UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen—ASD-ADHD Products Liability Litigation This Document Relates To: *All Cases*	Docket No.: 22-md-3043 (DLC)

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION EXPERTS' OPINIONS REGARDING ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Plaintiffs have proffered five experts—Drs. Andrea Baccarelli, Robert Cabrera, Eric Hollander, Stan Louie and Brandon Pearson—in an attempt to advance a theory that is not recognized by the scientific community and has been repeatedly rejected by the U.S. Food and Drug Administration ("FDA"): that maternal use of acetaminophen during pregnancy can cause Attention Deficit Hyperactivity Disorder ("ADHD") in children. Plaintiffs recently shared these experts' reports, along with a 21-page letter brief, with the U.S. Attorney for the Southern District of New York, hoping to change the FDA's mind and bolster their case. That effort failed. Instead, the U.S. Attorney reiterated the FDA's conclusion from March 2023 that "the limitations and inconsistent findings of current observational studies of [acetaminophen] and neurobehavioral . . . outcomes are unable to support a determination of causality."[1]

The FDA's conclusion is based on sound science. ADHD is highly influenced by genetics, and most of the relevant epidemiology does not properly adjust for genetic confounding, rendering it uninformative. *See* FDA 2023 Review, Ex. A at 27 (high quality studies must "[a]djust[] for potential confounders," including "genetic factors or . . . relevant familial factors such as parental neurobehavioral conditions (e.g., parental ADHD) or psychiatric conditions"). In 2021, however, researchers published a sibling-controlled study of maternal acetaminophen use and ADHD in an effort to eliminate the effect of potential genetic confounding on the results. Essentially, researchers studied mothers who took acetaminophen in one pregnancy but did not take acetaminophen in another pregnancy to determine whether the association between acetaminophen use and an elevated risk of ADHD would disappear. It did.

As the FDA has recognized, research on these issues is ongoing. But the question before

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[1] *See* Dkt. No. 1105 at 1-2 (emphasis added) (citation omitted) ("FDA 2023 Review").

the Court is whether plaintiffs' experts reliably opine, consistent with the existing science, that use of acetaminophen by pregnant women can cause ADHD in their children. For the reasons discussed below, they do not.

First, plaintiffs' experts apply an unreliable, results-oriented approach in analyzing the relevant science. Specifically, the experts rely on a highly limited and confounded body of literature, while dismissing better-conducted studies that undermine plaintiffs' theory of causation. They also base their opinions in large part on studies identifying associations between maternal acetaminophen use and various behaviors and traits that are only loosely related (if at all) to ADHD. Even if some of these behaviors were in fact proxies for a diagnosis of ADHD (and they are not), plaintiffs' experts' opinions would still be unreliable because the experts cherry-pick the findings that they believe support their opinions, while ignoring findings that do not support their opinions, often in the very same studies. This is a particular concern because of the risk of multiplicity errors in studies that consider numerous possible outcomes (i.e., the risk that when a study considers the effects of a single exposure on numerous outcomes, an association will likely be found for some of those outcomes due to the play of chance alone).

Second, to the extent some of plaintiffs' experts conduct "Bradford Hill" analyses to support their causation opinions, those analyses are similarly non-methodological and results-oriented. Most notably, plaintiffs' experts pretend that a weak association is "strong" in order to proclaim that strength of association is satisfied. They also describe a wildly contradictory body of studies as "consistent" by ignoring or subjectively disregarding findings that do not support their causation theories. And they strain to find evidence of a dose response in studies that do not have logical results and ignore the incoherent nature of the literature, including the fact that studies reach different results in terms of how much, and during which trimester of pregnancy,

acetaminophen use purportedly leads to an increased risk of ADHD. The fact that plaintiffs' experts have no idea how or when ADHD develops also makes it impossible to test whether their posited biological mechanisms are plausible or whether any study is evaluating acetaminophen exposure at the relevant stage of pregnancy, rendering their opinions concerning biological plausibility and temporality entirely speculative.

