UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Related To: All Cases**	**22md3043 (DLC)**

MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFFS' RULE 702 MOTION TO EXCLUDE DR. JENNIFER PINTO-MARTIN

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PRELIMINARY STATEMENT

Defendants proffer Dr. Jennifer Pinto-Martin as an expert in epidemiology, but her interpretation of epidemiological evidence—at least when she is retained to testify—is so conservative that it is virtually guaranteed to never find that an association is causal. Juries should not be confused by a witness who persistently refuses to apply her scientific skills to ascertain a question under a preponderance-of-the-evidence standard. *In re Ephedra Prods. Liab. Litig.*, No. 04 MD 1598 (JSR), 2005 WL 8178810, at *6 (S.D.N.Y. Sept. 20, 2005) ("The legal standard, after all, is preponderance of the evidence, *i.e.*, more-probable-than-not, and that applies to causality as to any other element of a tort cause of action.").

Scores of observational epidemiological studies show an association between prenatal acetaminophen exposure and autism spectrum disorder ("ASD") and attention-deficit/hyperactivity disorder ("ADHD") in offspring. In other words, they found that women who took acetaminophen while pregnant had children with ASD and ADHD at higher rates than women who did not. Nearly every study that measured for a dose response found one, which means that the *more* acetaminophen a woman took while pregnant, the *higher* the chance of having a child with ASD or ADHD. Most of the studies produced statistically significant results, which is tantamount to saying the association could not have happened by chance alone. And innovative methods designed to detect explanations other than causation have not come up with one: Neither pre-pregnancy nor post-pregnancy use of acetaminophen increased the risk, nor did taking competitor drugs like ibuprofen. The risk is one unique to during-pregnancy use of acetaminophen. Though few things in life or science are *certain,* the inference of causation is overwhelming.

To avoid making that inference, Dr. Pinto-Martin attempts to turn science into a Catch-22. First, she opined repeatedly that observational studies are *never* sufficient to establish causation,

even though the entire field of epidemiology is based on the opposite principle. Ex. 2, Pinto-Martin Dep. Tr. at 216:23–217:1 ("I'm not willing to say that something is causal based on observational studies."); *id.* at 120:3–4 ("[F]rom an observational study, I cannot establish causation."); *id.* at 133:16–18 ("Personally, I would not be willing to assign causality on the basis of observational studies."); *id.* at 90:23–25 ("I'm never going to say that I think an environmental factor causes autism."); *id.* at 137:17–19 ("I would never say an individual agent causes ASD or ADHD."). Next, she agreed that, in assessing the risk that prenatal ingestion of acetaminophen can cause neurodevelopmental disorders, scientists will *always* be limited to observational studies, because no woman would participate in a randomized controlled trial (RCT) precisely *because of* the alarming observational evidence she discards. *Id*. at 254:9–14 ("I think we're past [equipoise] now because there are studies suggesting a risk. And so, first of all[,] what women would enroll in a study like that? And it would be unethical."); *id.* at 258:24–259:2 (conceding that an RCT cannot be done because "there are reported elevated risk estimates from these studies that have been captured and publicized."). So the more observational evidence that piles up, the more unethical it would be to obtain the *only* type of evidence—an RCT—that Dr. Pinto-Martin will credit before taking action to protect pregnant women and their children.

Although Dr. Pinto-Martin styles that approach "conservative," *see id.* at 102:4–7, her application of the Bradford Hill criteria is an abject perversion of that foundational methodology. *No* authority cited by Dr. Pinto-Martin (or anybody else) supports her never-through-observational-evidence take on causality. The entire *purpose* of the Bradford Hill framework is to determine if a causal inference may be drawn from observational epidemiologic data. Ex. 3, Bradford Hill Address at 295 ("Our *observations* reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects

of that association should we especially consider before deciding that the most likely interpretation of it is *causation*?") (emphasis added). And those criteria have been employed to establish a causal link between hundreds of substances and their ensuing diseases, from tobacco and lung cancer, to thalidomide and the birth defect phocomelia, to valproic acid and the two conditions at issue here, ASD and ADHD. FDA-approved drug labels are full of warnings about causal risk factors that are based on observational data alone—including the valproic acid label that warns of a causal link between in utero exposure and both ASD and ADHD. And the pages of the federal reporters are full of cases that have gone to verdicts in plaintiffs' favor based on general causation evidence grounded in observational epidemiology.

If scientists had applied Dr. Pinto-Martin's personal methodology, we would still be waiting to conduct an "experiment" before making a causal inference about many of the substances we now know to cause certain diseases. Ex. 2, Pinto-Martin Dep. Tr. at 39:4–6 ("We cannot establish causality in an observational study because it is not an experiment."). Even in the context of tobacco and lung cancer, Dr. Pinto-Martin (based on her personal methodology) would not say whether "the people in the 1950s or early 1960s who said 'Yes, tobacco does cause lung cancer'" were "right or wrong." Ex. 2, Pinto-Martin Dep. Tr. at 302:14–303:1. After all, that epidemiological evidence, too, was merely "observational."

Although Dr. Pinto-Martin's report spans more than a hundred pages, it could have been a single syllogism: An RCT is required to establish causation; there have been no such RCTs done here because it would be unethical to do them; therefore there is no causation. But the major premise—that epidemiology can *never* establish a causal link—is erroneous *ipse dixit* that makes her opinion inadmissible under *Daubert*. *405 Condo Assocs. LLC v. Greenwich Ins. Co*., No. 11 CIV. 9662 (SAS), 2012 WL 6700225, at *3 (S.D.N.Y. Dec. 26, 2012).

The flaws in Dr. Pinto-Martin's testimony go beyond even this pervasive methodological error. She also engaged in speculation and "cherry-pick[ing] from the 'scientific landscape [in order to] [ ] present the Court with what [s]he believes the final picture looks like.'" *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17 CV 4188-LTS-JLC, 2021 WL 4037820, at *5, (S.D.N.Y. Sept. 3, 2021) (quoting *In re Rezulin Prods. Liab. Litig.*, 309 F.Supp.2d 531, 563 (S.D.N.Y. 2004)), *aff'd* 2023 WL 4837521 (2d Cir. July 28, 2023). She essentially dismisses the voluminous evidence showing a positive association based on unsubstantiated theories that the results are explained by (a) confounding by genetics, and (b) confounding by indication. Yet she admitted that those two theoretical possibilities are rarely ruled out in *any* study, no matter how perfectly designed. Ex. 2, Pinto-Martin Dep. Tr. at 270:8–15 ("Q. No matter how good your study is, it's always possible that there's some confounder out there that's actually driving the results A. Absolutely true."). More problematically, she admitted that she had no definitive *evidence* that either of these two types of confounding were actually driving the results. Her opinion indulges a mirage of her own making.

Start with genetics. Dr. Pinto-Martin admitted that "we don't have sufficient evidence to really support that as a… confounding variable" for ASD *at all*. Ex. 2, Pinto-Martin Dep. Tr. at 153:19–21. And she admitted that the evidence of genetic confounding for ADHD was "not incredibly powerful" and "barely statistically significant." *Id.* at 161:8–17. As for confounding by indication, she was forced to concede that she simply disagreed with the independent scientists working in this area who have examined this question and found *no evidence* of confounding by indication. *Id.* at 318:18–319:22, 325:13–22 (admitting that the Ricci meta-analysis "does not support confounding by indication."). At most, all Dr. Pinto-Martin has is a speculative hypothesis that these types of confounding *might* be driving these results. Big tobacco apologists said exactly

the same thing, pointing specifically to the exact same "genetic confounding" bogeyman that Dr. Pinto-Martin points to, *id.* at 280:13–281:12, thereby delaying widespread recognition of the causal link between smoking and lung cancer to the detriment of millions.

Finally, Dr. Pinto-Martin's application of the Bradford Hill factors reconfirms a results-oriented method meant to reach her preordained "no causation" answer. She cherry-picks the studies for her analysis and then applies objectively erroneous definitions of the Bradford Hill factors that defy basic epidemiological principles. At the threshold, she says that there is no "association" *at all* between prenatal acetaminophen exposure and ASD or ADHD, but that is simply denial. Even JJCI knows better, grudgingly conceding in its Motion to Dismiss that the relevant studies "suggest (at best) an association between exposure and injury." Dkt. 426 at 35. Some of Defendants' other experts—when not opining in this case—recognize the association and risk of ASD and ADHD. *See, e.g.*, Ex. 4, Ex. 771 to Faraone Dep. at 3, (listing acetaminophen exposure to the fetus as a "cause[] of ADHD" and a "modifiable environmental risk factor[]"); Ex. 5, Ex. 494 to Kolevzon Dep., at 198 (stating that "several prenatal exposures . . . emerge as potential risk factors for ASD," including "[m]ost notably" "prenatal use of acetaminophen."). *Every* author writing on this topic—including those who are not sure whether the association is causal—has recognized that the statistical association is a real one. In refusing to admit the basic math, Dr. Pinto-Martin truly stands alone.

