

MECHANISM OR CAUSATION? THE NEW BATTLE OVER BENZENE METABOLITES

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As part of the ongoing litigation battles between the plaintiffs' bar and the defense bar in cases involving benzene or products containing benzene, lawyers on both sides are starting to encounter and utilize scientific literature regarding benzene metabolites. Benzene metabolites have been discussed in reported cases, therefore requiring lawyers to be able to understand and apply the principles and concepts involving benzene metabolites. *See, e.g., Sutera v. The Perrier Group of Am. Inc.*, 986 F. Supp. 655 (D. Mass. 1997). This article is designed to help defense lawyers understand these concepts, allowing them to converse with and understand the discussion of experts on benzene metabolites and prepare examinations in both depositions and trials. This article is not a scientific treatise, but instead is written by lawyers and is designed for lawyers whether they are newcomers to the field of benzene litigation or seasoned veterans of

many previous benzene battles. With that introduction, it is appropriate to dive right into our topic.

1. What is a Benzene Metabolite?

A “metabolite” is defined as “any substance produced by metabolism or by a metabolic process.” Dorland’s Illustrated Medical Dictionary (26th ed. 1985), 803. Thus, a benzene metabolite is a substance produced by the metabolism of benzene in the human body. In other words, benzene metabolites are the substances produced as benzene is broken down, or metabolized, in the body. Scientists are attempting to understand the role, if any, that benzene metabolites may play in the development of certain diseases.

2. Focus on the Mechanism: The Metabolic Pathway of Benzene in the Body

To understand any arguments or contentions regarding benzene metabolites, one needs to examine what happens once benzene enters the human body. This requires a brief foray into biochemistry and complicated chemical names, but please bear with us. As benzene enters the body, an enzyme in the liver known as Cytochrome P-450 begins to metabolize the benzene and converts benzene into benzene oxide. Benzene oxide is further metabolized into phenol. Phenol is then metabolized into either hydroquinone or catechol. Catechol is further broken down into O-benzoquinone. Hydroquinone is broken down into P-benzoquinone and 1, 2, 4 trihydroxibenzene. This metabolic pathway is the mechanism by which benzene is broken down in the human body. Phenol, catechol, hydroquinone, P-benzoquinone and 1, 2, 4 trihydroxibenzene are benzene metabolites. They are substances that are produced by the body as the result of the metabolism of benzene.

These benzene metabolites do not appear in the body solely as the result of occupational exposure to airborne benzene or to other products such as toluene or xylene. In fact, there are

many additional natural sources of benzene metabolites such as hydroquinone and phenol in the human body. For example, various foods including coffee, milk, cheese, apples, cherries, asparagus, broccoli and onions are dietary sources of phenol or hydroquinone. *See* McDonald, TA, et al., Hypothesis: Phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia. *Leukemia*, 15: 14. Second, cigarette smoke contains phenol, catechol, hydroquinone, and benzene. *See id.* at 13-14. Third, over-the-counter medications, including Pepto-Bismol and Chloraseptic lozenges can result in increases in blood phenol levels. *See id.* at 13. Fourth, other foods with high levels of arbutin may increase the hydroquinone levels in the human body. *See id.* at 15. These foods include pears and wheat germ. Thus, the mere presence of benzene metabolites in the human body is not unusual or automatically linked to occupational exposure to benzene or to products containing benzene.

3. Plaintiffs' Lawyers' Use of Benzene Metabolites

Plaintiff's lawyers often like to focus on hydroquinone and its further metabolites. They may argue that hydroquinone and its metabolites are the actual causes of bone marrow damage and the cause of the development of diseases such as acute myelogenous leukemia (AML). Plaintiff's lawyers may argue that even low levels of exposure to benzene results in plaintiffs having benzene metabolites in their bodies. They may argue that the presence of these metabolites establishes that the plaintiff has suffered an injury caused by his or her exposure to benzene.

Plaintiff's lawyers will attempt to rely upon the metabolic pathway described above to establish legal causation. A careful defense lawyer must avoid this trap. A defense lawyer who follows a plaintiff's lawyer into this trap will allow the plaintiff's lawyer to choose the ground

for the fight over causation. Similar to a battlefield, a lawyer who allows his opponent to dictate the terms of the fight over causation will often be at a disadvantage.

Instead, a defense lawyer must seize the opportunity presented by the plaintiff's counsel and focus the attention of the case to the actual mechanism by which benzene is metabolized in the body. The simple fact that benzene is broken down into metabolites does not establish that the plaintiff's exposure to a benzene-containing product actually caused the plaintiff's disease or injury. In other words, the effects of the metabolites in the human body is insufficient evidence to establish causation. *See, e.g., Sutura*, 986 F. Supp. at 664.

4. Opportunities to Challenge Plaintiff's Use of the Metabolic Pathway of Benzene

From a defense lawyer's standpoint, the key to addressing arguments raised by plaintiff's counsel regarding benzene metabolites is to focus on the fact that scientific literature involving benzene metabolites attempts to explain the mechanism, or pathway, by which benzene is broken down in the human body and on how benzene, once metabolized, causes harmful effects. The metabolic pathway that benzene undergoes after it enters the body and is metabolized is thus a mechanism by which scientists are attempting to understand how benzene can cause certain diseases. It is not, however, a roadmap to establishing legal causation between exposure to benzene or a benzene-containing product. A knowledgeable defense lawyer will emphasize this point, use it to his or her advantage, and should use the opportunity presented by plaintiff's counsel's decision to rely on benzene metabolites to attack plaintiff's theory of the case.

