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In Chemical Litigation, Toxicology Fundamentals Matter

By Lucy Fraiser – August 30, 2016

Toxicologists are retained as experts in toxic tort cases, environmental lawsuits, and other litigation involving chemicals and health threats. Toxicologists evaluate the health effects of chemical exposure, including the mechanisms and doses at which such effects occur. This article describes some of the ways in which a toxicologist can help build a case, focusing on the importance of toxicology principles in determining whether a chemical can cause a particular effect under a specific set of circumstances and concluding with examples of how mechanisms of toxicity can be used to determine whether alleged harms are plausible.

Estimating Chemical Concentrations Does Not Constitute a Demonstration of Exposure

Plaintiffs in lawsuits must demonstrate a connection to, and harm from, the action being challenged. The fact that a chemical release occurred is not enough to substantiate a claim that people were harmed by it. When a complaint relates to an alleged injury or harm, demonstrating that the plaintiff *actually* came into contact with the emitted chemical or agent at a level and in a manner capable of causing the alleged injury will be critical to the case.

Predicting the concentration of chemicals in the air using air dispersion models, or determining the amount of chemicals released into soil or water, does not constitute a demonstration of exposure. Toxicologists help build a case by determining the dose that plaintiffs have potentially incurred and *physically* linking the plaintiffs and the released chemicals. This is what is known as an exposure assessment. Exposure assessment requires evaluating plaintiffs' activity patterns during or after the release, with a focus on determining whether they were present in locations, and at times, that would have allowed them to contact the agents released in a manner sufficient to cause the alleged harms.

Dose Is Important to Legal Findings of Harm

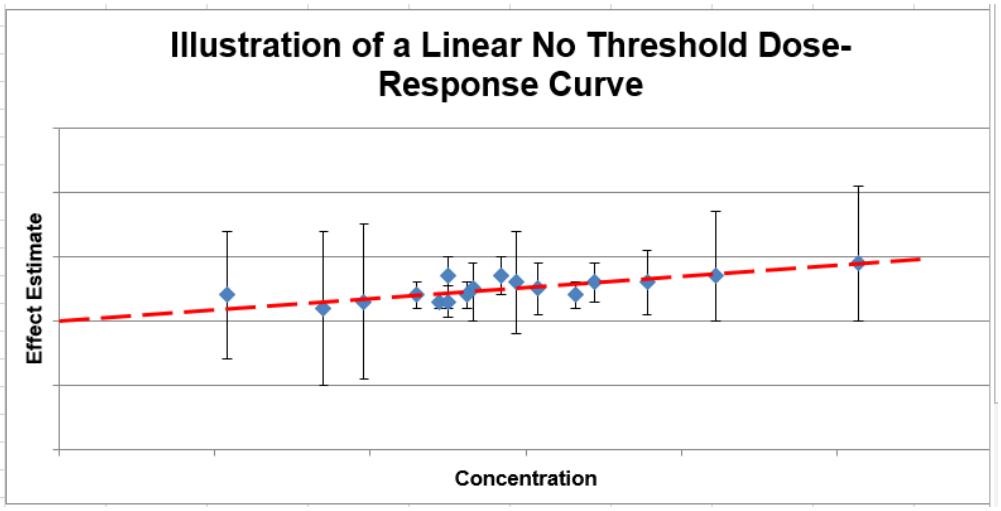
Dose is a term borrowed from pharmacology and medicine and is a central concept in toxicology. Dose is defined as the internal concentration of a chemical and is calculated as concentration multiplied by the frequency or duration of exposure—it is not simply the exposure level at a given point in time. Determining whether harm could occur from a chemical release requires an evaluation of the dose experienced by those alleging harm. Absent a realistic understanding of the potential dose to which plaintiffs have been subjected, the critical link between the chemical released and the alleged harm cannot be made. Despite this, those alleging harm often fail to perform any dose assessment whatsoever.