There is more. When evaluating "consistency," the leading authority cautions against the "fallacious" labelling of studies as inconsistent just because some are statistically significant and some are not. But Dr. Pinto-Martin admitted that she committed that exact fallacy in her report. Ex. 2, Pinto-Martin Dep. Tr. at 391:7–25. When evaluating the "strength" of an association, epidemiologists are to look at the magnitude of the risks alone. But Dr. Pinto-Martin imported her

own criticisms of the studies' exposure measurements into the strength analysis she provided during her deposition—something that she admitted that she did not do in her report and which is unsupported by any epidemiological authorities. *Id.* at 494:10–495:4. And although Dr. Pinto-Martin opined that there might be a "reverse causation" temporality problem in this literature—which preposterously supposes that a child's (later) ASD/ADHD diagnosis would somehow induce the mother to (years earlier) take acetaminophen while that same child was in the womb—she was ultimately forced to admit that this would be impossible without a "time machine." *Id.* at 532:25–538:9.

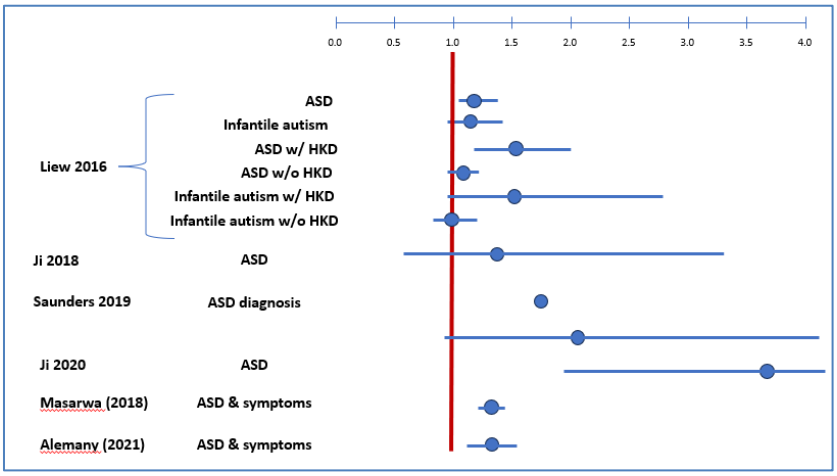
In her unguarded and unscripted moments, Dr. Pinto-Martin at least admitted that reasonable scientists could depart from her unscientific conservativism. In the "ongoing debate about whether there is any causal association" between acetaminophen, ASD, and ADHD, Ex. 2, Pinto-Martin Dep. Tr. at 138:18–20, Dr. Pinto-Martin agrees that "reasonable scientists" could and did sign on to the consensus statement, *id.* at 188:8–19, that it is "reasonable" to say that the evidence "supports the hypothesis of causality," *id.* at 230:20–231:20, and that scientists who *have* suggested causation employed "scientifically reasonable means to address the question using the data that they have available." *Id.* at 504:11–15. Just so. And yet, to engage with that ongoing debate in a reliable way, Defendants must put up an expert who is not a true "Dr. No"—an expert who will *always* reach the conclusion of "no causation" based on the unique, "personal" methodology that she employs when retained to testify in a court of law. The Court should exclude the testimony of Dr. Pinto-Martin.

BACKGROUND

I. There is Overwhelming Epidemiological Evidence on the Association Between Prenatal Use of Acetaminophen and ASD and ADHD.

More than 20 separate epidemiological studies have found a positive association between prenatal use of acetaminophen and neurodevelopmental disorders such as ASD and ADHD. These studies—all published in peer reviewed journals—have found time and time again, over multiple populations, different study designs, and at different times, that there is a positive association between prenatal use of acetaminophen and the neurodevelopmental disorders ASD and ADHD. The forest plots—even those documenting the results of the studies that Dr. Pinto-Martin hand-selected—illustrate the strength of the evidence for this causal association.

The below graphic plots the studies on which Dr. Pinto-Martin relies that focus on the association between acetaminophen and ASD, including meta-analyses:



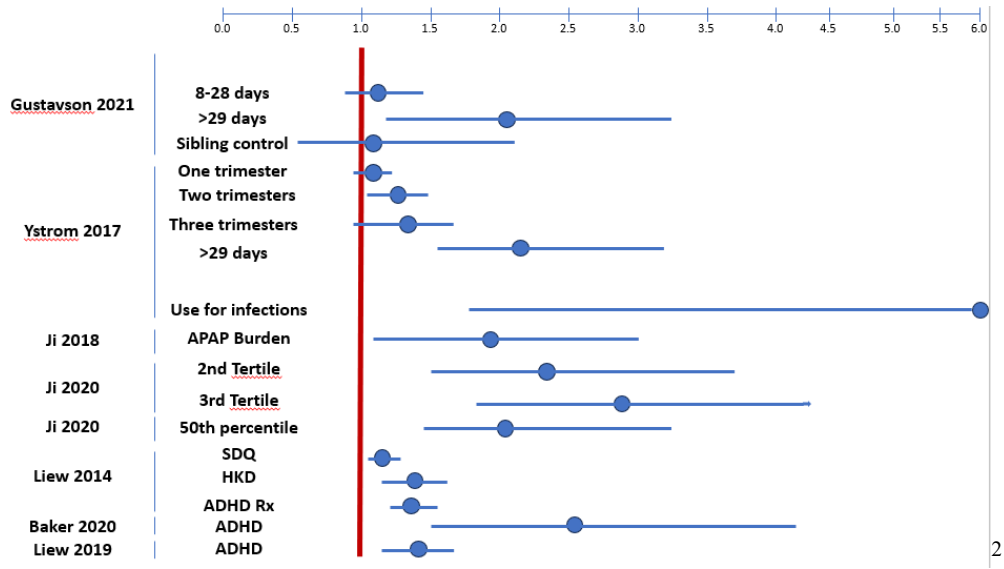
[1]

As Dr. Pinto-Martin was forced to admit, for all but one subgroup analysis in these studies, "the woman who was exposed to APAP…had a higher rate of having a child with ASD." Ex. 2, Pinto-Martin Dep. Tr. at 262:23–263:22.

[1] *See* Ex. 6, Ex. 634 to Pinto-Martin Dep.

In her report, Dr. Pinto-Martin stated that it was particularly "important" to her that the "better designed studies don't report an association" for ASD. *Id.* at 18:4–23; Ex. 1, Pinto-Martin Report at 5. But when pressed during her deposition to identify these "better designed studies," she could identify only one for ASD: Liew 2016. Ex. 2, Pinto-Martin Dep. Tr. at 22:5–6 ("Q. So just Liew 2016? A. Yes"). And by Dr. Pinto-Martin's own admission, that Liew 2016 study *does* show a statistically significant link between acetaminophen use and ASD. *Id*. at 24:17–25:3 ("Q. And my question for you is very simple, does Liew 2016 report an association between acetaminophen use and ASD?... Yes or no? . . . Does it do that? A. It does.").

The results are even more compelling for the association between more than 8 days of prenatal use of acetaminophen and ADHD:



Again, Dr. Pinto-Martin admitted the obvious: "100 percent of these studies had a point estimate showing a positive association between prenatal APAP exposure and the risk of ADHD diagnosis." Ex. 2, Pinto-Martin Dep. Tr. at 167:15–23. She also admitted that a full 13 of those results—*i.e.*, the ones she herself cherry-picked—were statistically significant. *Id.* at 170:19–

[2] *See* Ex. 6, Ex. 633 to Pinto-Martin Dep. at 2.

171:4. And these are studies that solely focus on ASD and ADHD as endpoints, the only kind that Dr. Pinto-Martin deems relevant. The evidence is even *more* compelling when accounting for studies that measure symptoms of ASD and ADHD.[3]

Meanwhile, the scientists working on this issue have employed advanced study designs to try to find evidence of explanations other than causation, but those efforts only confirm that causation is the most likely explanation. For instance, there are no studies showing a link between ibuprofen and autism, Ex. 2, Pinto-Martin Dep. Tr. at 335:18–24, and there are studies affirmatively showing *no* link between ibuprofen and behavioral and communication problems, suggesting that the mechanism is unique to acetaminophen alone. *See* Ex. 7, Brandlistuen (2013) at 1710 ("In contrast, we find no association between ibuprofen on the same neurodevelopmental outcomes, which suggests a specific effect of paracetamol less likely to be confounded by indication."). There are no studies showing a link between pre-pregnancy or post-pregnancy use of acetaminophen and ASD, Ex. 2, Pinto-Martin Dep. Tr. at 337:12–339:10, and there *are* studies affirmatively showing *no* link between pre- and post-pregnancy use and ADHD, suggesting that the above associations are being driven by the acetaminophen itself rather than some (unidentified) characteristic of those women who happen to take acetaminophen. *See* Ex. 8, Liew (2019) at 771 ("[T]he absences of associations with acetaminophen use in the prepregnancy and postpregnancy periods are the true NCE tests . . . and they suggest that . . . genetics, maternal chronic disease, or socioeconomic status . . . do not explain the association observed for acetaminophen exposure at

[3] Dr. Pinto-Martin considers but excludes studies that looked at anything other than ASD and ADHD diagnoses as endpoints, such as studies using as endpoints common symptoms of those neurodevelopmental disorders. *See* Ex. 1, Pinto-Martin Report at 4, 45–50, 86–91. Although studies with defined diagnoses as endpoints are particularly probative of a causal relationship, it is improper to ignore other, relevant evidence. *See* Ex. 10, Baccarelli Rebuttal Report at 18.

the time of pregnancy"); Ex. 9, Ystrom (2017) at 6 ("Maternal preconceptional use was not associated with ADHD . . . and is consistent with a causal link").