Finally, plaintiffs' experts try to salvage their speculative opinions by relying on animal studies that they claim demonstrate that in utero exposure to acetaminophen has neurological effects on rodents. But animal studies are useful only for generating hypotheses and confirming established associations; they cannot fill the analytical gaps in the epidemiologic literature. This is true in spades when it comes to ADHD studies, because animal brains differ greatly from human brains, and there is no such thing as an ADHD diagnosis in an animal. As a result, studies of rodent brains or behaviors cannot provide reliable proof of a causal effect between prenatal acetaminophen exposure and the complex human neurological condition of ADHD, which involves a variety of uniquely human behaviors and traits that rodents cannot exhibit. And the results of the animal studies are, in any event, highly inconsistent, further undermining plaintiffs' experts' causation analyses.

For all of these reasons, set forth in more detail below (and in defendants' other *Daubert* motions, which are incorporated herein), plaintiffs' experts should be precluded from testifying that exposure to acetaminophen during pregnancy can cause ADHD in children. Permitting plaintiffs' experts to tell a jury that a causal relationship has been established between acetaminophen and ADHD—despite the reasoned judgment of the FDA that it has not—would constitute an "abdication of [the] gatekeeping role," *Sardis v. Overhead Door Corp.*, 10 F.4th at 268, 284 (4th Cir. 2021), that could not be rectified through cross-examination.

BACKGROUND

A. ADHD And Its Etiology

"ADHD is a complex neurobiological disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsiveness." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 920 (Fed. Cir. 2011). "The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* ('the *DSM-5*') lists several criteria for an ADHD diagnosis." *Rochkind v. Stevenson*, 164 A.3d 254, 261 (Md. 2017). Specifically, a clinical diagnosis of ADHD requires a diagnostician to document at least six symptoms of inattention and/or six symptoms of hyperactivity-impulsivity persisting for a minimum of six months.[2] Additionally, because hyperactive and inattentive behaviors are relatively common, the DSM-5 requires that three "qualifying criteria" be met for a clinical diagnosis of ADHD:[3] (1) the symptoms must be present in two or more settings, such as home and school;[4] (2) the symptoms must be extreme relative to the individual's level of development;[5] and (3) more explanatory disorders must be eliminated.[6] Given the complexity of the DSM-5's diagnostic criteria, even plaintiffs' experts recognize that "ADHD diagnoses will typically be based on a thorough clinical assessment, entailing a history of deficits in both

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2 *See* American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), at 59-60.

3 *See id.* at 60 (Criteria C-E).

4 *Id.* ("Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school or work; with friends or relatives; in other activities).").

5 *Id.* ("There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.").

6 *Id.* ("The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).").

inattentive and hyperactive-impulsive domains."[7]

The ADHD diagnosis process often begins with one or more screening tests. These tests include, but are not limited to:

- The Strength and Difficulties Questionnaire ("SDQ"), "a screening tool that assesses 5 domains including emotional symptoms, conduct problems, hyperactivity, peer relationship, and prosocial behavior in children and adolescents ages 4 to 16 years."[8]
- The Ages and Stages Questionnaire ("ASQ"), which asks caregivers to observe a child and rate the extent to which the child typically exhibits mastery of different skill categories: (1) communication, (2) fine motor, (3) gross motor, (4) problem solving and (5) personal-social skills.[9]
- The Child Behavior Checklist ("CBCL"), which asks "parents . . . to rate their child on the extent to which they exhibit a wide variety of behaviors, such as 'Can't sit still or restless', 'avoids looking others in the eyes', and 'doesn't want to sleep alone', using a 3-point scale: 'Very true or often true', 'Somewhat or sometimes true', and 'Not true.'"[10]

These and other ADHD screening instruments are just the first step in an ADHD evaluation; they are not substitutes for a clinical diagnosis.[11] This is because the screening instruments are highly

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[7] Am. Rep. of Andrea Baccarelli ("Baccarelli Am. Rep.") at 39, June 23, 2023 (Ex. 2).

