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September 9, 2023

VIA ECF

The Honorable Denise L. Cote
United States District Court Judge
Southern District of New York
500 Pearl Street, Room 1910
New York, New York 10007

Re. *In Re: Acetaminophen – ASD–ADHD Products Liability Litigation*, Case No. 1:22-md-03043 (S.D.N.Y.) – Submission of Plaintiffs' Letter Referenced in the United States' Letter, Dkt. 1105
This Document Relates To: All Cases

Dear Judge Cote:

On September 8, 2023, Mr. Jacob Lillywhite submitted a Letter to the Court on behalf of the United States and declined the Court's April 19, 2023 Invitation for Statement of Interest. *See* Dkt. 1105. In his letter, Mr. Lillywhite referenced an August 31, 2023 letter from Plaintiffs submitted to the United States Attorney's Office for the Southern District of New York. *Id.*, n.1. Although Plaintiffs' August 31, 2023 letter contains information that will be relevant to Plaintiffs' Rule 702 briefs, Plaintiffs are providing the letter to the Court and Defendants in an effort to be fully transparent. It is attached hereto as **Exhibit A**.[1]

Respectfully submitted,

/s/ Ashley Keller

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[1] We are not attaching the exhibits referenced in the August 31, 2023 letter because those exhibits are quite voluminous and will be provided to the Court for the parties' upcoming Rule 702 briefing. If the Court would prefer to see the exhibits now, we will promptly provide the Court with electronic and hard copies of those exhibits.

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EXHIBIT A

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August 31, 2023

VIA U.S. MAIL & EMAIL

Damian Williams
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Re. *In Re: Acetaminophen – ASD–ADHD Products Liability Litigation*, Case No. 1:22-md-03043 (S.D.N.Y.)

Dear Messrs. Williams and Lillywhite:

As you know, we represent Plaintiffs in the above-captioned case. In our previous letter of August 1, we suggested that any "interest of the United States" that you might choose to "attend to" in this suit, 28 U.S.C. § 517, will arise in the context of Rule 702 motion practice assessing whether the parties' experts used accepted scientific methods to reach reasonable—even if reasonably disputed—conclusions. Our experts have now provided detailed reports[1] and given extensive deposition testimony.[2] We are operating on the assumptions that the United States is unwilling to sign the operative protective order and is unavailable to attend the remaining depositions of Defendants' experts. So to assist with your internal deliberations, we would like to take the opportunity to provide you with the non-confidential evidence that overwhelmingly supports the proposition that it is more likely than not that prenatal acetaminophen exposure causes autism spectrum disorder ("ASD") and attention-deficit/hyperactivity disorder ("ADHD") in offspring. It is simply irrefutable that reasonable scientists, deploying time-tested scientific methods, can and do arrive at this unfortunate conclusion. It follows that, whether considered through the lens of the governing Rule 702 standard or through the lens of what the science supports, Plaintiffs' proposed label is accurate, warranted by the scientific evidence, and consistent with approved warnings on other drugs.

The evidence is detailed further below and in the enclosures, but to summarize: Over the past decade, studies from around the world have followed hundreds of thousands of mothers who took acetaminophen while pregnant. More than 20 times now, those studies have shown that the children of those women have a significantly higher risk of developing neurodevelopmental disorders such as ASD and ADHD. That is a disturbing result that begs the critical question: Why do women who take acetaminophen have children with ASD and ADHD at higher rates?

[1] Those Reports, attached here as Exhibits 1–5 (reports), Exhibits 6–10 (rebuttal reports), and Exhibits 21–22 (supplemental reports), synthesize the complicated science to reach those conclusions. Since the United States has not signed the Protective Order, we are providing redacted versions of the experts' reports and deposition testimony.
[2] That testimony has also been provided for your review. Exhibits 11–15.

Plaintiffs' own expert epidemiologist—the Chair of Environmental Health at Columbia University—was initially skeptical that the association was causal, and hypothesized alternatives that could explain away the association. Perhaps pregnant women who take acetaminophen also engage in behavior, like smoking or drinking, that is the true cause of neurodevelopmental disorders; perhaps pregnant women who take acetaminophen have disproportionately more genetic risk factors for ASD or ADHD; perhaps maternal fever (for which acetaminophen is taken) is the true culprit. The list of alternative causes evaluated in these studies goes on.

Tragically, however, no compelling evidence for *any* of these alternative explanations has emerged. Dozens of potential confounders have been explicitly controlled for in the scientific literature, and they do not explain the results: Consuming acetaminophen while pregnant increased the risk of ASD and ADHD in offspring for drinkers and teetotalers, for smokers and non-smokers, for mothers with a febrile illness and those who never had a temperature. Specificity studies show that other, similar drugs taken while pregnant—such as ibuprofen and aspirin—did not cause an increase in ASD and ADHD rates, suggesting an effect unique to acetaminophen alone.

Faced with this alarming evidence, more recent negative-control studies searched desperately for some evidence of residual confounding by evaluating women who took acetaminophen before or after becoming pregnant but not during pregnancy. Those women did *not* have children with ASD and ADHD at higher rates. Only the women who took acetaminophen *while* pregnant did. As two independent researchers in this field put it, over the past years, global scientists have tried numerous analyses and varied study designs in an effort to "make the association 'go away.'"[3] The link between prenatal acetaminophen exposure and neurodevelopmental disorders persists. That is why numerous independent scientists have published papers stating that they believe causation—and not confounding—is the true driver of these results.

To be sure, it is impossible to conclusively rule out the theoretical possibility of some future, unknown, and unmeasurable confounder being the true cause of the disturbing results. But applying a preponderance of the evidence standard to the weight of the current scientific evidence, which is called for by Rule 702, acetaminophen more likely than not causes ASD and ADHD.

The laboratory evidence reinforces the epidemiological literature. Although epidemiological studies may have confounders that must be controlled for, preclinical animal models are not confounded in the same way because the test subjects can be ethically isolated from confounding variables. In other words, the preclinical studies eliminate *any* possibility of confounding. And, here, Plaintiffs' experts reviewed in vivo, in vitro/ex utero, and in silico data, and each type of preclinical data showed a positive signal in support of a causal relationship between acetaminophen and ASD and ADHD.

The animal data also provided evidence of possible biological mechanisms to explain the causal relationship, a key indication of causation. For instance, the preclinical literature shows that acetaminophen sets off a cascade of molecular processes that cause oxidative stress, which can lead to DNA damage, mitochondrial dysfunction, epigenetic changes, and cell death. In terms

[3] Jørn Olsen et al., *Fetal programming of mental health by acetaminophen? Response to the SMFM statement: prenatal acetaminophen use and ADHD*, 16 Expert Opinion Drug Safety 1395 (2017) (hereinafter Olsen (2017)).

of in vivo experiments in animals, out of 27 peer-reviewed studies published by research teams across the world, 26 showed measurable changes in animals treated with acetaminophen. These changes include rich gene expression data. Critically, biomarkers of oxidative stress have also been found in multiple human studies, showing concordance in terms of biologic plausibility.

A more detailed summary of the evidence is below.