If the plaintiff's counsel attempts to use benzene metabolites and the metabolic pathway by which benzene is metabolized in the human body to establish causation, this opens several opportunities to challenge the plaintiff's lawyer's theory.

First, there are many other sources of benzene metabolites that may be found in the body. Scientific literature indicates that diet, the catabolism of tyrosine and other substrates by gut bacteria, ingestion of arbutin-containing foods, cigarette smoking, and the use of some medications can contribute to the levels of phenol or hydroquinone found in the human body. *See* McDonald, TA, et al., Hypothesis: Phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia. *Leukemia*, 15: 10-20. As a result, it is not unnatural for phenol or hydroquinone to be present in the human body. The presence of these metabolites in the human body is not evidence of causation.

In another method of attack, plaintiff's lawyers may argue that P-benzoquinone and 1, 2, 4 trihydroxibenzene can cause the translocation of chromosomes 7 and 8, which may be an indicator of benzene-induced AML. However, the ingestion of coffee can cause the translocation of the same chromosomes. The *Sutera* court confronted this argument. In *Sutera*, the plaintiff's expert attempted to support his theory that plaintiff's consumption of bottled water caused plaintiff to develop a form of AML because benzene metabolites could cause the translocation of specific chromosomes. Plaintiff suffered from the same translocation of those particular chromosomes. However, defendant's expert testified that the translocation at issue was commonly found in "virtually all patients with promyelocytic leukemias, including both those who have been exposed to chemical solvents and those who have not." *Sutera*, 986 F. Supp. at 664. The court rejected plaintiff's expert's contention: "[T]he translocation of chromosomes is insufficient to support causation." *Id.*

The biological process described above is simply a mechanism, or a metabolic pathway, that explains the metabolization of benzene after it enters the human body. What it does not do is establish causation. Scientific literature does not link benzene metabolites such as

hydroquinone or phenol to the development of AML in humans. Buttrressing this point is the fact that the International Agency for Research on Cancer (“IARC”) has not identified either hydroquinone or phenol as human carcinogens.¹ *See* McDonald, TA, at 16. A plaintiff’s lawyer cannot prove causation based on benzene metabolites because there is no scientific literature that supports the conclusion that benzene metabolites can cause AML. Causation can only be established, if at all, through the quantification of plaintiff’s exposure to benzene and the use of scientific literature that supports the proposition that such a level of exposure can cause AML, generally at least 40 ppm-years of cumulative exposure.

Plaintiff’s lawyers’ efforts to establish causation based on benzene metabolites is further hampered by the absence of any scientific literature that establishes that metabolites such as hydroquinone can cause damage to bone marrow in humans.

This basic review of benzene metabolites shows that a careful defense lawyer should view and analyze a plaintiff’s lawyer’s use of benzene metabolites as a mechanism for how benzene is broken down in the human body, not as a road map for causation. There is no scientific evidence that hydroquinone or phenol can cause AML. When a plaintiff’s lawyer suggests that the harmful effects of hydroquinone establish causation between exposure to benzene and the development of AML, it is an accurate response to state that drinking coffee can replicate those same effects.

5. Toluene Inhibits the Metabolism of Benzene

A plaintiff’s lawyer’s attempt to establish causation in a trace benzene case using benzene metabolites and the metabolic pathway described above is open to a further line of

¹ *See* International Agency for Research on Cancer (IARC). Re-evaluation of some organic chemicals, hydrazine, and hydrogen peroxide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC: Lyon, 1999; 71: 433-452, 749-768.

attack from the defense perspective. For example, in a case where the actual exposure is not to pure benzene but is to toluene, a plaintiff's counsel may attempt to establish causation by relying on the scientific literature involving benzene metabolites and by arguing that exposure to toluene exposes the plaintiff to those same metabolites. This attempt to prove causation is also able to be nimbly attacked.

Toluene inhibits the metabolism of benzene in the human body and the hematological effects of benzene. The Agency for Toxic Substances and Disease Registry ("ATSDR") noted in May of 2004 that studies of the influence of toluene on benzene toxicity have shown that exposure to toluene inhibits "benzene-induced hematologic and immunologic effects in animals." *See* ATSDR, Interaction Profile for: Benzene, Toluene, Ethylbenzene and Xylene (BTEX), 15 (May 2004). Studies reviewed by the ATSDR also indicate that toluene has a greater suppressive effect on the metabolism of benzene than does benzene on the metabolism of toluene. *See id.* at 14. Thus, if a plaintiff's lawyer attempts to suggest that the trace amounts of benzene in toluene can cause AML through the effect of benzene metabolites, this provides an opening for the defense lawyer to argue that the presence of toluene itself inhibits the very metabolism which the plaintiff's lawyer suggests may cause AML.

This argument can also be useful in other types of cases as well. For example, gasoline typically contains 10-12% toluene, and, as a result, the toluene in gasoline would inhibit the metabolism of benzene in gasoline. Thus, in a case involving exposure to gasoline, the effects of toluene on the metabolism of benzene can be brought to bear in the favor of the defense. This argument is useful in any solvent case involving toluene.

Furthermore, epidemiologic literature has not established that toluene can cause AML. Toluene also has not been identified as a human carcinogen. *See, e.g.,* ATSDR, Toxicological

Profile for Toluene, 138 (September 2000) (“Human and animal studies generally do not support a concern for the carcinogenicity of toluene.”); IARC Monograph: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. (1999) 71: 829 (“There is inadequate evidence in humans for the carcinogenicity of toluene.”).

6. Conclusion

From a defense lawyer’s standpoint, the use of benzene metabolites is not a roadmap to establish causation. In actuality, it is a path through which the defense lawyer has several options for attacking his adversary’s primary theory, and, hopefully, prevailing in the case.