proximity to agricultural fields, time spend in certain areas and other proxies for actual exposure data will hamper a proper analysis of individual dose. Exposure quantification is very difficult to do in environmental epidemiology studies, but that should not suffice as an excuse, particularly when allegations of cause and effect hinge on evidence of exposure.

VII. References


Pai, Madhukar MD, PhD, Assistant Professor, Department of Epidemiology & Biostatistics, McGill Univ http://www.teachepi.org/documents/courses/fundamentals/Pai_Lecture5_Bias_Big%20Picture.pdf.


Endnotes

1 In a test tube, petri dish, or otherwise not in a whole animal.
2 In a whole animal.