I. The Epidemiological Evidence Shows a Causal Relationship between Prenatal Use of Acetaminophen and ASD/ADHD.

Plaintiffs' experts are world-renowned scientists in their field. These scientists hail from prominent scientific institutions and are considered preeminent experts in their respective fields. They are:

- Dr. Andrea Baccarelli, Chair of Department of Environmental Health Services/Professor of Epidemiology at Columbia University
- Dr. Brandon Pearson, Assistant Professor of Environmental Health Sciences at Columbia University
- Dr. Robert Cabrera, Professor for the Center for Precision Environmental Health, Department of Cellular and Molecular Biology, Baylor College of Medicine
- Dr. Eric Hollander, Professor in the Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine
- Dr. Stan Louie, Professor of Clinical Pharmacy, Director of Clinical Experimental Therapeutics Program, Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences at the University of Southern California

Dr. Andrea Baccarelli is a medical doctor and an epidemiologist who has published over 600 articles. Like any good scientist, Dr. Baccarelli did not approach his review of the epidemiological evidence with a preordained conclusion. In fact, before he started studying the association, he testified that he thought there was no causal relationship between prenatal use of acetaminophen and ASD and ADHD in offspring precisely because women and doctors are routinely told that acetaminophen is entirely safe to take while pregnant. And when he "reviewed the literature for this case, [he] was blown away by the consistency." As he testified, "I couldn't believe my eyes that there were so many studies showing so much association, **a level of consistenc[y] I've never seen before in my life**." Ex. 11, Baccarelli Dep. at 45:23–46:6.

For Dr. Baccarelli to reach his conclusion in this case, he undertook a systematic review of the epidemiological studies by applying the Navigation Guide and a Bradford Hill analysis. The Navigation Guide system is based on the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation) and allows scientists to systematically grade and assess the quality of the evidence related to environmental exposures where—as here—there is no available randomized control trial. Through the Navigation Guide, Dr. Baccarelli applied a systematic rating and review for each study for bias, strength of evidence, and other indicia of quality. His review and ratings of each study are included in Appendix 1 to his report. Based on

this review, he concluded that acetaminophen is "known to be toxic" with regard to neurodevelopment disorders like ADHD and ASD. Ex. 1, Baccarelli Amended Report at 146, 152, 158.

Dr. Baccarelli also undertook a Bradford Hill analysis, which is the "canonical approach" for inferring causation and is "widely cited in the health sciences."[4] Dr. Robert Cabrera, who is a teratologist and runs the Finnell/Cabrera Lab at Baylor University, similarly undertook a Bradford Hill analysis. *See* Exhibit 2, Cabrera Amended Expert Report at 189–95. There are nine, non-exclusive factors/elements considered under the Bradford Hill method to assess causation: (1) strength of association, (2) consistency, (3) temporality, (4) dose response (biological gradient), (5) biological plausibility, (6) coherence, (7), specificity, (8) experiment, and (9) analogy. Drs. Baccarelli and Cabrera found that all but one factor—specificity—supported a causal relationship between prenatal use of acetaminophen and ASD and ADHD. We have provided a short summary of that analysis:

- **Strength of Association:** Dr. Baccarelli found this factor satisfied because "observational studies have consistently found a statistically significant association between acetaminophen use during pregnancy and an increased risk of NDDs in children."[5] Ex. 1, Baccarelli Amended Report at 159. Notably, Dr. Baccarelli opined that "[a]lthough the association in these studies is moderate, these results are nevertheless significantly stronger than other, known causal associations. The associations shown here are stronger than for other exposures 'generally agreed to reflect causal effects,' including the link between 'air pollution and mortality,' 'smoking and heart disease,' and 'environmental tobacco smoke [i.e., secondhand smoke] and lung cancer.'" *Id.* (citing Lash et al. (2020)). Although the associations in these studies were moderate, between 1.0 and 2.0, Dr. Baccarelli explained that because the studies were forced to rely on maternal self-reporting, those estimates likely biased the risk estimates towards the null and artificially depressed risk ratios. *Id.* In studies where exposure was measured directly via meconium[6] or umbilical-cord blood,[7] the strength of the association was much larger—above 2.0, suggesting a *doubling* of the risk of neurodevelopmental disorders like ADHD and ASD for the children of women who took acetaminophen while pregnant with them. *See id.* (citing Baker (2020) and Ji (2020)).

  Dr. Cabrera came to a similar conclusion, stating that "the totality of data is consistent with 'clear evidence of developmental toxicity' as stated by the National Toxicology Program (NTP)." As a teratologist, Dr. Cabrera also looked to the animal data, which is further

[4] Timothy L. Lash et al., *Modern Epidemiology* (4th ed. 2020) (hereinafter Lash et al. (2020)).
[5] Neurodevelopmental disorders are often referred to as "NDDs."
[6] Brennan H. Baker et al., *Association of Prenatal Acetaminophen Exposure Measured in Meconium with Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity*, 174 JAMA Pediatrics 1073 (2020) (hereinafter Baker (2020)).
[7] Yuelong Ji et al., *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure with Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood*, 77 JAMA Psychiatry 180 (2020) (hereinafter Ji (2020)).

discussed *infra* section II. He stated that "animal studies remove indication and other confounders, and as supported by numerous well controlled animal studies, APAP[8] has been shown to cause neurodevelopmental toxicity and impaired learning and social behaviors consistent with ASD and ADHD at clinically relevant therapeutic doses." Ex. 2, Cabrera Amended Report at 190.

- **Consistency**: As Dr. Baccarelli explained, "[a] consistent finding is an association reported across multiple populations, over time, and using different study designs." Ex. 1, Baccarelli Amended Report at 161 (citing Bradford Hill). He determined this factor was satisfied because "[t]he association between prenatal acetaminophen exposure and NDDs in children has been observed in multiple studies—including extremely large cohort studies and meta-analyses—across many different time periods and patient populations." *Id.*; *see also* Ex. 2, Cabrera Amended Report at 190 (emphasizing that the association has been reported by "several different laboratories working independently and publishing in different peer-reviewed journals" and "has been observed in Spanish, Brazilian, Swedish, Norwegian, English and Danish cohorts, each independently reporting neurodevelopmental impacts."). Dr. Baccarelli went on to explain that "[t]here are at least ten (10) studies showing a statistically significant association between prenatal acetaminophen use and ADHD. There are at least three (3) high-quality studies showing a statistically significant association between prenatal acetaminophen use and ASD. And there are at least five (5) high quality studies showing a statistically significant association between prenatal acetaminophen use and symptoms of NDDs." Ex. 1, Baccarelli Amended Report at 161. Dr. Baccarelli acknowledged that some studies did not show a statistically significant association between prenatal use of acetaminophen and NDDs, but that "those studies are in the extreme minority-the vast majority of studies *did* show a statistically significant association," and that "[i]ndeed, nearly all studies published to date support this [causal] conclusion." *Id.*

- **Temporality**: This factor assesses whether exposure to a substance precedes the onset of the disease, and Dr. Baccarelli concluded that this factor is satisfied because prenatal use precedes a child's ASD or ADHD diagnosis. *Id.* at 163; *see also* Ex. 2, Cabrera Amended Report at 191.