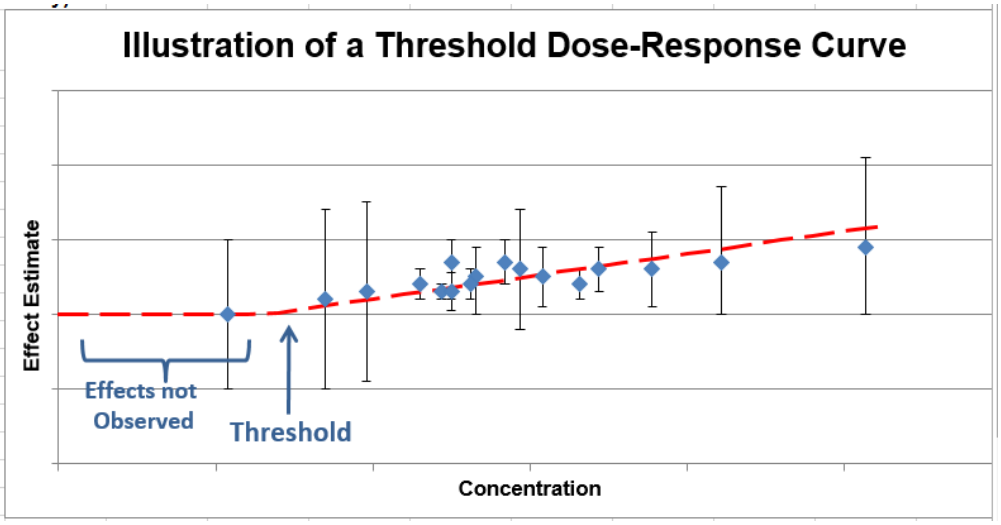
Although plaintiffs usually focus on whether a chemical *can* cause a particular health effect, rather than a chemical's strength or potency, dose issues are crucial to determining whether an agent could have caused a particular effect under a specific set of circumstances. While plaintiffs may present experts claiming that dose is irrelevant to causation, dose is generally considered to be pertinent to specific causation (did the agent in question cause disease in a particular individual?). However, dose is also central to the general causation issue (is the agent capable of causing the disease in question?) because the dose dictates the possible effects. Bernard D. Goldstein, "Toxic Torts: The Devil Is in the Dose," 16 *J.L. & Pol'y* 551 (2008).

Mechanism of Toxicity Is Important to Legal Findings of Harm

Another core tenet of toxicology is that chemicals are specific in their biological actions because of their unique chemical structure and the laws of biology that govern toxic responses. In other words, toxic agents have different effects depending on their inherent nature (i.e., a specific chemical affects certain biological systems but not others). This is what is known in today's parlance as the "mechanism of toxicity."

Dose-response relationships. An important concept in toxicology is the dose-response relationship, which is useful in understanding the mechanism of toxicity and extrapolating results from animals to humans. A dose-response curve is the relationship between the amount of a toxic agent that is administered, encountered, or absorbed and its toxicity. There are two types of dose-response curves: (1) those that have a toxicity "threshold," and (2) those that do not have a "threshold," which are often referred to as being "linear." The figures below illustrate the two types of dose-response curves.





A threshold means that an exposure may not cause disease until the exposure exceeds a certain dose. Thresholds are of obvious importance in cases where injury or harm is alleged, because for chemicals that exhibit a threshold, there will be some level that is too low to cause harm. Goldstein, *supra*.

Thresholds and cancer. Thresholds have historically been presumed for all agents except those producing effects through mutation (i.e., alteration in structure of a gene), such as many carcinogens. The linear no-threshold theory of cancer has a historical basis, although it does not address genetic repair, which is known to occur. With cancer, it is presumed that each mutation happens all or none, not by degree as with other forms of toxicity that require failure of entire organ systems. Because proliferation of a single malignantly transformed cell through a series of cell divisions develops into a life-threatening tumor, it is generally presumed by regulators and many in the health sciences that no threshold exists below which the risk of cancer is zero, although there are clearly *some* carcinogens that exhibit thresholds. Hence, the no-threshold presumption should be examined on a chemical-by-chemical basis, rather than blindly accepted, even for carcinogens.

Thresholds and noncarcinogens. Generally speaking, epidemiological and toxicological studies are both used in identifying health effects caused by chemicals. Recently however, overreliance on epidemiology studies, which are not usually capable of detecting thresholds due to their focus on populations rather than individuals, has led to assertions that some non-cancer causing agents lack toxicity thresholds.

