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BLOG

In re Acetaminophen MDL Decision Reaffirms Need for Causation Experts to Account for Known Confounders Under Rule 702

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A recent and thorough opinion in *In re Acetaminophen – ASD-ADHD Products Liability Litigation*[1] reaffirms the need for parties' general causation experts to meaningfully engage with known confounding factors to ensure the admissibility of their opinions.

In *In re Acetaminophen*, Judge Denise Cote of the Southern District of New York granted motions by a manufacturer and retailers of acetaminophen products to exclude all five of the plaintiffs' general causation experts under Federal Rule of Evidence 702.[2] The *Acetaminophen* MDL includes more than 600 plaintiffs who allege that the manufacturer of Tylenol and retailers of store-branded acetaminophen products violated state-law duties to warn that children may develop autism spectrum disorder (ASD) or attention deficit-hyperactivity disorder (ADHD) from in utero exposure to the drug.[3] The plaintiffs disclosed five general causation experts, including an epidemiologist, toxicologist, teratologist and geneticist, pharmacologist, and psychiatrist, and the defendants moved to exclude the opinions of all five.[4]

Judge Cote excluded all five of the plaintiffs' experts in a detailed order that provides guidance on multiple issues under Rule 702, several of which will be discussed in separate posts on this blog. Although the court recognized that "[e]ach of the plaintiffs' experts is well qualified to render an opinion in the areas addressed by their reports," the court noted that none "has published research that expresses the ultimate opinions they offer" in the litigation and that "the plaintiffs' lead expert on causation … co-authored a study on the prenatal effects of acetaminophen that cautioned against any change in clinical practice."[5] In fact, the study coauthored by that lead plaintiff expert recognized that further studies were required to, among other things, rule out confounding factors.[6] Yet the plaintiffs' expert failed to critically engage with known confounding factors in his report—a deficiency the court held "[b]y itself … requires the exclusion of his opinion."[7]

Confounding is a major source of error in epidemiological studies,[8] which are typically crucial to establishing general causation in pharmaceutical products liability cases. As the Reference Manual on Scientific Evidence explains, "it is critical to determine whether [an] association is causal or the result of confounding" when an association is observed in an epidemiological study.[9] "Confounding occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and outcome of interest."[10] An oft-cited example is a study showing that people with gray hair have a higher rate of death than people with hair of a different color. Age—rather than hair color—may explain the results, and is a potential confounding factor.[11]

The court recognized that there were two primary sources of confounding at issue in the *Acetaminophen* litigation: confounding by indication and confounding by genetics.[12] Confounding by indication is when "the reason a pregnant person takes acetaminophen itself causes ASD or ADHD."[13] For instance, if fever is associated with ASD *and* whether a pregnant person takes Tylenol, an association between prenatal exposure to Tylenol and ASD could be due to the confounding factor fever.[14] Confounding by genetics means that "there could be genetic factors that make pregnant people more likely to take acetaminophen during pregnancy, and also make it more likely that their offspring will have ADHD or ASD."[15] The court recognized that genetic factors could play a significant role in the development of ASD and ADHD. The heritability of those conditions—a measure of how much variation in those traits is due to genetic influence rather than environmental factors—was estimated to be 80% and 74%, respectively.[16]

Despite that "identified risk of genetic confounding," the court found that the plaintiffs' epidemiology expert gave "short shrift to the issue" with a discussion that was "incomplete, unbalanced, and at times misleading."[17] Specifically, the plaintiffs' expert failed "to assess with sufficient rigor the relevant evidence of confounding by genetics."[18] That failure rendered his Bradford-Hill analysis "unreliable" and "require[d] the exclusion of his opinion."[19] (For a more in-depth discussion of the Bradford-Hill criteria, see our prior posts here and here.)

In fact, the court noted that both the FDA and many of the studies relied on by the plaintiffs' expert recognized that confounding by genetics was a significant limitation to the epidemiological literature. The court noted that the FDA had recently concluded that studies are "still limited by . . . the possibility of unmeasured confounding by factors such as indication, other medications, and genetic factors," and that future studies should adjust for "genetic factors or . . . relevant familial factors such as parental neurobehavioral conditions (e.g., parental ADHD) or psychiatric conditions."[20] And many of the studies relied on by the plaintiffs' expert "acknowledge the need for more work to account for the confounding effect of genetics."[21] Yet the plaintiffs' expert "repeatedly ignore[d] authors' cautions that familial or genetic confounding may explain, at least in part, the observed association" and "downplay[ed] those studies that undercut his causation thesis and emphasize[d] those that align with his thesis."[22] The court concluded that such a "result-driven analysis" "does not reflect a reliable application of scientific methods" and required the exclusion of his opinion.[23]

STRATEGIC TAKEAWAYS

The *Acetaminophen* court's holding reaffirms the importance to the Rule 702 analysis of accounting for known confounding factors. Although litigants sometimes argue that consideration of confounding factors goes to the *weight* of an expert's opinion, the court's ruling confirms that the failure to account for confounding factors can represent an unreliable application of scientific methods that renders an opinion inadmissible.

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[1] *In re Acetaminophen – ASD-ADHD Prods. Liab. Litig.*, No. 22MD3043 (DLC), 2023 WL 8711617 (S.D.N.Y. Dec. 18, 2023).

[2] *Id.* at *1.

[3] *Id.*

[4] *Id.*

[5] *Id.* at *15.

[6] *Id.* at *19.

[7] *Id.* at *31.

[8] Reference Manual on Scientific Evidence (3d ed. 2011) at 591.

[9] *Id.*

[10] *Id.*

[11] *Id.*

[12] *In re Acetaminophen*, 2023 WL 8711617, at *6.

[13] *Id.*

[14] *Id.*

[15] *Id.*

[16] *Id.* at *4, 31.

[17] *Id.* at *32.

[18] *Id.* at *31.

[19] *Id.*

[20] *Id.*

[21] *Id.*

[22] *Id.* at *32, 33.

[23] *Id.* at *32, 33.

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