- **Dose Response (Biologic Gradient)**: Dr. Baccarelli found this factor satisfied because "virtually every study that was powered to evaluate, and did in fact evaluate, dose response found such an association between the number of days of prenatal acetaminophen use or its cumulative dose and NDDs in children." Ex. 1, Baccarelli Amended Report at 163. As reflected in Dr. Baccarelli's tables in Appendix 1 of his report, six studies assessed dose

[8] "APAP" is shortform for acetaminophen.

response for ADHD,[9] two studies assessed dose response for ASD,[10] and three studies assessed dose response for general neurodevelopment.[11]

- **Biological Plausibility**: This factor is further discussed below, *see infra* section III, but Dr. Baccarelli found this factor satisfied because there are multiple plausible biological mechanisms in the scientific literature. *Id.*; *see also* Ex. 2, Cabrera Amended Report at 191–92.

- **Coherence**: This factor "looks at whether a 'cause-and-effect interpretation of the data seriously conflicts with the generally known conflicts of the nature and biology and the disease.'" Ex. 1, Baccarelli Amended Report at 164 (citing Bradford Hill). Dr. Baccarelli concludes that there is "no such conflict" here and that the causal relationship between prenatal use of acetaminophen and ASD and ADHD "is coherent with existing knowledge and understanding of the diseases and causes." *Id.* Specifically, environmental factors are known to affect neurodevelopment and pregnancy is considered a time of high susceptibility to environmental factors. Dr. Cabrera similarly concludes that "[a] causal relationship between APAP and neurodevelopmental harm is consistent with the expected timing and results of exposure." Ex. 2, Cabrera Amended Report at 192.

  The rising rates of NDDs over the past few decades also correspond to rates of prenatal use of acetaminophen. For example, the below figure cited in Dr. Baccarelli's report shows the ecologic relationship between ASD and events that altered acetaminophen use in California:

[9] Brennan H. Baker et al., *Association of Prenatal Acetaminophen Exposure Measured in Meconium With Adverse Birth Outcomes in a Canadian Birth Cohort*, 10 Frontier Pediatrics 1 (2022); Ji (2020); Eivind Ystrom et al., *Prenatal Exposure to Acetaminophen and Risk of ADHD*, 140 Pediatrics 1 (2017) (hereinafter Ystrom (2017)); Zeyan Liew et al., *Maternal Use of Acetaminophen during Pregnancy and Risk of Autism Spectrum Disorders in Childhood: A Danish National Birth Cohort Study*, 9 Autism Res. 951 (2016) (hereinafter Liew (2016)); Claudia B Avella-Garcia et al., *Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms*, 45 Int'l J. Epidemiology 1987 (2016); Zeyan Liew et al., *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168 JAMA Pediatrics 313 (2014) (hereinafter Liew (2014)).

[10] Ji (2020); Liew (2016).

[11] Kosuke Inoue et al., *Behavioral Problems at Age 11 Years After Prenatal and Postnatal Exposure to Acetaminophen: Parent-Reported and Self-Reported Outcomes*, 190 Am. J. Epidemiology 1009 (2021); Sheryl L Rifas-Shiman et al., *Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour*, 34 Pediatrics Perinatal Epidemiology 287 (2020), Eva Skovlund et al., *Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids*, 26 Pharmacoepidemiology Drug Safety 625 (2017).

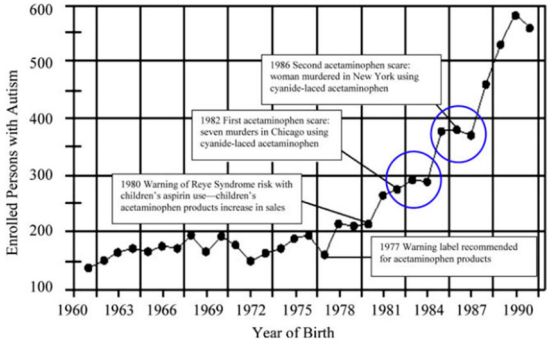


Fig. 1. Number of enrolled persons with autism in California by year of birth (adapted from: changes in the population of persons with autism and pervasive developmental disorders in California's developmental services system: 1987 through 1998. A report to the legislature (DDS, 1999). Fig. 1, P. 8. Available at: <http://www.dds.cahwnet.gov/Autism/docs/autism_report_1999.pdf>) with addition of events in the history of acetaminophen. The post-1982 and post-1986 downward inflections are circled.

- **Specificity**: As Dr. Baccarelli explains, specificity is satisfied when the disease is caused by only one substance—such as mesothelioma and asbestos—or when an exposure causes only one disease. He notes this is generally thought to be a "weak or irrelevant from an epidemiologic standpoint" because many causal relationships do not satisfy this factor. Ex. 1, Baccarelli Amended Report at 162. That is true here, and Drs. Baccarelli and Cabrera concluded this factor was not satisfied. *Id.*; Ex. 2, Cabrera Amended Report at 192. As even the Bradford Hill criteria themselves state, however, not every criterion needs to be satisfied, and specificity in particular often is not, even with respect to widely accepted causal risk factors such as tobacco smoke.

- **Experiment**: This factor means "evidence 'obtained from reducing or eliminating a supposedly harmful exposure and seeing if the frequency of disease subsequently declines.'" Ex. 1, Baccarelli Amended Report at 162. More modern approaches look at "not just human experiments but animal, toxicologic, and epigenetic experiments as well." *Id.* Under both conceptions, Dr. Baccarelli found this factor satisfied.

- **Analogy**: This factor looks to whether similar drugs have shown the same outcome of interest. Dr. Baccarelli cited to Depakote and valproic acid, which share similar biological mechanisms for causing neurodevelopmental disorders. *Id.* Valproic acid is further discussed *infra* section IV. Dr. Cabrera stated, "[t]here are analogies with other substances that are known to have neurodevelopmentally toxic effects during pregnancy, including Δ9-THS, mercury, and valproic acid, supporting a common oxidative stress mechanism for mercury, like APAP, and chemical-pharmaceutical causes of ADHD and ASD." Ex. 2, Cabrera Amended Report at 193.

After applying the Bradford Hill factors, Dr. Baccarelli concluded that "my opinion is that this association is causal," Ex. 1, Baccarelli Amended Report at 174, and Dr. Cabrera concluded that "[t]herapeutic dosages of APAP taken by pregnant women are sufficient to cause

neurotoxicity, neurodevelopmental disorder, ASD, and ADHD in exposed offspring." Ex. 2, Cabrera Amended Report at 196.

Aside from the formal Bradford Hill analysis, there are simply no likely explanations other than residual confounding. Even as a theoretical matter, there are only three possibilities when an association is identified: (1) chance; (2) bias (particularly confounding); and (3) causation. Through Dr. Baccarelli's analysis, he concluded that causation is "by far the most likely explanation because other explanations are less plausible." Ex. 1, Baccarelli Amended Report at 5. Defendants' experts generally attempt to attribute the association to confounding, particularly genetic confounding. We address this and other alternative explanations below:

- **Chance:** As Dr. Baccarelli explained in his report, "the association between prenatal acetaminophen exposure and NDDs cannot be due to random noise in the sample populations studied. It has been replicated far too many times. Although the result of a single study might occur due to chance, that is almost impossible when the result occurs more than 20 times." *Id.*

- **Bias: "**If researchers have good data on potential confounders, they can control for those confounders in the data analysis. There are several analytic approaches to account for the distorting effects of a confounder, including stratification or multivariate analysis." Reference Manual at 596. Here, "to attempt to rule out the possibility of confounding . . . the studies controlled for factors that might be correlated with acetaminophen use and also correlated with NDDs. To do so, the studies controlled for maternal age, maternal illness, maternal use of medications, maternal intelligence, parental education levels, child birth weight, child gestational age, socioeconomic status, maternal drinking, maternal smoking, maternal drug use, genetic confounding, confounding due to indication (i.e., the clinical reason for taking the medication), and many other potential risk factors. The association persists despite controlling for those confounders." Ex. 1, Baccarelli Amended Report at 5.