Many of authors of the studies charted above—all independent scientists—have suggested that causation is driving the results:

- The Olsen authors noted that recent research—including data from several cohorts from around the world—has "increased the probability that the association is causal." Ex. 11, Olsen & Liew (2017) at 1395.
- The authors of the Gou study concluded that, though not definitive, the epidemiology findings thus far "lend weight to the hypothesis that the association is causal." Ex. 12, Gou (2019) at 204.
- The authors of the Ystrom study concluded that one set of their results was "consistent with a causal link." Ex. 9, Ystrom (2017) at 6.
- The authors of the Stergiakouli study noted that their findings (combined with previous ones) were "consistent with an intrauterine effect," *i.e.*, with causation. Ex. 13, Stergiakouli (2016) at 967.
- The authors of the Alemany study reviewed the Bradford Hill methodology for assessing causation and concluded that the "causal" elements of "biological plausibility," "coherence," "consistency," "temporality," and "dose response" had all been demonstrated. Ex. 14, Alemany (2021) at 1000–01.
- In fact, Silvia Alemany (the lead author of the above study) said in an interview discussing that study that "[w]hat emerges from our results is that if paracetamol is being consumed when it is not strictly necessary, perhaps its consumption should be decreased and with it, the likelihood of developing certain neurodevelopmental problems in the future."[4]
- One of the lead authors of the Consensus Statement published in Nature, Dr. Shanna Swan, told the press that their results were not merely "correlative"; she even compared the results to those initially showing that "smoking causes lung cancer" and that "lead lowers IQ."[5] Dr. Swan was in fact one of Dr. Pinto-Martin's graduate school

[4] *Sílvia Alemany (ISGlobal): "I think the use of paracetamol during pregnancy should be monitored more tightly"*, El·lipse (June 22, 2021), https://ellipse.prbb.org/silvia-alemany-isglobal-i-think-the-use-of-paracetamol-during-pregnancy-should-be-monitored-more-tightly.

[5] Victoria Forster, *Is Taking Painkiller Acetaminophen Safe During Pregnancy?*, Forbes (Oct. 12, 2021), https://www.forbes.com/sites/victoriaforster/2021/10/12/is-taking-painkiller-acetaminophen-safe-during-pregnancy/.

professors, and Dr. Pinto-Martin agreed that Swan was "a solid biostatistician from my experience with her in class." Ex. 2, Pinto-Martin Dep. Tr. at 183:2–5.

- The Bornehag authors suggested that "women take the precautionary action of limiting their use of" acetaminophen while pregnant. Ex. 15, Bornehag (2018) at 102.
- The Brandlistuen authors stated that "[i]f replicated, these findings may suggest limiting long-term use of [acetaminophen] during pregnancy." Ex. 7, Brandlistuen (2013) at 1712.
- The Baker 2020 authors recommended that FDA and other institutions should "consider reevaluating the evidence regarding the safety of fetal acetaminophen exposure." Ex. 16, Baker (2020) at 1080.

II. Dr. Pinto-Martin Misapplies Basic Epidemiological Principles to Reach Her Pre-Ordained Causation Opinion.

Faced with this tidal wave of evidence, Dr. Pinto-Martin apparently chose to bend the ordinary rules by which epidemiologists interpret data and draw causal inferences. In her report, Dr. Pinto-Martin acknowledged that the goal of epidemiology—which employs observational data—is to identify "upstream causal factors that can be modified to reduce the risk of acquiring the disease." Ex. 1, Pinto-Martin Report at 5. In other words, she acknowledged that epidemiology was theoretically capable of identifying exposures that are most likely causal in nature. In practice, however, Dr. Pinto-Martin consigns her entire field to the limited role of saying we do not, and will never, know enough. She repeatedly testified that she would never—*never*—make a causal inference on the basis of observational studies. Ex. 2, Pinto-Martin Dep. Tr. at 117:22–25; *see also id.* at 90:90:23–25;3–25; 120:3–4; 133:16–18; 216:23–217:1216:23–217:1; *see also e.g.*, *id.* at 137:17–19 ("I would never say an individual agent causes ASD or ADHD."); *but see id.* at 37:5-15 (testifying that she has spent a significant part of her career researching modifiable risk factors—or "a risk factor we can do something about" for ASD).

Aside from that nihilistic disclaimer of her entire scientific field, Dr. Pinto-Martin's other response to the data was to ascribe it to confounding. There are only four theoretical explanations

for the study results described above: chance, bias, confounding, and causation. Ex. 2, Pinto-Martin Dep. Tr. 68:10–19 ("Q. My question, though, is, are there other theoretical possibilities for what's going on here besides chance, bias, confounding and causation? A. In standard epidemiologic textbook explanation, no."). She admitted that chance was not her "primary objection" to these studies, *id.* at 176:19–25, which is unsurprising: the more than a dozen statistically significant results *individually* had less than a 5% chance of being a chance finding. *Id.* at 479:3–10 ("Q. [Statistical significance] means less than 5 percent likelihood of being a chance finding there, right? A. That's the definition of statistical significance, yes."). The likelihood of that 1-in-20 result happening a dozen times in a row is truly infinitesimal: .05 x .05 x .05 x .05 and so on. The result is a decimal point followed by many zeroes.[6] Dr. Pinto-Martin also admitted that a bias, like exposure misclassification, would bias the results to the null, leading to a *reduction* in the strength of the association, *id.* at 410:3–20, *i.e.*, making acetaminophen use appear *less* dangerous than it really is.

In light of those admissions, to avoid the only other "theoretical" possibility—namely causation—Dr. Pinto-Martin had no choice but to say that the results were due to "confounding." *Id.* at 150:10–14 ("Q. And you think that this is what's going on here. You think there's a confounder associated with prenatal APAP use and autism? A. Correct."). Pressed to identify

[6] Confronted with this mathematical reality, Dr. Pinto-Martin attempted to say that one needed to examine the "underlying data" before deciding whether an association is statistically significant or not. This is simply not correct. When assessing statistical significance, epidemiologists simply calculate the mathematical probability of a result being due to chance. Fed. Jud. Ctr., *Reference Manual on Scientific Evidence* at 250–53 (3d ed. 2011) (hereinafter "Ref. Manual"). There is no authority suggesting that one needs to delve into the quality of the "underlying data" before running that calculation. To be sure, the quality of the data is relevant to other aspects of the causation inquiry, but Dr. Pinto-Martin was dissembling when she suggested that data quality is used to determine whether an association is statistically significant or not.

these hypothetical confounders, Dr. Pinto-Martin could only name two: (a) genetics, and (b) indication. *Id.* at 151:11–24; 317:8–12, 320:16–23.

As Dr. Pinto-Martin admitted, however, these two confounders can *theoretically* explain *every* observed association, including ones that we now know are causal, like the association between cigarette smoking and lung cancer. *Id.* at 270:8–15 ("Q. No matter how good your study is, it's always possible that there's some confounder out there that's actually driving the results. A. Absolutely true.").

For this reason, Dr. Pinto-Martin admitted that before ascribing a result to confounding "you need evidence both that [the potential confounder] is associated with the outcome and that it's associated with the exposure." *Id.* at 220:22–25. Here that means that—to have a chance of explaining the study results above—a confounder would need to *both* cause ASD/ADHD *and* somehow be associated with a woman's propensity to take acetaminophen while pregnant. *Id.* at 151:2–10. For genetics, she acknowledged that "we don't have sufficient evidence to really support that as…a confounding variable" for the acetaminophen/ASD link, because there is *no study* showing that the genes associated with ASD are also associated with a woman's prenatal acetaminophen use. *Id.* at 153:15–21. On the contrary, there was a study specifically designed to assess whether this kind of genetic confounding was at play—the Leppert 2019 paper—and that paper reported "null" results. *Id.* at 158:2–14. In other words, it found affirmative evidence that the genes associated with ASD *do not* make a woman more likely to take acetaminophen while pregnant. If Dr. Pinto-Martin had been reviewing the data in an objective way, that should have been the end of her genetic confounding theory for ASD.

Even for ADHD, Dr. Pinto-Martin was forced to admit that the evidence suggesting genetic confounding was weak at best. Although the Leppert paper showed a small increase in

acetaminophen use among women with genes associated with ADHD, Dr. Pinto-Martin had to admit that these were "barely" statistically significant results that even she would not characterize as "incredibly powerful." *Id.* at 161:8–17.