Despite the fact that thresholds are consistently demonstrated in controlled human exposure studies of particulate matter (PM), statements by the EPA and other regulatory entities about the lack of *observable* thresholds from epidemiology studies involving PM has fueled a number of citizen suits. *See* EPA, EPA/600/R-08/139F, *Integrated Science Assessment for Particulate Matter* (2009) [hereinafter*EPA ISA*]. Citizen suits are lawsuits brought by private individuals/organizations for alleged environmental violations when public authorities have not sued. Alleged injuries in these citizen suits are premised on the assertion that there is no safe level of PM and that any increase, regardless of whether any health-protective regulatory levels were exceeded, increases PM-related health effects.

The no-threshold concept for PM, however, is at variance with an enormous amount of repeatable observations, which consistently demonstrate that nonmutagenic toxic effects are elicited only when the critical concentration is sustained for the necessary period of time. As discussed in the next section, presenting evidence on the mechanism by which toxicity occurs can help to counter baseless claims about causation in some circumstances.

Is the Alleged Harm Plausible?

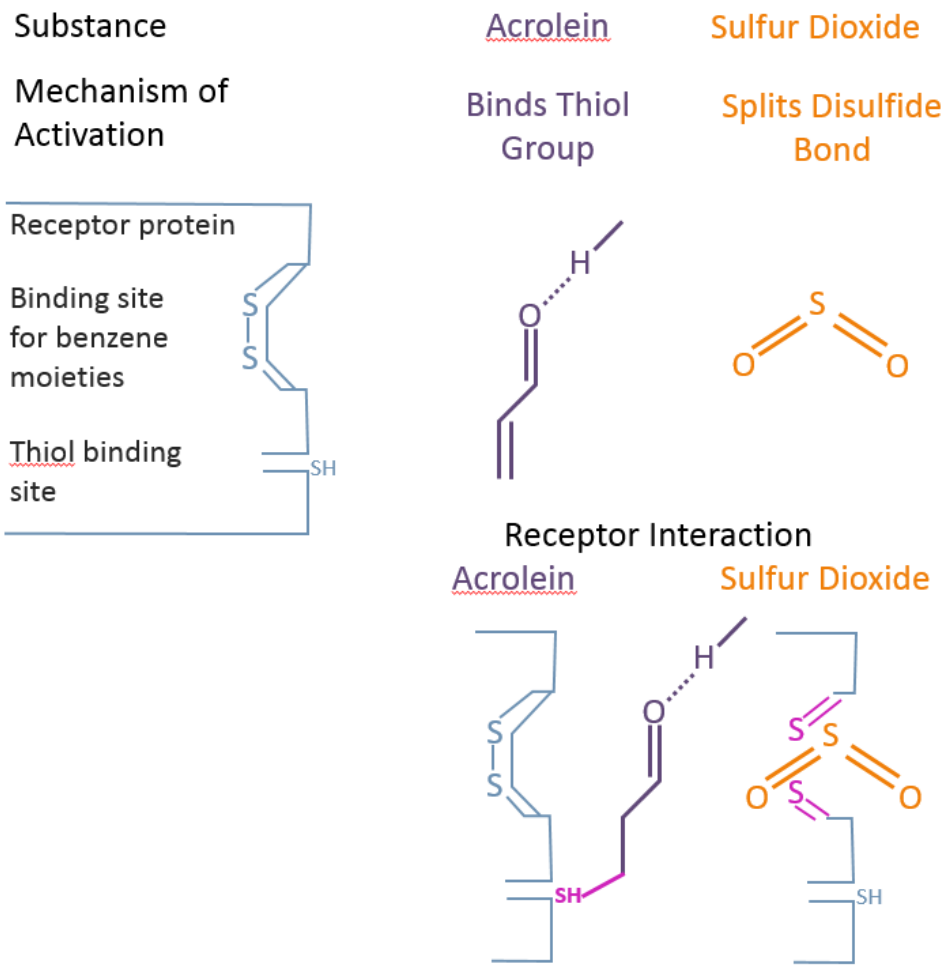
To successfully argue that harm or injury has resulted from a chemical release, there must be a biologically plausible toxicological mechanism by which the chemicals released can cause the harm or injury alleged.