  In addition to controlling for potential confounders directly, other researchers have employed negative controls to assess the possibility of residual confounding. Aside from one study showing that *paternal* acetaminophen use was correlated with NDDs in the children—a result even those authors suggested might be causal—the results have been **uniform** in suggesting that residual confounding is not driving these results. Neither pre-pregnancy acetaminophen use, nor post-pregnancy acetaminophen use, nor ibuprofen use is associated with NDDs in the children: The observed effect is linked to acetaminophen use during pregnancy alone.

  Dr. Baccarelli's rebuttal report included a table he prepared with all of the studies that used negative control exposure analysis and illustrates that residual confounding did not drive the results:

Table. Studies of the association between acetaminophen use during pregnancy and neurodevelopmental conditions that include negative control exposure analyses.

Outcome	Study	Effect of maternal acetaminophen use during pregnancy	Negative Control Exposure	
			Type	Effect estimate
ADHD	Ystrom, 2017	HR: 1.20 (95% CI: 1.02, 1.24) (ever use)	Maternal acetaminophen use six months before pregnancy	HR: 0.95 (95% CI 0.85–1.06)
			Paternal acetaminophen use 6 months before pregnancy	HR: 1.27 (95%CI 1.08, 1.49)
ADHD	Stergiakouli, 2016	RR=1.43 (95% CI 1.18-1.73)	Maternal postnatal acetaminophen use 61 months postnatally	RR: 1.10 (95% CI 0.89-1.36)
			Partner's acetaminophen use 61 months postnatally	RR: 1.27, 95% CI: 0.96-1.69
ADHD	Liew, 2019	OR = 1.34 (95% CI: 1.05, 1.72)	Maternal acetaminophen use 4 years before pregnancy	OR: 1.12 (95% CI: 0.91, 1.38)
			Maternal acetaminophen use 4 years after pregnancy	OR: 1.05 (95% CI: 0.88, 1.26)
ADHD	Chen, 2019	OR = 1.20 (95% CI 1.01, 1.42)	Maternal acetaminophen use three months before pregnancy	OR: 1.06 (95% CI 0.90, 1.25)
Other neuro-developmental outcomes	Tronnes, 2020	Communication problems: RR: 1.18 (95%CI 0.86, 1.60) Externalizing problems: RR: 1.22 (95%CI 0.93, 1.60) Internalizing problems: RR: 1.36 (95%CI 1.02, 1.80) Emotionality: Beta: 0.13 (95%CI -1.08, 1.33) Activity levels: Beta: 0.51 (95%CI -0.57, 1.60) Sociability: Beta: -0.07 (95%CI -1.02, 0.88) Shyness: Beta: -0.24 (95%CI -1.27, 0.80)	Maternal acetaminophen use six months before pregnancy.	Communication problems: RR: 1.19 (95%CI 1.02, 1.38) Externalizing problems: RR: 0.99, (95% CI 0.87, 1.14). Internalizing problems: RR: 0.96 (95% CI 0.84, 1.10). Emotionality Beta: 0.36 (95% CI -0.08, 0.81) Activity levels Beta: -0.80 (95% CI: -1.23, -0.36) Sociability RR: 0.22 (95% CI -0.22, 0.66). Shyness: RR: 0.35 (95% CI -0.10, 0.80).

HR: Hazard ratio

Thus, despite numerous attempts to show that bias and confounding might be responsible for the link between prenatal acetaminophen exposure and NDDs, the association has persisted. As one paper put it, researchers have applied numerous methodologies trying to "make the association 'go away.'"[12] Attempts to provide evidence for alternative explanations—other than causation—"have so far been unsuccessful" despite many, many attempts.[13]

It is always possible to speculate that some as-yet-unidentified variable—such as genetics—is confounding the observed association. Indeed, the papers cited, for example, in FDA's valproic acid label do just that, and the label nevertheless goes on to state that causation is the most likely explanation.[14] But here, even more so than for valproic acid, there are reasons to affirmatively think that genetics is not confounding the association. To begin with, a study that examined polygenic risk scores (a controversial marker of genetic predisposition to disease) found essentially no evidence that women who have genes linked

[12] Olsen (2017).
[13] *Id.*
[14] For a full discussion of the label for valproic acid, *see infra* section IV.

to NDDs are more likely to take acetaminophen while pregnant.[15] For genes associated with ASD, there was no link with acetaminophen at all. And for genes associated with ADHD, the association was as weak as they come (risk ratios hovering at 1.1) and barely statistically significant (confidence intervals very near 1.0). To be a confounder, a variable must be associated not only with the outcome but with the exposure as well. Thus, if the genes associated with NDDs do not make women take substantially more acetaminophen while pregnant—and the evidence suggests they do not—genetics alone cannot confound (or explain) the association between acetaminophen and NDDs.

Moreover, researchers have conducted sibling-controlled studies, which compared two children born to the exact same mother. In one of those studies, the sibling exposed to acetaminophen in utero had significantly higher rates of NDDs than the sibling not exposed to acetaminophen in utero.[16] In the other, the child exposed to acetaminophen in utero still had higher rates of NDDs, though not statistically significant.[17] These results are all the more remarkable given the well-known fact that sibling controlled studies are particularly likely to produce false negatives given that they are underpowered and eliminate the effect of any genetic mediators along the causal pathway from exposure to outcome.[18] Finally, the negative control analyses discussed above provide even more evidence against genetic confounding. A mother's genes remain constant before, during, and after pregnancy. The fact that only during-pregnancy exposure to acetaminophen is associated with NDDs (but not exposure before or after pregnancy) provides particularly compelling evidence that the association is causal and not due to genetics.

Given that there is little evidence that the observed association is due to chance or bias, "[t]hat leaves causation as the most likely—indeed the only—explanation for the association. As one study put it (quoting the Bradford Hill methodology and Sherlock Holmes), 'Once you have eliminated the impossible whatever remains, no matter how improbable, must be the truth.'" Ex. 1, Baccarelli Amended Report at 5.