Dr. Pinto-Martin was left relying exclusively on the result of one study—Gustavson 2021—that compared the likelihood of an ADHD diagnosis among siblings exposed to acetaminophen while in utero. In the first place, even that study showed a positive result. Specifically, it showed that the sibling exposed to acetaminophen for more than 29 days in utero had a 6% increased risk of later being diagnosed with ADHD than her sibling who was not exposed to acetaminophen in utero. Ex. 17, Gustavson (2021) at 7. Although Dr. Pinto-Martin pointed out that those results were not statistically significant, that is hardly a surprise given the small sample size. Most of the studies in this literature had sample sizes in the tens or hundreds of thousands. The sample size for the Gustavson sibling-control analysis was just 34 mothers. Ex. 2, Pinto-Martin Dep. Tr. 450:21–451:2. Dr. Pinto-Martin admitted that "the sample size is small" in that study, *id.* at 453:10–11, and that small sample sizes can "lead to false negatives" in terms of statistical significance. *Id.* at 413:1–13. "Does this [Gustavson] prove that this is all about genetics? No." *Id.* at 466:15–16.

Meanwhile, the Brandlistuen (2013) study showed that the sibling exposed to acetaminophen had a greater likelihood of demonstrating behavioral, hyperactivity, and communications problems—classic symptoms of ADHD—and showed an even greater, statistically-significant difference between the exposed and unexposed siblings than the Gustavson study showed. As Dr. Pinto-Martin said, that result is "evidence against genetic confounding," *id.* at 406:7–15, and "argues against the genetic effect." *Id.* at 421:9–14. In the end, she conceded

that, even in her own one-sided opinion, she could not say that genetic confounding explains the entire association between prenatal acetaminophen use and ASD or ADHD. *Id.* at 471:12–472:13.

As for confounding by indication—Dr. Pinto-Martin's only other theory to try to explain "what's going on here"—she was forced to admit that independent scientists working in this field had carefully examined the issue. For example, the actual "*objective* of the [Ricci (2023)] study was to assess the extent to which the association is due to confounding by indication." *Id.* at 320:10–15 (emphasis added). The authors' conclusion? "Confounding by indication did not explain the association," and the association "did not appear to be explained by confounding by indication." *Id.* at 321:5–322:4. Although Dr. Pinto-Martin testified that she disagreed with that conclusion, she conceded that is what the actual *data* showed: The results from the Ricci analysis does not support confounding by indication. *Id.* at 325:13–18. Indeed, looking at the literature more broadly, Dr. Pinto-Martin conceded that "many of the study authors have said that confounding by indication is unlikely." *Id.* at 318:18–319:5. She simply disagreed with them. *Id.*

To render her hollow opinion, Dr. Pinto-Martin did not apply the same epidemiological principles that she would outside the courtroom. Likely for this reason, she stated in her deposition: "I'm not opining as Jennifer Pinto-Martin, professor of epidemiology. I'm opining as an expert witness based on my review of the published literature, and that's what I am – I'm here to talk about." *See id.* at 442:17–22. No doubt, the professor-of-epidemiology version of Dr. Pinto-Martin could answer questions "about the basics of epidemiological technique" contained in the Federal Reference Manual—created by the Federal Judicial Center in order to help courts like this one in complex science cases.[7] *Id.* at 441:12–18. But not the version "opining as an expert

[7] "*The Reference Manual on Scientific Evidence* . . . is formulated to provide the tools for judges to manage cases involving complex scientific and technical questions." Ref. Manual at xv. *See Atkins v. Virginia*, 536 U.S. 304, 327 (2002) (Rehnquist, C.J., dissenting) ("The Federal Judicial Center's Reference Manual

witness." *Id.* at 442:17–22. She refused to answer questions about fundamental epidemiological precepts described in that Manual that would undermine her opinions—like what "a study with lower power" means when it "fails to show a significant effect," *id.* at 443:18–444:19—because that was not what she was asked to do by Defendants. *Id.* No doubt finding that the association between prenatal acetaminophen exposure and neurodevelopmental disorders in offspring is causal is not what she was asked to do by Defendants either. "An expert in the relevant field" of epidemiology would obviously answer basic questions about epidemiology. *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 265–66 (2d Cir. 2002) (quoting *Kumho Tire Co. Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999)). Dr. Pinto-Martin's refusal to do so while "in the courtroom" rather than the classroom is grounds for exclusion under Rule 702. *Id.*

LEGAL STANDARD

Plaintiffs refer the Court to the Rule 702 legal standard set forth in Plaintiffs' Memorandum in Support of their Rule 702 Motion to Exclude Dr. Wendy Chung, Dkt. 1138 at 3–5.

ARGUMENT

I. Dr. Pinto-Martin's Causal Conclusion Was Pre-Ordained, in Violation of Basic Epidemiological Principles.

A. Dr. Pinto-Martin's Methodology Is Designed to and Will Always Lead to One Answer: No Causation.

Daubert does not tolerate methodologies "aimed at achieving one result." *Faulkner v. Arista Recs. LLC*, 46 F.Supp.3d 365, 381 (S.D.N.Y. 2014). It is hard to imagine a clearer example of that situation than the one here.

Dr. Pinto-Martin repeatedly testified that she will *never* find "causation" when presented with observational epidemiological studies, no matter how strong they are. Ex. 2, Pinto-Martin

on Scientific Evidence . . . offer[s] helpful suggestions to judges called upon to assess the weight and admissibility of [scientific] evidence on a factual issue before a court.").

Dep. Tr. at 90:23–25; 120:3–4; 133:16–18; 137:17–19; 216:23–217:1*; see also id.* at 133:16–23 ("Personally, I would not be willing to assign causality on the basis of observational studies. Other epidemiologists may be more willing to do that, so we may have different opinions based on our willingness to assign causality on the basis of observational data."). The only way to develop stronger evidence would be to do an RCT. But Dr. Pinto-Martin acknowledged an RCT to assess the association between prenatal use of acetaminophen and ASD and ADHD cannot ethically be done. *See id.* at 253:13–21. And why can it not ethically be done? Because "there are studies suggesting a risk" of ASD and ADHD, *id.* at 254:3–11, such that the science is no longer at the "moment of what we call equipoise." *Id.* That being so, "[y]ou can't randomly assign women to receive a medication that at this point has some suggestion of harm." *Id.* at 253:13–21. In other words, Dr. Pinto-Martin's view is that the observational epidemiology *cannot* establish causation, and the only way *to* establish causation is now ethically forbidden precisely *because of* the powerful inference created *by* the observational studies. The circularity is Kafkaesque.

And convenient. Based on this kind of methodology, the causation answer will be "no" in *every* case involving an environmental exposure found to be associated with a certain disease based on epidemiology. The epidemiological evidence will make RCTs unethical; and in Dr. Pinto-Martin's view, only an RCT can suggest causation. It was not even entirely clear whether an RCT would have been enough for her. She stated that she was not even sure if she had "ever made a causal determination on the basis of an RCT," but merely allowed that she "would be more likely to accept evidence from an RCT than [ ] an observational study with respect to establishing a causal association." *Id.* at 252:6–15. The theme is clear: absent something approaching revealed truth, Dr. Pinto-Martin will always reject the inference of causation. Dr. Pinto-Martin's causal opinion was therefore a foregone conclusion, since she is "not willing to say that something is

causal based on observational studies," *Id.* at 216:23–217:1, but also understood that the human data must be limited to such observational studies. *Id.* at 253:13–256:23.

In short, Dr. Pinto-Martin's methodology is the definition of one "aimed at achieving one result," and *Daubert* forbids that kind of methodology. *Faulkner*, 46 F.Supp.3d at 381.

B. Dr. Pinto-Martin's "Personal" Hyper-Conservative Approach to Causation Is Not Consistent With Standard Epidemiological Practice.

Daubert also does not permit experts to rely on methodologies that other experts in their field would not employ outside the courtroom. *See Daniels-Feasel*, 2021 WL 4037820, at *4 ("The district court must also ensure that experts are employing 'in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'"). And no epidemiologist would approach the causation inquiry in the way that Dr. Pinto-Martin does, *beginning* with the premise that observational epidemiology can *never* lead to a causal inference.

The entire purpose of the Bradford Hill factors—which Dr. Pinto-Martin agrees are the standard methodology for epidemiologists, Ex. 2, Pinto-Martin Dep. Tr. at 526:5–14—is to analyze observational data and make causal inferences. As Bradford Hill himself put it, the purpose is to look at "observations [that] reveal an association" and decide whether "the most likely interpretation of it is causation." Ex. 3, Bradford Hill at 295. That mission statement—on which the entire field of epidemiology is based—makes no sense given Dr. Pinto-Martin's view that the answer is "never."[8] For example, there has never been an RCT on the link between smoking and lung cancer—and there never will be for ethical reasons—but the link was first

[8] As the authoritative textbook in the field puts it, the Bradford Hill criteria are used to determine "whether epidemiologic evidence reflects a causal association." Ex. 23, Lash et al. at 22. Chapter 2 of that textbook is called "Causal Inference and Scientific Reasoning." *Id*. at 59–60. Chapter 3 is called "Formal Causal Models." Ex. 28, Lash et al. (2021) at 96–97. The list goes on. To be sure, inferring causation from observational data is always a matter of scientific judgment—more akin to "clinical judgment than experimental science," Ex. 23, Lash et al. at 62—but there is simply no basis for Dr. Pinto-Martin's unique view that it can *never* be done.

identified (and deemed causal by the U.S. Surgeon General) based on observational data alone. Ex. 2, Pinto-Martin Dep. Tr. at 68:23–70:17.