Relevance of thresholds in determining plausibility. Continuing with the PM example, it is believed that particles exert their primary toxic effects by increasing production of reactive oxygen (ROS) and nitrogen species (RNS). ROS and RNS tend to react chemically, causing damage by "attacking" cell structures and genetic material (e.g., DNA). While very high levels can lead to DNA damage, there is little evidence to suggest that PM can damage DNA in the absence of inflammation, which is a threshold phenomenon due to the many feedback and control processes involved. *EPA ISA*, *supra*. The mutagenicity of some hydrocarbon components of ambient PM has been established for decades, but the ability of PM-associated organics to cause DNA damage depends on their release from the particles (i.e., the particles themselves do not cause the mutation). Roel P. Schins & Ad M. Knaapen, "Genotoxicity of Poorly Soluble Particles," 19 *Inhalation Toxicology* 189 (2007). Therefore, even though PM may be capable of causing mutation at high levels, the available information does not support that there is no threshold for this effect. The concept that there is a threshold for PM-induced toxicity is supported by mechanism-of-action studies for PM conducted in living animals and human experiments. *EPA ISA*, *supra*. Thus, allegations that *any* increase in PM (no matter how small) will cause harm are not well supported by the science.

Plausibility of cumulative toxicological effects. Another issue in lawsuits alleging harm or injury is the potential impact of cumulative exposure, defined as simultaneous exposure to multiple chemicals at once. The basis for such claims is that chemicals in the mixture may interact in such a way that the doses are additive and the mixture is more potent than any one of the individual chemicals by themselves.

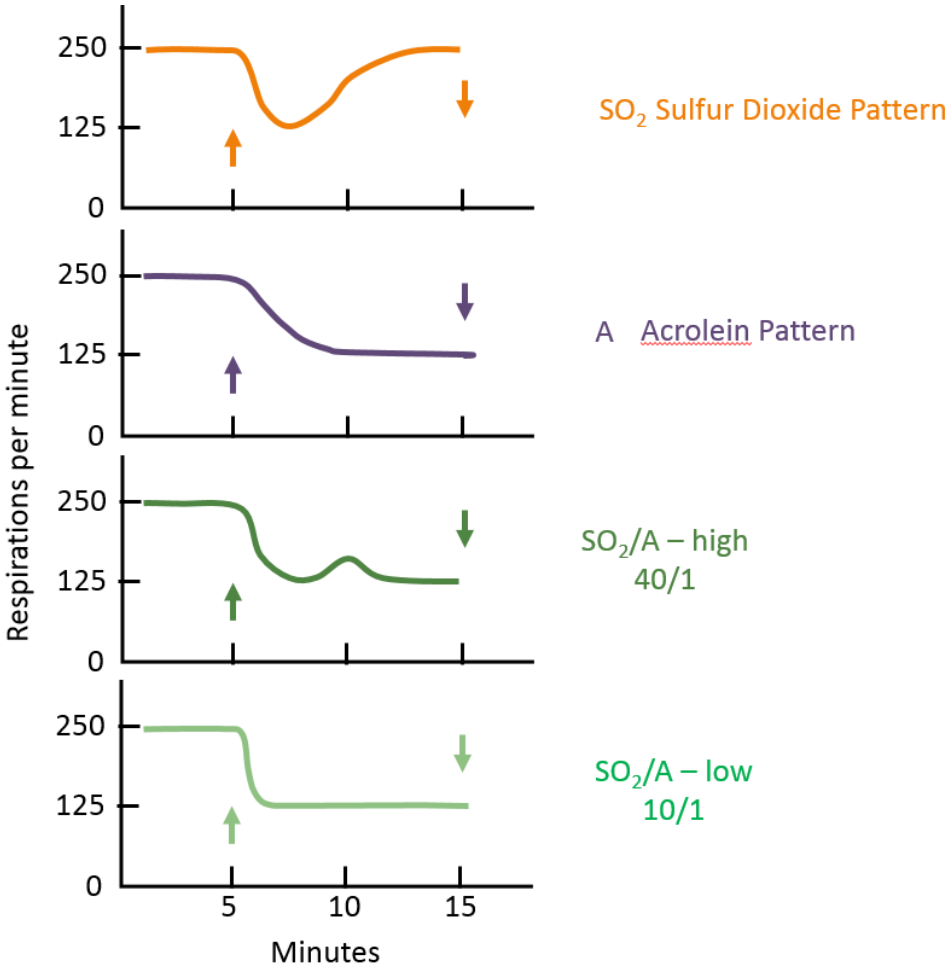
Unfortunately, the scientific literature on chemical interactions is extremely limited. However, one cannot simply assume that the health effects caused by simultaneous exposure to two chemicals that cause the same toxic effect can be accurately predicted by simply summing the doses of the components. Understanding the mechanisms by which the individual chemicals cause the toxic effect is critical to determining whether the response will be additive because strict dose additivity is generally only considered to occur when chemicals exert their toxic effects by the same mechanism of action. ATSDR, *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures* (2004); EPA, EPA/600/8-90/064, *Technical Support Document on Health Risk Assessment of Chemical Mixtures* (1990).