II. The Preclinical Evidence Further Buttress the Conclusion that Acetaminophen Can Cause ASD and ADHD.

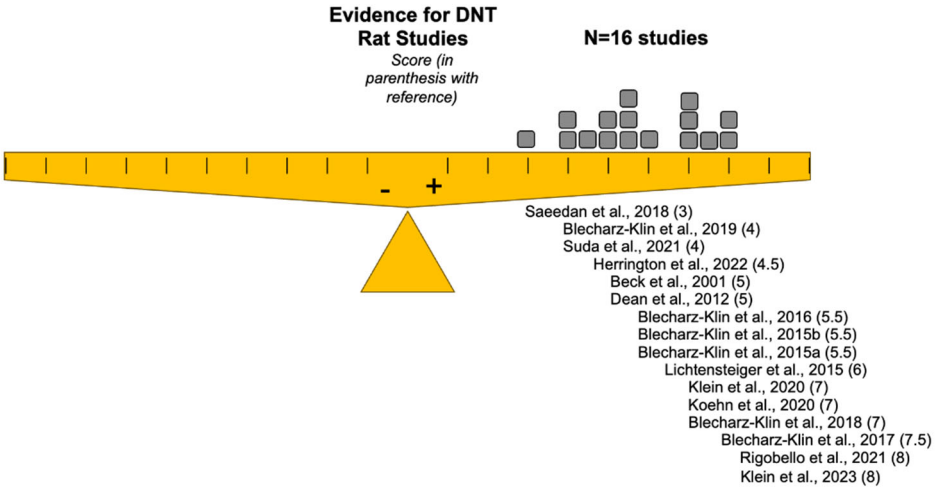
It is appropriate to look to animal data to demonstrate the effectiveness of a drug when adequate and well-controlled efficacy studies in humans cannot be ethically conducted. *See* 21 C.F.R. §§ 314.600–650. Here, the FDA has recognized the importance of preclinical data in assessing the causal relationship, stating that "[a]dditional long term studies of behavioral

[15] Beate Leppert et al., *Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures*. 76 JAMA Psychiatry 834 (2019).
[16] Ragnhild Eek Brandlistuen et al., *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Sibling-Controlled Cohort Study*, 42 Int'l J. Epidemiology 1702 (2013) (hereinafter Brandlistuen (2013).
[17] Kristin Gustavson et al. *Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study*, 1 JCPP Advances 1 (2021).
[18] For a thorough discussion on the limitations of sibling-controlled studies, *see* Ex. 6, Baccarelli Rebuttal Report at 5-6.

development in children following prenatal exposure to APAP would certainly be useful, but would not provide direct evidence of causality. Preclinical data may be more informative in that regard." Ex. 16, FDACDER000008; *see also* Ex. 18, FDACDER000115 ("To better understand the impact of prenatal APAP exposure on neurobehavioral and urogenital development, nonclinical toxicological studies continued to be needed."). That is particularly true to analyze the relationship between acetaminophen and NDDs, because ethical concerns preclude a randomized control trial, so preclinical data provides an avenue to assess causation without facing potential confounding by indication or genetics. *See* Ex. 3, Pearson Amended Expert Report at 126. ("While epidemiological studies may have confounders that must be controlled for, preclinical animal models are not confounded in the same way because the test subjects can be isolated from confounding variables.").

Plaintiffs' expert, Dr. Brandon Pearson, is the co-investigator and lab director of the Columbia Center for Children's Environmental Health, which is one of the leading sites in the world for studies regarding prenatal exposures and children's neurodevelopmental health outcomes. Dr. Pearson has studied acetaminophen toxicity for over ten years. He has never testified as a litigation expert before but felt a moral obligation to do so here. He reviewed the preclinical evidence and undertook a weight of the evidence analysis to assess whether the preclinical data supports a causal relationship, and he concluded that it does. Dr. Cabrera undertook a similar analysis and came to the same conclusion. Dr. Pearson examined animal studies consisting of rat and mice in vivo studies—meaning cultured cells or tissue that are grown in plates or dishes in an incubator, outside of the body—and in vitro studies—meaning experiments where acetaminophen is given systematically to the intact animal. He also looked at in silico studies, which mean computational studies.

Dr. Pearson looked at 16 DNT rat studies, and his conclusion about the weight to be assigned those is illustrated by the graphic below. Notably, of the 15 DNT rat studies Dr. Pearson reviewed, the FDA had only reviewed one of them based on the documents the Administration produced.



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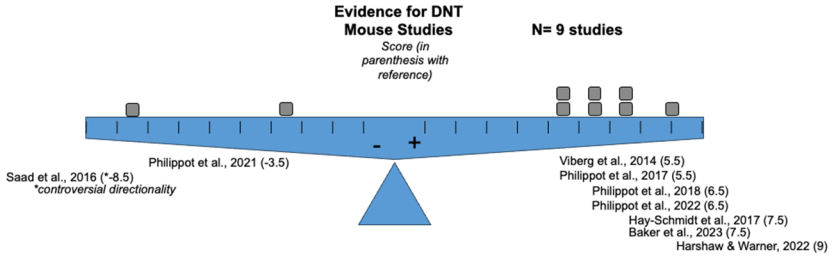
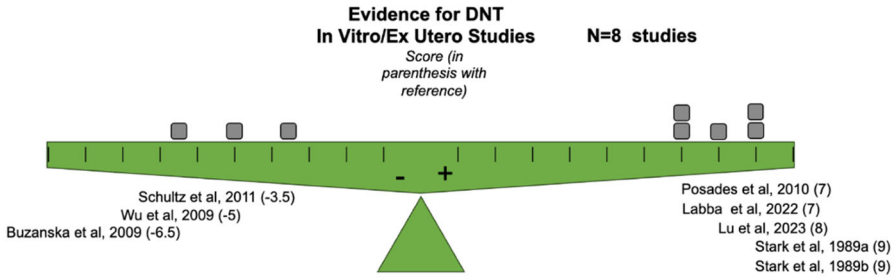
Dr. Pearson looked at 9 in vivo DNT mouse studies; the FDA had only reviewed 4 of those studies.



Of the 10 developmental neurotoxicity studies involving mice, only one showed no effect. Both Dr. Pearson and plaintiffs' teratologist, Dr. Cabrera, independently came to the conclusions that the study's directionality is in question because the researchers involved used an overly conservative statistical correction given the number of animals tested. Dr. John Talpos, director of neurotoxicology for the National Center for Toxicological Research, agreed, noting that this study was "really weak" and "way underpowered for their requirement for significance." Ex. 19, Email from John Talpos to Brandon Pearson (March 20, 2023), PEARSON_01198.

Dr. Pearson also reviewed a number of in vitro/ex utero studies, often studies in which APAP was used as a control but in fact showed effects. Dr. Pearson reviewed assigned those studies the below weights:



Finally, Dr. Pearson reviewed the in silico data. Dr. Pearson examined several sources of evidence including ToxCast (https://comptox.epa.gov/dashboard/), which shows that APAP "has potent activity for androgen receptor (AR), nuclear receptor family, in general (inclusive of many hormone receptors including sex steroids and stress hormones), cytochrome P450 enzymes, and finally SOX1 activity which is a developmentally important transcription factor implicated in neurodevelopmental disturbances." Dr. Pearson also examined data from the Comparative Toxicogenomics Database (CTDbase.org), a publicly available, government-funded resource devoted to collecting and integrating information from scientific literature to provide insights into the relationships between chemicals, genes, diseases, and other biological entities. Results from the Comparative Toxicogenomics Database show the top two disease categories linked with APAP as being Liver Cirrhosis and ASD.

Overall, Dr. Pearson summarized the weight of the evidence assigned to the categories of evidence described above:

Line of Evidence	Reliability	Relevance	Weight Assigned	Signal
In Silico	LOW to MEDIUM	LOW	LOW	Positive
In Vitro/ Ex Utero	HIGH	MEDIUM	MODERATE	Positive
In Vivo	MEDIUM	HIGH	MODERATE to HIGH	Positive

Importantly, every strand of evidence—in vivo, in vitro/ex utero, and in silico—showed a positive signal. Based on this analysis, Dr. Pearson concluded that "it is my opinion to a reasonable degree of scientific certainty based on my analysis of the weight of the evidence in this case as described above that APAP is a developmental neurotoxicant capable of causing neurodevelopmental disorders in both humans and animals." *Id.* at 127.