Though this dispositional conservatism would never fly at a faculty roundtable, it does ensure that Dr. Pinto-Martin has plenty of work from the defense bar. She has served as a serial defense expert, testifying five times on behalf of defendants against the inference of causation. *Id.* at 31:14–18; 32:9–33:3. In *In re: Proton Pump Inhibitor Products Liability Litigation*, MDL 2789 (D.N.J), she deployed her never-enough-evidence approach to opine that proton pump inhibitors ("PPI") do not cause fractures. The label for that drug, based on the very evidence she rejected, now contains a fractures warning. *Id.* at 33:4–14.[9]

Dr. Pinto-Martin acknowledged that she is less willing to make a causal determination as compared to other, mainstream scientists, stating that "[s]ome people are very willing to say causation. I myself am I think perhaps more conservative than others," Ex. 2, Pinto-Martin Dep. Tr. at 102:3–6, and that she "personally" is simply unwilling to "assign causality on the basis of observational studies." *Id.* at 133:16–18. That self-awareness is commendable—if understated—but it does not make her jury-rigged methodology any more admissible. An "expert in the relevant field" of epidemiology, *Daniels-Feasel*, 2021 WL 4037820, at *4, would not disclaim the ability of his or her profession to do what it has always done: Identify causal relationships in observational epidemiological data. Because Dr. Pinto-Martin did just that, her opinions must be excluded. *Id.*

Doubling down on her always-say-no methodology, Dr. Pinto-Martin went so far as to testify she could say "*with certainty* that there's no causal relationship between prenatal APAP

[9] *See* Ex. 24, Prescribing Information for Nexium, at § 5.4 Bone Fracture, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021153s056,021957s023,022101s020lbl.pdf, ("Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk of osteoporosis-related fractures of the hip, wrist, or spine.").

exposure and ASD." Ex. 2, Pinto-Martin Dep. Tr. at 141:14–18 (emphasis added). The only thing certain is that Dr. Pinto-Martin herself disagreed with that wild, outcome-driven hyperbole later in the deposition, saying: no "credible epidemiologist" would "say I've read the literature and I can say with 100 percent certainty that prenatal APAP exposure doesn't cause autism." *Id.* at 143:9–20. An epidemiologist offering an opinion that "no credible" epidemiologist could offer is definitionally peddling "junk science." *In re Ephedra Prods. Liab. Litig.*, 2005 WL 8178810, at *6. Despite the liberal rules of admissibility, courts should keep such testimony from the jury. Dr. Pinto-Martin, perhaps momentarily lapsing into her role as "Jennifer Pinto-Martin professor of epidemiology," has supplied the basis to exclude Dr. Pinto-Martin the "expert witness." Suffice it to say that *Daubert* does not allow an expert to give opinions that even she says are not "credible."

C. Dr. Pinto-Martin's Conclusions Regarding Valproic Acid Confirm That Her Methodology for Acetaminophen Is Result-Driven.

Dr. Pinto-Martin's results-oriented methodology suddenly reverts to sound epidemiological practice as soon as she is looking at an exposure *other* than acetaminophen. For example, there has never been an RCT to investigate the link between prenatal valproic acid exposure and ASD or ADHD. The data is "observational" only. So, applying the methodology that Dr. Pinto-Martin says she used here—"I would not be willing to assign causality on the basis of observational studies," Ex. 2, Pinto-Martin Dep. Tr. at 133:13–18—Dr. Pinto-Martin's conclusion should have been straightforward: No causal link between valproic acid, ASD, and ADHD.

Curiously, that was not Dr. Pinto-Martin's conclusion with respect to valproic acid. She testified that she "agreed the evidence supports a causal link" between valproic acid and ASD and

indeed agreed that "the most likely explanation is causation." *Id.* at 122:10–123:12.[10] The makers of valproic acid agree on this conclusion: The valproic acid label states, "Although the available studies have methodological limitations, the weight of the evidence supports a causal association between valproate exposure in utero and subsequent adverse effects on neurodevelopment, including increases in autism spectrum disorders and attention deficit/hyperactivity disorder (ADHD)."[11] In other words, the valproic acid label does what Dr. Pinto-Martin (as a litigation expert) says is impossible—make a causal inference based on observational epidemiology alone.[12] There is simply no way around the glaring methodological inconsistency in Dr. Pinto-Martin's approach to causation for these two drugs.

II. Dr. Pinto-Martin's Opinion Regarding Confounding Is Based on Mere Conjecture and Flawed Scientific Reasoning.

Dr. Pinto-Martin's opinion that the observed association between prenatal ingestion of acetaminophen and ASD and ADHD is due to confounding by genetics or indication is based on

[10] Dr. Pinto-Martin had reviewed the underlying valproic acid literature for her report and concluded that the "data establishing the association between ASD and valproic acid is considerably more robust than the data on prenatal acetaminophen exposure." Ex. 1, Pinto-Martin Report at 35. Perhaps realizing her that conclusion conflicted with her stated methodology in real-time at her deposition, Dr. Pinto-Martin later backtracked from her report and initial testimony and said she did not "know" whether she could "answer" whether the most likely explanation for the valproic acid association with ADHD is causation, claiming that there would need to be more studies. Ex. 2, Pinto-Martin Dep. Tr. at 136:18–137:2. Confronted with a video recording from about 2011 or 2012, in which she described valproic acid as a known, strong risk factor for ASD, *id.* at 128:8, Dr. Pinto-Martin insisted that her views had "evolved with the science," *id.* at 129:2–9, even though the evidence in support of a causal link between valproic acid has grown stronger (not weaker) since 2012. Suffice it to say that it is not helpful to an expert's reliability when she gives contradictory testimony on the same question during the course of a single deposition.

[11] *See Depakote ER Full Prescribing Information*, U.S. Food & Drug Admin. 25 (Feb. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019680s053lbl.pdf.

[12] The causal evidence for that association is at a minimum comparable (and arguably much weaker) than what is available for the association between prenatal use of acetaminophen and ASD and ADHD. In support of the warning about autism and ADHD, the valproic acid label cites a *single* observational study in support of the ASD warning and a *single* observational study by the same author in support of the ADHD warning. Jakob Christensen et al., *Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring*, 2 JAMA Network Open e186606 (2019) (hereinafter "Christensen (2019)").

flawed scientific reasoning and *ipse dixit*, because she does not rely on sufficient evidence for these conclusions. "The law is clear that mere ipse dixit is not appropriate expert testimony because it is not based on reliable methodology, as *Daubert* requires." *S.E.C. v. Tourre*, 950 F. Supp. 2d 666, 678 (S.D.N.Y. 2013). The same is true of cherry-picking the evidence to support a preset conclusion. *In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 296 (S.D.N.Y. 2018), *aff'd sub nom. In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 982 F.3d 113 (2d Cir. 2020). But in support of her theory that the associations here are driven by genetic confounding and confounding by indication, *ipse dixit* and cherry-picking are all Dr. Pinto-Martin has.

A. Dr. Pinto-Martin's Opinion Regarding Genetics Is Entirely Based on a Flawed Scientific Premise.

As an initial matter, Dr. Pinto-Martin's critique is predicated on "junk science" because it elides the non-debatable scientific consensus about the interplay between environmental factors (such as acetaminophen) and genetics. Specifically, she advances the following definition of "heritability": "Recently, large-scale twin studies have reported that the heritability of ASD—in other words, the percentage of ASD cases attributable to inherited genetic factors**—rather than environmental factors or random chance**—changes from 80 to 90%." *See* Ex. 1, Pinto-Martin Report at 27. But this conception of heritability is flat-out wrong.

In *The Heritability Fallacy*, geneticists David Moore and David Shenk explain that "measurable heritability of a trait *does not* tell us how 'genetically inheritable' that trait is," nor does it "inform us about what causes a trait, the relative influences of genes in the development of a trait, or the relative influence of the environment in the development of a trait." Ex. 25, Moore & Shenk (2016) at 1; *see also* Pls. Memo. to Exclude Dr. Wendy Chung at 10–20 (describing how the eggshell skull principle means that environmental factors like acetaminophen can legally be

considered causal under the heritability principle). Moore and Shenk also observed, as illustrated by Dr. Pinto-Martin's incorrect representation of the meaning of heritability, that the "term 'heritability,' as it is used today in human behavioral genetics, is one of the most misleading in the history of science." Ex. 25, Moore & Shenk at 1.[13] Unsurprisingly, then, confronted at her deposition with a video of herself opining that "the genetics matter, but there has to be an environmental trigger that's operating on that genetic structure to actually trigger the autism," Ex. 30, Ex. 639.2 to Pinto-Martin Dep. Dr. Pinto-Martin was forced to backtrack, admitting that "heritability does not determine what proportion of the trait is determined by the environment." Ex. 2, Pinto-Martin Dep. Tr. at 95:16–22. In other words, as Dr. Pinto-Martin also agreed, "a heritability of .7 does not mean that a trait is 70 percent caused by genetic factors." *Id.* at 97:21–98:2. That is presumably why, as recently as 2014, Dr. Pinto-Martin recorded video lectures making clear her view that there needs to be "an environmental trigger in addition to the genetics to actually trigger the autism." *Id.* at 82:15–22. During her deposition, however, while she was willing to agree that "a heritability of .7 does not mean that a trait is 70 percent caused by genetic factors" she was unwilling to concede that principle applies to ASD. *See id.* at 98:3–99:16

It is black letter law that an opinion resting "on a faulty assumption" may not be based on "'good grounds'" and, therefore, the faulty assumption may render the opinion unreliable and inadmissible. *Amorgianos,* 303 F.3d at 269. Dr. Pinto-Martin's understanding of heritability as a proxy for causation runs aground on this principle.