Consider a case in which the plaintiffs claimed cumulative exposure to several compounds potentially emitted from a refinery. Among the chemicals potentially emitted were acrolein, a potential byproduct released when something is burned, and sulfur dioxide (SO2). Both compounds have the potential to cause sensory irritation (i.e., burning, stinging, tingling of eyes and upper airways). Sensory irritation is a receptor-mediated process, which means that receptor proteins bind stimulating agents, causing the body to react in a particular way. Airborne chemicals activate the system mainly at mucous membranes (inside nose, eyes, etc.), where there is easy access to the nerves. The mechanism by which SO2 causes irritation is by splitting the disulfide bond (indicated as S-S in the receptor figure below) on the receptor protein. Other compounds, like acrolein, chemically interact with (i.e., bind) thiol groups (indicated as S-H in the receptor figure below) at the receptor. Gunnar Damgård Nielsen, "Mechanisms of Activation of the Sensory Irritant Receptor by Airborne Chemicals," 21 *Critical Revs. in Toxicology*183 (1991).



As shown in the top panel of the figure below, when mice are exposed to SO2 alone, there is a rapid drop in respiration (experimental indicator of irritation) five minutes after exposure begins, but respiration rebounds to approximately normal within eight minutes, even though exposure to SO2 continued for 15 minutes. The second panel illustrates a different response pattern for acrolein in that, although a decrease in respiration occurred at five minutes, it was slower (i.e., less steep) and the respiration rate did not rebound. (Laurel E. Kane & Yves Alarie, "Interactions of Sulfur Dioxide and Acrolein as Sensory Irritants," 48 *Toxicology & Applied Pharmacology* 305 (1979).

The next two panels show response patterns following simultaneous exposure of mice to SO2 and acrolein at high (40:1 ratio) and low (10:1 ratio) SO2 concentrations. When the ratio of SO2 to acrolein is higher, the rapid drop in respiration followed by rebound at eight minutes that are characteristic of SO2 occur, but then the respiration drops again and plateaus, which is characteristic of the acrolein response. When the ratio of SO2 to acrolein is lower, the response looks almost identical to the acrolein response, except that the drop in respiration at five minutes is faster (i.e., steeper).



Source: Kane & Alarie, *supra*.

These figures show that although the response shows characteristic patterns of each of the individual chemicals when mice are exposed to SO2 and acrolein simultaneously, the response is not additive (i.e., the two are not more potent together). As shown above, the lowest respiration rate is 125 per minute, regardless of whether mice are exposed to SO2 alone, acrolein alone, or SO2 and acrolein simultaneously. Thus, when allegations of cumulative toxicity are made, a toxicologist can help determine whether the mechanisms of action of the chemicals allegedly involved support that simultaneous exposure could potentially be more harmful.

Conclusion

A good expert must be able to demonstrate the theory upon which scientific evidence is based and that the theory is valid and properly applied. A qualified toxicologist can help build a case that includes consideration of dose, toxicological mechanism of action, and the potential impact of simultaneous exposure to multiple chemicals. The dose to which a plaintiff has potentially been exposed and the mechanism by which the chemical agent causes toxic effects are each critical to determining whether the event in question could have caused the alleged harms.

Keywords: environmental litigation, chemical exposure, toxicologist, exposure assessment, dose, mechanism of toxicity, toxicity threshold

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