III. Plausible Biological Mechanisms Explain the Causal Relationship Between Prenatal Use of Acetaminophen and ASD and ADHD.

Further supporting the causal relationship between prenatal use of acetaminophen and the neurodevelopmental disorders of ASD and ADHD is the fact that there are several very plausible mechanisms by which acetaminophen could cause NDDs. It is widely accepted—and shown by the available human and preclinical data—that acetaminophen readily crosses the placenta and accumulates in placenta or fetal tissues. Ex. 3, Pearson Amended Expert Report at 10; Ex. 2, Cabrera Amended Expert Report at 9. And it is important to understand that a fetus is not just a smaller adult; fetuses' metabolite pathways are fundamentally different. Ex. 3, Pearson Amended Expert Report at 11. In short, the fetal liver does not function the way an adult liver functions, and the fetus's remaining tissues are unable to metabolize and eliminate acetaminophen in the same way an adult can. *Id.*

Significant bias exists around the false belief that acetaminophen is an inherently safe drug. It is not. The effect of acetaminophen is so well established in preclinical literature that several recent research efforts actually focus on finding therapeutics that can repair acetaminophen-induced damage to the developing brain.[19] And as Dr. Cabrera notes in his report, "[w]hile APAP is promoted as one of the most popular and safe pain-relief medications, APAP toxicity is responsible for almost half (46%) of all acute liver failure cases in the United States, and it is estimated that half of these cases are unintentional." Ex. 2, Cabrera Expert Report at 19–20.

[19] *See* Joshua A Herrington et al., *Elevated ghrelin alters the behavioral effects of perinatal acetaminophen exposure in rats*, 64 Developmental Psychobiology e22252 (2022); Navneet Suda et al., *Therapeutic doses of acetaminophen with co-administration of cysteine and mannitol during early development result in long term behavioral changes in laboratory rats*, 16 PLOS ONE e0253543 (2021).

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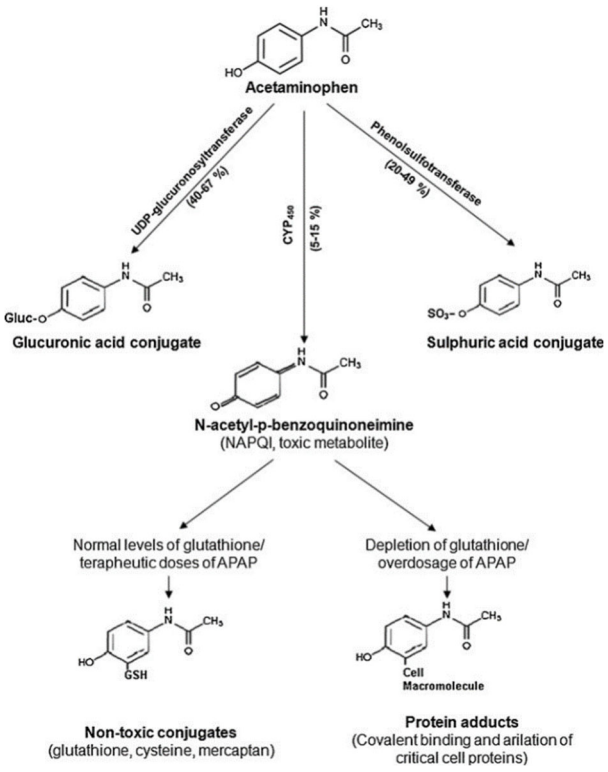
Indeed, it is one of the most common causes of poisoning worldwide. Ex. 2, Cabrera Amended Expert Report at 8; *see generally* Ex. 3, Pearson Amended Expert Report at 7–10.

The expert reports of Dr. Pearson, Dr. Cabrera, Dr. Baccarelli, and Dr. Hollander outline the extensive evidence regarding acetaminophen's intertwined mechanisms of action that disrupt normal neurodevelopment in the fetus. *See* Ex. 3, Pearson Amended Expert Report at 50–66; Ex. 2, Cabrera Amended Expert Report at 38–76; Ex. 1, Baccarelli Amended Expert Report at 44–51; Ex. 4, Hollander Amended Expert Report at 75–86. Based on his review of the mechanistic and pharmacological data and consistent with Plaintiffs' other expert reports, Dr. Louie shows how these mechanisms cause a twofold increase in the risk of ASD/ADHD development if a pregnant mother takes acetaminophen in the therapeutic dose range for at least 28 total days of pregnancy, though evidence suggests that even shorter exposures can also increase that risk. *See* Ex. 5, Louie Amended Expert Report at 9.

As further detailed in Plaintiffs' expert reports, acetaminophen sets off a cascade of molecular processes in the body. First, acetaminophen readily passes the placental and blood brain barriers. As the body detoxifies acetaminophen, its toxic metabolite, NAPQI, is formed through the body's CYP2E1 enzymes. The formation and clearance of NAPQI is the primary driver of acetaminophen's hepatotoxicity.



However, studies show that CYP2E1 enzymes are also present in the fetal brain. NAPQI creates an imbalance of reactive oxygen species within the brain, in turn creating oxidative stress and depleting glutathione, a critical antioxidant. Oxidative stress can lead to DNA damage,

mitochondrial dysfunction, epigenetic changes, and cell death. Oxidative stress has been widely shown to be present in studies of children with ASD. Research shows that acetaminophen also acts on the endocannabinoid system, disrupting key signaling pathways crucial to neurodevelopment. Preclinical literature has also shown that acetaminophen exerts effects on neurotransmitters and their metabolites, as well as other molecules and hormones critical to normal neurodevelopment (including serotonin, prostaglandins, and BDNF). Endocrine disruptions, and disruptions in neurotransmitters have been linked to both ASD and ADHD in children. These various mechanisms have complex and often bidirectional relationships with one another. For example, oxidative stress can increase inflammation, and inflammation can contribute to oxidative stress. In short, acetaminophen can set off a complex cascade of molecular events within the highly sensitive developing brain, causing issues that manifest over the course of an individual's lifetime.

In terms of in vivo experiments in animals, out of 27 peer-reviewed, published studies, written by research teams across the world, 26 showed measurable changes in animals treated with acetaminophen. These changes include rich gene expression data, including RNA-seq data published in Baker (2023).[20] Critically, biomarkers of oxidative stress have also been found in multiple human studies, showing concordance in terms of biologic plausibility. In addition to the rich body of literature on acetaminophen's effects in animals, other lines of evidence from the preclinical literature also support biologically plausible evidence of acetaminophen's effect on neurodevelopment.

IV. Plaintiffs' Proposed Label is Unassailably Accurate.

As the Government is aware, Plaintiffs submitted a proposed label on April 7, 2023, Dkt. 551, which states:

> **Autism/ADHD**: Some studies show that frequent use of this product during pregnancy may increase your child's risk of autism and attention deficit hyperactivity disorder. If you use this product during pregnancy to treat your pain and/or fever, use the lowest effective dose for the shortest possible time and at the lowest possible frequency.

As outlined above, the first sentence is undisputedly true: Some studies have shown that frequent use of acetaminophen while pregnant may increase a child's risk of ASD and ADHD.[21] One might

[20] Brennan Baker et al., *Sex-Specific Neurobehavioral and Prefrontal Cortex Gene Expression Alterations Following Developmental Acetaminophen Exposure in Mice*, 177 Neurobio. Disease 1 (2023).