[13] For a full discussion of the causal interplay between the environment and genetics as causes of ASD and ADHD, *see* Pls. Motion to Exclude Defendants' Expert Dr. Wendy Chung. Like Dr. Pinto-Martin, Dr. Chung presents an inaccurate representation of the heritability of these neurodevelopmental disorders and—in a departure from both of their statements outside of this litigation—minimizes the role environmental exposures play in such disorders.

B. Dr. Pinto-Martin Relies on Speculation and Cherry-Picking in Support of Her Theory Concerning Genetic Confounding.

Dr. Pinto-Martin's opinion that genetics explains the association between acetaminophen and ASD and ADHD is inadmissible for another reason: It relies on an unsubstantiated theory for ASD and cherry-picking for ADHD.

1. Dr. Pinto-Martin's genetics theory for the ASD association is based on pure speculation.

"Expert testimony should be excluded if it is speculative or conjectural." *Boucher v. U.S. Suzuki Motor Corp.*, 73 F.3d 18, 21 (2d Cir. 1996). Dr. Pinto-Martin's almost wholesale attribution of the documented association to genetic confounding is based on precisely *nothing* for ASD.

Specifically, she herself agreed that for a confounder to explain an association one needs "*evidence* both that it's associated with the outcome and that it's associated with the exposure." Ex. 2, Pinto-Martin Dep. Tr. at 220:22–25. She nevertheless conceded that "[i]n the autism literature," "*we don't have sufficient evidence to support that [genetics] as a -- as a confounding variable*." *Id.* at 153:15–23 (emphasis added); *see also* Ex. 1, Pinto-Martin Report at 56 ("The first and most significant potential source of confounding is genetics . . . [N]one of the studies of ASD has adequately addressed the possibility of genetic confounding. None of the studies that use ASD diagnosis as an endpoint has applied either a sibling control or a negative control to limit genetic confounding."). To the contrary, the *one* study that looked at whether the genes that are associated with autism are also associated with acetaminophen use—Leppert (2019)—showed that the answer was "no." Ex. 2, Pinto-Martin Dep. Tr. at 396:13–15 ("Leppert did not report an association for autism."); *see also id.* at 157:23–158:6. Dr. Pinto-Martin opines that a scientist must have evidence of confounding to conclude that confounding is responsible for an association.

Yet she concedes that she has no evidence of genetic confounding explaining acetaminophen's association with ASD. By her own standard, and the one embraced by the law, Dr. Pinto-Martin's *ipse dixit* that genetic confounding is the true reason for the stubborn association must be excluded. *Kumho Tire Co.*, 526 U.S. at 157.

2. Dr. Pinto-Martin's theory for the ASD association is based on minimal evidence and cherry-picked data.

To reach her desired conclusion for ADHD, Dr. Pinto-Martin cherry picks the available data. "Cherry-picking is a form of '[r]esult-driven analysis,' which 'undermines principles of the scientific method' by 'applying methodologies (valid or otherwise) in an unreliable fashion.'" *See Daniels-Feasel*, 2021 WL 4037820 at *8 (quoting *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prods. Liab. Litig. (No II)*, MDL 2502, 892 F.3d 624, 634 (4th Cir. 2018)). For ADHD, Dr. Pinto-Martin bases her opinion on a single pair of studies, Gustavson (2021) and Leppert (2019), the former of which had a sample size of 34 and the latter of which Dr. Pinto-Martin agreed was "barely statistically significant" and "not. . . incredibly powerful." Ex. 2, Pinto-Martin Dep. Tr. at 161:8–21.

An expert is of course permitted, in her professional judgment borne of experience, to prefer some studies to others. Though Plaintiffs believe that Gustavson has many flaws, and their experts *explain why* in their analyses, Plaintiffs would not move to exclude Dr. Pinto-Martin merely for thinking Gustavson is more probative than it is. What Rule 702 forbids, however, is cherry-picking. A reliable expert cannot latch onto one (here, the only) study that supports her conclusions, downplay its limitations, and wave away all of the overwhelming, contrary literature.

That is precisely what Dr. Pinto-Martin did with her treatment of Gustavson. Dr. Pinto-Martin fails to acknowledge or analyze *any* of the study's limitations—limitations that she eagerly cites to disqualify or minimize *other* studies that happen to support Plaintiffs' position. As she

squarely put it during the deposition, "I do not critique Gustavson," *id.* at 436:15–16, even though she was more than willing to level pages of criticisms against studies that undermined her conclusion. Under cross-examination, she admitted that the *number* of discordant pairs of siblings contributes power to a sibling-control analysis, but nowhere in her report does she record the actual number of discordant pairs in the Gustavson sibling study. *See id.* at 428:2-431:25; 449:9–15.[14] That number is 34. But her report makes it seem as if there were 21,448 children in the sample population. Ex. 1, Pinto-Martin Report at 74. That is off by more than two orders of magnitude. Ex. 17, Gustavson (2021) at 10. Dr. Pinto-Martin admitted that it was "error" to conceal the real "number for Gustavson." Ex. 2, Pinto-Martin Dep. Tr. at 432:23–25.

Even if Dr. Pinto-Martin thinks this undeniable limitation is outweighed by the study's strengths—an opinion a reasonable scientist might reach—she was obligated to at least acknowledge, not conceal, this shortcoming. "When a study with low power fails to show a significant effect, the results may therefore be more fairly described as inconclusive than negative." Ref. Manual at 253–54; *see also* Ex. 1, Pinto-Martin Report at 14 ("There is another type of statistical error known as a Type II error in which a conclusion to accept the null hypothesis of no association is reached when, in fact, an association does exist (i.e., false negative). This is a function of the statistical power of the study, which is related to the study's sample size and other factors."). The Gustavson authors did what Dr. Pinto-Martin did not, noting no less than three times that the statistical power of the sibling control study was low:

- "As only discordant siblings contribute to information in sibling control models, even the current very large birth cohort provided limited statistical power." Ex. 17, Gustavson (2021) at 8.

[14] In this context, discordant pairs are siblings in which only one was exposed to acetaminophen in utero and only one was diagnosed with ADHD.

- "[T]he finding of similar risk for ADHD in siblings discordant for long-term maternal acetaminophen use must be interpreted with caution and needs to be replicated in other studies." *Id.* at 5.
- "These numbers show that statistical power to detect within effects was relatively low. Hence, these results should be interpreted with caution." Ex. 26, Gustavson Supp. Information at 7.

When confronted with that sin of omission, Dr. Pinto-Martin dissembled and redefined herself as Dr. Pinto-Martin the expert witness rather than a professor of epidemiology:

> Q. Okay. Do you agree when a study with low power fails to show a significant effect, the results may be more fairly described as inconclusive than negative? Do you agree with that?
>
> A. Again, you're asking me to agree with a statement that I have no knowledge of its purpose, its origin, who wrote it. I'm not willing to opine about random statements from [the Federal Reference Manual] that I know nothing about.
>
> . . .
>
> Q. And you're telling me that in order to tell me whether this basic principle of epidemiology is true or false, you need to know who wrote it?
>
> A: I'm saying that my assignment here, if you will, was not to opine on statements about statistical significance and study power. My assignment was to review the published epidemiologic literature, and I'm just going to stay there. This is not something I've ever seen before. It's not -- I'm not opining as Jennifer Pinto-Martin, professor of epidemiology. I'm opining as an expert witness based on my review of the published literature, and that's what I am -- I'm here to talk about.

Ex. 2, Pinto-Martin Dep. Tr. at 440:22–442:22.

Gustavson has other limitations, and Dr. Pinto-Martin ignored them as well. For instance, the study authors themselves noted that the reduced power of the sibling control study was reflected in a wide confidence interval, which was 0.51–2.05. That interval *includes* the realistic possibility of very strong associations that Dr. Pinto-Martin denies. Ex. 17, Gustavson (2021) at 5. Though she said not one word about that wide confidence interval as to Gustavson, Dr. Pinto-Martin spilled much ink noting the exact same limitation for studies with results that did not support her ultimate conclusion. *See* Ex. 1, Pinto-Martin Report at 33 (discounting Baker (2020) because "[t]he reported effects are imprecise with extremely wide confidence intervals,

demonstrating a lack of precision of these estimates."); *id.* 44 (noting that for Ji (2020), "[b]ecause the sample sizes of affected children were quite small, the results were inexact and the confidence intervals large."); *id.* at 60 (stating that for Leppert (2019), "while the point estimates were positive, the confidence intervals were so wide that the results were not statistically significant or were too broad to be meaningful").

Other examples abound. A central tenet of Dr. Pinto-Martin's criticism of the acetaminophen observational evidence in general is that most of the studies rely on maternal self-reporting. *See, e.g.*, Ex. 1, Pinto-Martin Report at 83 (criticizing Liew (2014) for the limitation of maternal recall); *id.* at App'x I at 15 (noting the same for Liew (2016)); *id.* at App'x I at 16 (noting the same for Parker (2020)); *id.* at 92 (noting the same for Ricci (2023)); *id.* at 101 (noting the same for Ystrom (2017)); *id.* App'x I at 24 (noting the same for Tovo-Rodrigues (2018)); *id.* at App'x I at 7 (noting the same for Brandlistuen (2013)). But the same is true of Gustavson, though the Court would never learn that from reading Dr. Pinto-Martin's report.

To return to a common refrain, any reasonable epidemiologist seeking to uncover the truth must *acknowledge* Gustavson's limitations, especially if she is content to identify the exact same limitations in the much greater body of literature that supports Plaintiffs' position. "[Dr. Pinto-Martin's] propensity to cherry-pick the findings [s]he agrees with and h[er] failure to acknowledge the express limitations that render those findings unreliable, while disregarding those studies that do not support h[er] conclusions because they suffer from the same limitations, casts significant doubt on the reliability of both h[er] weighting of the studies [s]he reviewed, which [s]he does not explain, as well as h[er] subsequent analyses." *Daniels-Feasel*, 2021 WL 4037820 at *9.

C. Dr. Pinto-Martin's Opinion Regarding Confounding by Indication is Also Not Based on Actual Evidence but on Her Unsubstantiated Theory.

Dr. Pinto-Martin's attempt to pin the association on confounding by indication fares no

better. *See Boucher v. U.S. Suzuki Motor Corp*., 73 F.3d at 21; Ex. 1, Pinto-Martin Report at 4; Ex. 2, Pinto-Martin Dep. Tr. at 150:1–152:9. Confounding by indication occurs where the *underlying* reason for taking a drug is itself the true cause of an outcome. For instance, there is an undeniably strong association between undergoing chemotherapy and dying of cancer. Without more evidence, however, nobody thinks chemotherapy, rather than the preexisting cancer, is causing cancer deaths. Dr. Pinto-Martin muses, however, that mothers' underlying reasons for taking acetaminophen actually cause the strong association with ASD and ADHD in offspring. Ex. 1, Pinto-Martin Report at 4.

Many study authors themselves, however, disagree with Dr. Pinto-Martin and state that confounding by indication is *unlikely*. For instance, Ricci (2022) concluded that "[c]onfounding by indication did not explain the association between in utero acetaminophen exposure and child ADHD." Ex. 18, Ricci (2022) at 2; *see also* Ex. 29, Brandlistuen (2015) at 7 ("[P]rolonged exposure to paracetamol was associated with adverse neurodevelopmental and behavioral outcome, but without the limitation of potential residual confounding by indication"). Dr. Pinto-Martin acknowledges that study authors said confounding by indication was unlikely, Ex. 2, Pinto-Martin Dep. Tr. at 318:18–319:17 ("I know that study authors have said that"), but stated that she simply disagreed. *Id.* at 319:16–22. Experts do not have to blindly accept a study authors' conclusions, but nor are they entitled to unilaterally disregard what the study authors themselves say in the papers without a valid basis. *See generally Daniels-Feasel*, 2021 WL 4037820 at *4. That is yet another species of *ipse dixit.*

D. Dr. Pinto-Martin's Approach to Valproic Acid Again Reveals That Her "Confounding" Theory Is Litigation Driven.

Once again, when the drug at issue is not acetaminophen, Dr. Pinto-Martin returns to the realm of reasonable epidemiology. Neither of the studies cited in the label for valproic acid makes

any definitive conclusion about causation, and both studies caution that the possibility of residual confounding remains—in particular confounding by genetics and by indication, the two sources of confounding that Dr. Pinto-Martin clings to here. *See* Ex. 19, Christensen (2013) at 10 ("However, not all parents with alcohol abuse or psychiatric disorders were identified from the registers, and residual confounding by unmeasured psychiatric disorders in the mother or father can therefore not be entirely excluded."); *See* Ex. 20, Christensen (2019) at 8 ("Thus, we cannot exclude that the association between maternal valproate use in pregnancy and ADHD in the offspring may be, at least in part, due to unmeasured confounding."). Nevertheless, despite these limitations, the makers of valproic acid, the FDA, and Dr. Pinto-Martin (at least initially) had no hesitation about labelling the association a likely causal one.

Although Dr. Pinto-Martin fixates on the risk of unmeasured confounding for the acetaminophen studies, she entirely ignores that same risk in the valproic acid studies. This, even though the authors of those valproic acid studies recognized their limitations. Notably, Wiggs (2020) described the limitations of the prior valproic acid studies, stating that "[t]he majority of research does not adjust for many, if any, confounding factors (e.g., adjustment for and severity of maternal epilepsy). Ex. 27, Wiggs (2020) at e3233. Further, Wiggs (2020) did not control for genetics and stated that, "[g]iven these disorders are heritable, this is a likely source of confounding in the present study." *Id.* at e3238. *See* Ex. 2, Pinto-Martin Dep. Tr. at 362:17–363:21 (agreeing Wiggs (2020) did not control for heritability). Dr. Pinto-Martin faults the much larger body of acetaminophen literature for not adequately controlling for genetic confounding. But that *precise* limitation is no impediment to her conclusion that prenatal exposure to valproic acid most likely causes ASD and ADHD in children.

In yet another rendition of heads-Defendants-win-tails-Plaintiffs-lose, Dr. Pinto-Martin conceded that she had not "seen a sibling study on valproic acid," which according to her is the *only* way to control for genetic confounding. *Id.* at 363:19–22. She excused this limitation by explaining how "challenging" those studies are because they require a large cohort with discordant pairs. *Id.* at 363:21–364:22. But Dr. Pinto-Martin sees things differently when she is an expert witness as opposed to a professor of epidemiology. *See, e.g.*, Ex. 1, Pinto-Martin Report at 98 ("Dr. Baccarelli's related argument that other studies have ruled out a genetic explanation without sibling controls through the use of a 'negative control' is flawed"); *id.* at 4, 22, 31, 56. Turnabout should be fair play: If Dr. Pinto-Martin applied the same approach to valproic acid as she does to acetaminophen, she would be forced to switch sides. That is proof positive that she is cherry-picking the science to reach a preordained conclusion.

III. Dr. Pinto-Martin's Application of Certain Bradford Hill Factors Is Unreliable.

Finally, Dr. Pinto-Martin abandoned basic epidemiological principles and flagrantly misapplied several Bradford Hill factors. "The Bradford Hill criteria derive from a 1965 lecture by a British epidemiologist and statistician, Sir Austin Bradford Hill," and the factors "start with an association demonstrated by epidemiology and then apply eight or nine criteria to determine whether that association is causal." *In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d at 242 (internal quotation marks omitted). "[T]he expert's bottom-line conclusion need not be independently supported by each of the nine Bradford Hill factors, [but] in analyzing the factors, separately and together, the expert must employ 'the same level of intellectual rigor' that [s]he employs in his academic work." *Id.* at 247–48 (quoting *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 26 (1st Cir. 2011)).

Dr. Pinto-Martin did not meet that standard. She misstated the test for the Bradford Hill factors of consistency, biological plausibility, temporality, strength of association, and dose

response. As a gut check, it is notable that Dr. Pinto-Martin does not find a *single* Bradford Hill criteria is satisfied for either ASD or ADHD. *See* Ex. 1, Pinto-Martin Report at 53–66 (ASD); 93–109 (ADHD). In the context of this litigation, a witness who cannot acknowledge that the other side has even a single point in its favor is not an unbiased truth seeker. She is either a fanatic or a mercenary. The public-health ramifications of this case are too important to allow such a tendentious witness to testify. *In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213 at 248; *see id.* (excluding expert when "he finds that all nine criteria support a finding that Mirena causes IIH" and "nowhere concedes that any criterion even is only weakly supportive of a finding of causation.").

A. Despite the Repeated Positive Associations for Prenatal Use of Acetaminophen and ASD and ADHD, Dr. Pinto-Martin Incorrectly Maintains That There Is No Association.

Generally, a study showing a positive association serves as a prerequisite for applying the Bradford Hill factors. *See In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 188 (S.D.N.Y. 2009) (requiring an association from a controlled study before undertaking a Bradford Hill is proper); *In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d at 242 (noting that Bradford Hill criteria start with an association); *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 679 (M.D.N.C. 2003) ("The first step in the causation analysis pursuant to Bradford Hill is an epidemiological study that has identified an association between two variables."). A single study with a positive association is sufficient to call for a Bradford Hill analysis. *See* Ref. Manual at 598–99; *see generally In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 916 (D.S.C. 2016) (collecting cases).