[21] *See, e.g.*, Brandlistuen (2013); John M.D. Thompson et al., *Associations Between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years*, 9 PLOS ONE 1 (2014) (hereinafter Thompson (2014)); Liew (2016); Evie Stergiakouli et al., *Association of Acetaminophen Use During Pregnancy with Behavioral Problems in Childhood: Evidence Against Confounding*, 170 JAMA Pediatrics 964 (2016) (hereinafter Stergiakouli (2016)); Ji (2020); Silvia Alemany et al., *Prenatal and Postnatal Exposure to Acetaminophen in Relation to Autism Spectrum and Attention-Deficit and Hyperactivity Symptoms in Childhood: Meta-analysis in Six European Population-based Cohorts*, 36 Eur. J. Epidemiology 993 (2021) (hereinafter Alemany (2021)); Liew (2014); Ystrom (2017); Zeyan Liew et al., *Use of Negative Control Exposure Analysis To Evaluate Confounding: An Example of*

even say there are *many* such studies. But Plaintiffs are content to be conservative, knowing that "some" is an amount definitionally included within "many."

There is overwhelming evidence supporting the prudent advice of our label's second sentence. As our April 7, 2023 letter noted, that sentence is taken from the European Union's label for paracetamol, which is the name for acetaminophen in Europe. *See* Dkt. 551-1 at § 4.6. Surely the United States does not believe that no reasonable scientist—deploying reliable scientific methods—could agree with the European Medicines Agency. That is not Plaintiffs' mere conjecture or hyperbole. Scientists *within the FDA* in 2022 supported a similar warning, noting that "it may be prudent, as a precautionary measure, to issue a communication emphasizing that APAP use in pregnancy should be judicious." Ex. 18, FDACDER000115. In 2016, FDA epidemiologists urged FDA to "bring this issue [of prenatal acetaminophen's link neurodevelopmental disorders] to the attention of consumers and healthcare providers through one of the communication avenues available to the agency." Ex. 16, FDACDER000014.

Moreover, the Briggs *Drugs in Pregnancy and Lactation* textbook, which is considered an authoritative "reference guide to fetal and neonatal risk," cautions against use of acetaminophen while pregnant. Specifically, it states that "long term use suggests risk" and goes on to state that "although originally thought not to cause harm, this assessment must change because of recent data" linking several weeks' worth of prenatal acetaminophen use to "decreased IQ, ADHD, and other problems in neurodevelopment." Briggs G. Briggs, *Drugs in Pregnancy and Lactation* 8 (12th ed. 2021). The textbook concludes that, although "the drug should not be withheld if required for maternal fever," "routine use of acetaminophen should be avoided" by pregnant women. *Id.*

When considering the propriety of Plaintiffs' proposed label, we trust that the United States wishes to ensure that it takes consistent positions. We therefore direct your attention to the label for valproic acid, also marketed as Depakote, which warns of the risks of ASD and ADHD from prenatal use. Valproic acid is an anti-seizure medication used to treat manic episodes, bipolar disorders, and migraines, and its label warns that "[a]lthough 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)."[22] In support of that statement, the label cites a *single* observational study in support of the autism warning[23] and a *single* observational study by the same author in support of the ADHD warning.[24]

Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II, 188 Am. J. Epidemiology 768 (2019) (hereinafter Liew (2019); Baker (2020).

[22] *Depakote ER Full Prescribing Information*, U.S. Food & Drug Admin. 31–32 (Feb. 2019), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021168s039lbl.pdf.

[23] Jakob Christensen et al., *Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism*, 309 J. Am. Med. Ass'n 1696 (2013) (hereinafter Christensen (2013))

[24] 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)).

Neither of these studies make any definitive conclusion about causation, and both studies caution that the possibility of residual confounding remains.[25] The Depakote label states that "conclusions regarding a causal association" "cannot be considered definitive," but nevertheless warns that "the weight of the evidence supports a causal association."[26] The "weight of the evidence" supporting a "causal association" between frequent prenatal acetaminophen use and ASD/ADHD is far heavier than it is for valproic acid. Pregnant women who are not afflicted with migraines or bipolar disorder deserve to be warned of risks just as much as pregnant women who do suffer these conditions.

Our review of FDA's partially redacted production appears to reveal the Administration's concern that any warning would dissuade women from taking acetaminophen when needed for fever, which is problematic because "there are no alternative OTC medications to manage pain and/or fever during pregnancy." Ex. 17, FDACDER000053. But Plaintiffs' proposed label specifically encourages episodic use to treat maternal fever. And the entire premise of our Nation's OTC drug-labelling regime is that consumers can process accurate information to make informed health-care decisions. The United States can trust pregnant women to be empowered by the truth, enabling them to evaluate *both* the benefits and the risks of acetaminophen. That may well mean consuming acetaminophen for a few days to treat a high maternal fever while avoiding daily use of the drug for minor aches and pains.

V. Plaintiffs' Proposed Label is Unquestionably Supported by the Science.

The opinions of Plaintiffs' five general causation experts, as documented in their reports, rebuttal reports, and deposition testimony, show that the science unquestionably supports Plaintiffs' proposed label.

The experts' conclusions are not outliers. But because the United States is being asked to weigh in on scientific issues on the eve of Rule 702 briefing, it is important to recognize the differences between how scientists address the causation standard in peer reviewed literature versus the way parties must approach it in a court of law. As the Federal Reference Manual on Scientific Evidence explains, "[g]enerally, researchers are conservative when it comes to assessing causal relationships, often calling for stronger evidence and more research before a conclusion of causation is drawn." Fed. Jud. Ctr., *Reference Manual on Scientific Evidence* 599 (3d ed. 2011) (hereinafter "Ref. Manual"); *see id.* n.143 (collecting cases). And, for our purposes, "*Daubert* was designed to exclude 'junk science.' It was never intended to keep from the jury the kind of evidence scientists regularly rely on in forming opinions of causality simply because such evidence is not definitive. The legal standard, after all, is preponderance of the evidence, *i.e.*, more-probable-than-

[25] *See e.g.*, Christensen (2013) ("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."); Christensen (2019) ("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.").
[26] *Depakote ER Full Prescribing Information*, *supra* note 22.

not, and that applies to causality as to any other element of a tort cause of action." *In re Ephedra Prod. Liab. Litig.*, No. 04 MD 1598 (JSR), 2005 WL 8178810, at *6 (S.D.N.Y. Sept. 20, 2005); *see also DeLuca by DeLuca v. Merrell Dow Pharms., Inc.*, 911 F.2d 941, 957 (3d Cir. 1990) ("The fact that a scientific community may require a particular level of assurance for its own purposes before it will regard a null hypothesis as disproven does not necessarily mean that expert opinion with somewhat less assurance is not sufficiently reliable to be helpful in the context of civil litigation.").