Dr. Pinto-Martin fantastically claims there is no association "perfectly clear-cut and beyond what we could care to attribute to chance" between prenatal use of acetaminophen and ASD and ADHD. Ex. 1, Pinto-Martin Report at 53 (ASD); *id.* at 93 (ADHD). That assertion

boggles the mind. There are more than a dozen studies showing a positive association between prenatal acetaminophen exposures and relevant neurodevelopmental outcomes like ADHD and ASD. The notion that all of these associations are due to chance is too outlandish to be maintained. The forest plots shown above speak for themselves: an association has unquestionably been demonstrated here, as *all* authors in the published literature have conceded. Yet defiance of rudimentary statistics encapsulates Dr. Pinto-Martin's position. *Id.* at 53 (ASD); *see also id.* at 93 (ADHD). Even Defendants' other experts acknowledged what Dr. Pinto-Martin will not. *See* Ex. 21, Faraone Dep. Tr. at 356:20–357:4 (admitting that it is "the scientific consensus that exposure to acetaminophen during pregnancy is a risk factor for ADHD"); Ex. 22, D'Alton Dep. Tr. at 29:2–13 (testifying that it has been "reported" there is "an association" between acetaminophen and ASD and ADHD, but she does not believe it is causal). To be sure, association is not proof of causation, but it is a necessary precondition for such a finding. Dr. Pinto-Martin's refusal to even acknowledge that an association exists when it so plainly does is disqualifying.

Unsurprisingly, Dr. Pinto-Martin tried to downplay her position on this point during her deposition. Ex. 2, Pinto-Martin Dep. Tr. 176:2–17 (stating that chance was not her "primary objection" to the studies). She also conflated association with *other factors*, reverting to her cherry-picked limitations that inform different parts of the Bradford Hill criteria. *Id*. at 180:25–181:17 ("So, again, we're not talking just about chance here. We're talking about the criteria of Bradford Hill, and what goes into that evaluation includes all of the things that I mentioned before: The context of the studies, the sample size, the selection bias, the assessment of exposure.").

Dr. Pinto-Martin's conclusion that there is not even an association here is also fundamentally inconsistent with the rest of her opinion. After all, she says that the results of the studies are due to confounding by genetics and confounding by indication. *See supra*, pp. 11–16.

But one looks for confounding *only* when there has been an association demonstrated. If there is no association, there is nothing to confound. Dr. Pinto-Martin appears to believe that the results of the studies are due to confounding. That belief is not based on evidence, as detailed above, but at a minimum she should be able to accept the implication of her own position, namely that there is an association, albeit a confounded one.

In the end, it is simply a fact: there is an association between prenatal exposure to acetaminophen and ASD and ADHD in offspring. Even if the Court admits other parts of Dr. Pinto-Martin's opinion, it should exclude any opinion that defies objective reality. *In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d at 247–48.

B. Dr. Pinto-Martin Applies a "Completely Fallacious" Definition of Consistency.

Dr. Pinto-Martin can only conclude that the consistency criteria is not satisfied by redefining it. Ex. 1, Pinto-Martin Report at 58–59 (ASD); *id.* at 101–02 (ADHD). The consistency factor asks whether the association has been "repeatedly observed by different persons, in different places, circumstances, and times?" Ex. 3, Bradford Hill at 296; *see* Ref. Manual at 604 ("It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists."). Again, the forest plots above speak for themselves.

To blindfold the reader's supposedly lying eyes, Dr. Pinto-Martin attempts to excise all results that are not statistically significant. Ex. 1, Pinto-Martin Report at 58–59 (ASD); *id.* at 101–02 (ADHD). That is a textbook error, literally. The Rothman textbook—which Dr. Pinto-Martin thinks is a "good textbook on epidemiology," Ex. 2, Pinto-Martin Dep. Tr. at 388:19–20—states: "One mistake in evaluating consistency is so common and yet wrong that it deserves special mention. It is sometimes claimed that a literature or a set of results is inconsistent because some results are statistically significant and some are not. This sort of evaluation is completely

fallacious." Ex. 23, Lash et al. (2021) at 66. However liberal the Federal Rules of Evidence may be, they will not countenance attempts to dupe the jury with "completely fallacious" scientific methods. And yet even on Dr. Pinto-Martin's fallacious terms, the evidence of consistency is overwhelming: her list of cherry-picked studies includes more than a dozen statistically significant results. There can be no doubt that the association has been observed over and over again.

C. Dr. Pinto-Martin's Speculation About a Potential Reverse-Causation Problem Is Entirely Unfounded.

In what may be the most remarkably inadmissible opinion ever offered—and that is not hyperbole—Dr. Pinto-Martin claimed the temporality factor was not satisfied. Temporality describes what is compelled by common sense and basic logic: "[i]f an exposure causes a disease, the exposure must occur before the disease develops. If the exposure occurs after the disease develops, it cannot have caused the disease." Ref. Manual at 601.

When describing the temporality factor, Bradford Hill explained that it answers the question of "which is the cart and which the horse? . . . Does a particular diet lead to the disease or do the early stages of the disease lead to those peculiar dietic habits?" Ex. 3, Bradford Hill at 297. One can certainly envision many cases where the temporality factor is an open and difficult question that reasonable scientists can debate. Sticking with a generic version of Hill's dietary example: not eating enough food can cause health problems, but some health problems suppress the appetite. Which came first, and thus which may have caused which, is not always clear cut.

Here it is clear cut: Does a pregnant woman's consumption of acetaminophen precede her child's ASD or ADHD (in which case temporality is satisfied) or does the child's ASD or ADHD—discovered *after* the child is born—potentially cause the pregnant woman to consume acetaminophen while pregnant (in which case temporality is not satisfied). Dr. Pinto-Martin initially refused to admit that such reverse causation was impossible, conceding only that it was a

"highly unlikely scenario." Ex. 2, Pinto-Martin Dep. Tr. at 535:13–537:24. Even that guarded acquiescence should be enough to exclude her opinion on this factor since a "highly unlikely scenario" is definitionally not true by a preponderance of the evidence. Pressed whether it would even be possible without a time machine, Dr. Pinto-Martin ultimately conceded, "I don't think it's possible." *Id.* at 537:17–538:9. The contrary opinion expressed in Dr. Pinto-Martin's expert report and deposition testimony cannot go to the jury.

D. Dr. Pinto-Martin Erroneously Defines "Strength" in a Way That Is Unrecognizable Under the Bradford Hill Framework.

Dr. Pinto-Martin accurately noted that "[t]he first Bradford Hill criterion, strength of association, considers how strong the association is that has been reported in the literature." Ex. 1, Pinto-Martin Report at 54. Here, some studies show a 2-fold and 3-fold increase in the risk of ADHD and ASD for women who take acetaminophen while pregnant. So Dr. Pinto-Martin attempted to redefine this factor in her deposition, claiming strength of association is not simply a matter of "how strong the association is," *id.*, but rather is determined by a variety of other factors such as exposure measurement, dose, and other indicia of proper "context." Ex. 2, Pinto-Martin Dep. Tr. at 493:16–24.

That is simply not what "strength" means here. In the Bradford Hill address itself, strength is defined as strength: In the classic example, it was the fact that "the death rate . . . in heavy cigarette smokers is twenty to thirty times as great" as in non-smokers, a metric he compared to the weaker "death rate from coronary thrombosis in smokers" that was "no more than twice, probably less." Ex. 3, Bradford Hill Address at 295–96. These are simple statements about the magnitude of the observed risk ratios, not an invitation to conduct a multi-factor balancing test that takes into account every limitation of a study before deciding whether an association is strong. By importing these extraneous considerations of strength into her discussion during her deposition—

though tellingly, not into her report, which interpreted "strength" to mean "strength"—Dr. Pinto-Martin badly misapplied this criterion. She was right the first time, and should not be permitted to offer a newfangled definition of a Bradford Hill criteria that is cut from whole cloth. Ex. 2, Pinto-Martin Dep. Tr. at 494:10–18 (admitting she "can't cite you something specific" that supports her redefinition of strength of association).

E. To Avoid Admitting Biological Plausibility, Dr. Pinto-Martin Improperly Redefines the Term "Plausible."

Dr. Pinto-Martin erroneously states that the biological plausibility factor has not been met for ASD and ADHD "because the biological mechanisms are hypothetical," and "[t]he biological plausibility consideration requires an established biological mechanism, not simply a hypothesis about how such a mechanism might work." Ex. 1, Pinto-Martin Report at 66 (ASD); *see also id.* at 108-09 (ADHD). Dr. Pinto-Martin is waging an assault on the English language. Plausible means possible or believable, not "established," as Dr. Pinto-Martin essentially conceded during her deposition. Ex. 2, Pinto-Martin Dep. Tr. at 542:22–25 ("Q. And what does the word 'plausible' mean? A. Possible. I don't know what a synonym would be. Possible."). "That the mechanism remains unknown does not mean that the one proposed [ ] is not widely accepted as plausible." *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d at 183.

Applying the right definition, Dr. Pinto-Martin concedes that there is published "literature that hypothesized causal mechanisms." Ex. 2, Pinto-Martin Dep. Tr. at 541:19–542:11; 543:4–14. Due to ethical constraints, as Dr. Pinto-Martin testified, there will never be human data *establishing* biological mechanisms. That is precisely why the test is plausibility, which Dr. Pinto-Martin should not be permitted to redefine through unreliable testimony. See *id.* at 253:13–255:18.

CONCLUSION

For the reasons stated above, Dr. Pinto-Martin's opinions should be excluded in their entirety under Rule 702. Alternatively, they should be excluded in part on the issues described above.

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Respectfully submitted,

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