The available human data on the issue of whether acetaminophen can cause neurodevelopmental disorders consist of epidemiological studies, and individual epidemiological studies do not generally make a definitive causal finding (as the valproic acid literature discussed above demonstrates). As the United States Court of Appeals for the Second Circuit noted,"[b]y its nature, epidemiology is ill-suited to lead a factfinder toward definitive answers, dealing as it does in statistical probabilities and the continual possibility of confounding causal factors." *In re Joint E. & S. Dist. Asbestos Litig.*, 52 F.3d 1124, 1133 (2d Cir. 1995). "Instead, epidemiology enables experts to find associations, which by themselves do not entail causation," and "[u]ltimately, causation is a judgment for epidemiologists and others interpreting the epidemiolocal data." *In re Bair Hugger Forced Air Warming Devices Prod. Liab. Litig.*, 9 F.4th 768, 779 (8th Cir. 2021) (internal citations and quotations omitted); *see generally In re Neurontin Mktg., Sales Pracs., Prod. Liab. Litig.*, No. CIV.A. 04-10981-PBS, 2011 WL 1048971, at *9 (D. Mass. Mar. 18, 2011) (permitting an expert to testify where his published paper "only suggests an association" but his expert report opines that the study shows causation). *Blanchard v. Eli Lilly & Co.*, 207 F. Supp. 2d 308, 319 (D. Vt. 2002) ("None of the published material submitted to the Court however goes so far as to opine that SSRIs in general or Prozac in particular trigger suicidal thoughts or violent behavior. This of course is not determinative of whether an opinion indicating a causal link is admissible evidence.").

Surprisingly, given the much higher standard of proof employed in academic writing, the fact that numerous independent scientists have even suggested that causation is the most likely explanation for the repeated association shown across studies is significant:

- 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."[27]
- 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."[28]

[27] Olsen (2017).

[28] Xiaoyun Gou et al., *Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis,* 53 Aus. & N.Z. J. Psychiatry 195 (2019).

- The authors of the Ystrom study concluded that one set of their results were "consistent with a causal link."[29]
- The authors of the Stergiakouli study noted that their findings (combined with previous ones) were "consistent with an intrauterine effect," *i.e.*, with causation.[30]
- 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.[31]
- In fact, Silvia Alemany 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."[32]
- 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" and compared the results to those initially showing that "smoking causes lung cancer" and that "lead lowers IQ."[33]
- The Bornehag authors suggested that "women take the precautionary action of limiting their use of" acetaminophen while pregnant.[34]
- The Brandlistuen authors stated that "[i]f replicated, these findings may suggest limiting long-term use of [acetaminophen] during pregnancy."[35]
- The Baker 2020 authors recommended that FDA and other institutions should "consider reevaluating the evidence regarding the safety of acetaminophen exposure."[36]

These scientists' work and statements all support the view that prenatal use of acetaminophen can cause ASD and ADHD. As detailed above, this is evidenced by (1) the epidemiological evidence showing a causal relationship between acetaminophen and ASD/ADHD; (2) preclinical evidence

[29] Ystrom (2017).
[30] Stergiakouli (2016).
[31] Alemany (2021).
[32] *Silvia 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.
[33] 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/.
[34] Carl-Gustaf Bornehag et al., *Prenatal Exposure to Acetaminophen and Children's Language Development at 30 Months*, 51 Eur. Psychiatry 98, 102 (2018).
[35] Brandlistuen (2013) at 1712.
[36] Baker (2020) at 1080.

further supporting this conclusion; and (3) plausible biological mechanisms that explain the causal relationship.

VI. Reasonable Scientists Can Disagree as to Whether the Evidence Supports a Causal Relationship.

The overwhelming evidence thus shows there is more likely than not a causal relationship between prenatal use of acetaminophen and ASD and ADHD in offspring. The science *does*, then, warrant the addition of the additional warning Plaintiffs have proposed. *See supra* section V. In any event, the Rule 702 inquiry is less demanding. In the context of this litigation, the question before the Court will be whether reasonable scientists employing accepted methodologies can reasonably opine that causation is likely—even if other scientists might interpret the evidence differently. If the United States chooses to attend to any interests it may have in this case, we respectfully submit it should bear in mind its cross-cutting interest in ensuring that the Federal Rules of Evidence are consistently and properly applied. Whether reasonable scientific experts can reach different conclusions does not turn on whether certain government professionals support one side or the other of a scientific debate. To the contrary, claiming that respected, impeccably credentialed scientists have deployed "junk science"—and therefore should not be able to offer expert testimony—merely because they disagree with *some* FDA scientists risks chilling scientific inquiry, shutting down scientific debate, and biasing research to support preferred conclusions.

The United States can proceed with confidence that Plaintiffs' experts' conclusions are reasonable, and thus consistent with Rule 702, because they are shared by scientists *employed* by the United States. In 2016, FDA epidemiologists urged FDA to "bring this issue [of prenatal acetaminophen's link neurodevelopmental disorders] to the attention of consumers and healthcare providers through one of the communication avenues available to the agency." Ex. 16 at FDACDER000014. Specifically, "even in the absence of *proof* of a causal relationship," the epidemiologists urged that pregnant women be told that "the current data raise the possibility of neurodevelopmental harm to the fetus from maternal APAP use." *Id.* (emphasis added). FDA ultimately did not heed that advice, but that hardly makes the professional epidemiologists who tendered it practitioners of "junk science."

Three years later, FDA epidemiologists again stated that the studies "on neurodevelopmental outcomes" "suggest that its use during pregnancy is not necessarily completely benign for the fetus." Ex. 20 at JJCI_APAP_FOIA000022. The reviewers then (again) suggested that FDA needed to take action to tell women about this risk. Given that many women "perceive acetaminophen to be risk free," the reviewers noted, "it would be desirable for the agency to communicate this message"—about the risks of "neurodevelopmental outcomes"—"to healthcare providers and pregnant women, considering that acetaminophen is so commonly used during their pregnancies." *Id.* Specifically, the reviewers recommended telling women that "heavy use [of acetaminophen] for other reasons [other than fever] may have risks," and that "women should be careful about casual use of acetaminophen when it is not strongly needed for pain or other purposes" other than fever. *Id.* at 30. As recently as 2022, FDA scientists supported

a similar warning to the one proposed by Plaintiffs, noting that "it may be prudent, as a precautionary measure, to issue a communication emphasizing that APAP use in pregnancy should be judicious." Ex. 18, FDACDER000115.

Once again, the Administration did not follow that recommendation, but it similarly did not say or even intimate that the reviewers' opinions were born of unreliable methods divorced from the scientific evidence. If there is disagreement as to the state of the science even within the United States' own scientific ranks—and based on internal documents, there appears to be—then it follows *per force* that Plaintiffs' experts offer reliable conclusions. Indeed, Plaintiffs hope the analysis explained and enclosed here will better inform FDA's ongoing deliberations and lead the Administration to embrace the position some of its scientists first espoused years ago.

Regardless, to ensure that FDA receives honest opinions and unbiased evidentiary development on all matters—not merely those associated with the important questions surrounding acetaminophen—Plaintiffs respectfully urge the United States not to mislabel well-founded, good faith, and overwhelmingly supported scientific opinions as "quackery." That is not what Rule 702 is for. Plaintiffs' experts have unquestionably offered defensible conclusions based on reliable methodologies. The United States should say so, even if some scientific employees of the United States, relaying on their own scientific judgment, come to different conclusions.

VII. Conclusion

The extensive scientific evidence shows there is a causal relationship between prenatal use of acetaminophen and ASD/ADHD in offspring. Pregnant women are entitled to this vital information so they can make well-informed healthcare decisions for themselves and their unborn children.

We hope this summary of evidence provides you and your colleagues with the information you may need to meet your responsibilities. If you would like to discuss the science summarized here or any other aspect of this case, we are at your disposal.

Respectfully submitted,

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