[8] Liew, *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168(4) JAMA Pediatrics 313, 315 (2014) ("Liew 2014"); *see also* Tovo-Rodrigues, *Is Intrauterine Exposure to Acetaminophen Associated With Emotional and Hyperactivity Problems During Childhood? Findings From the 2004 Pelotas Birth Cohort*, 18 BMC Psychiatry 1, 2 (2018) ("Tovo-Rodrigues 2018"). Copies of all studies cited herein are attached to the Declaration of Kristen L. Richer as Exs. 24-169.

[9] *See* Squires, *Revision of a Parent-Completed Developmental Screening Tool: Ages and Stages Questionnaires*, 22(3) J. Pediatr. Psychol. 313, 314 (1997); *see also, e.g.*, Brandlistuen, *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Sibling-Controlled Cohort Study*, 42(6) Int'l J. Epidemiol. 1702 (2013) ("Brandlistuen 2013"); Vlenterie, *Neurodevelopmental Problems at 18 Months Among Children Exposed to Paracetamol in Utero: A Propensity Score Matched Cohort Study*, 45(6) Int'l J. Epidemiol. 1998 (2016) ("Vlenterie 2016").

[10] Sznajder, *Maternal Use of Acetaminophen During Pregnancy and Neurobehavioral Problems in Offspring at 3 Years: A Prospective Cohort Study*, 17(9) PloS One 1, 4 (2022) ("Sznajder 2022"); *see also* Trønnes, *Prenatal Paracetamol Exposure and Neurodevelopmental Outcomes in Preschool-Aged Children*, 34(3) Paediatr. Perinat. Epidemiol. 247, 249 (2020) ("Trønnes 2020").

[11] Russell, *The Strengths and Difficulties Questionnaire as a Predictor of Parent-Reported Diagnosis of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder*, 8(12) PloS One 1 (2013) ("Russell 2013"); *see also* Gualtieri & Johnson, *ADHD: Is Objective Diagnosis Possible?*, 2(11) Psychiatry 44, 48 (2005) (systematic rating tools "are a necessary component of the diagnostic process, but [are] not sufficient"); Crunelle, *International Consensus Statement on Screening, Diagnosis and Treatment of Substance Use Disorder Patients with Comorbid Attention Deficit/Hyperactivity Disorder*, 24(1) Eur. Addict. Res. 43, 48 (2018) ("If the screening result is positive

sensitive (meaning they aim to be overinclusive and sweep in everyone who might have ADHD), but they are not specific and therefore identify many people who do not have ADHD.[12]

At present, there are no reliable biomarkers for ADHD.[13] There is no single brain lesion associated with ADHD; nor is there a brain measure that predictably differentiates the brain of an individual with ADHD from the brain of an individual without ADHD.[14] As a consequence, neuroimaging cannot be used to accurately diagnose the condition.[15]

While there are a number of unknowns regarding the etiology, or cause, of ADHD, studies have confirmed that ADHD is a predominantly genetic condition.[16] Indeed, twin studies conducted across various cultures suggest heritability rates for ADHD of around 71-90%.[17] Genome-wide association studies ("GWAS") support these findings by tying several common genetic variants to ADHD.[18] And, although many studies have reported positive associations between various prenatal environmental exposures and ADHD in children, properly controlling

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or if ADHD is clinically suspected, a physician or clinical psychologist with specialist training on the differential diagnosis of ADHD and experience in addiction care should initiate a more extensive diagnostic examination.").

[12] *See* Russell 2013, *supra* note 11, at 5 (finding that the SDQ's positive predictive value ("PPV") for ADHD was as low as 12%, suggesting a false positive rate of 88%).

[13] Thome, *Biomarkers for Attention-Deficit/Hyperactivity Disorder (ADHD): A Consensus Report of the WFSBP Task Force on Biological Markers and The World Federation of ADHD*, 13(5) World J. Biol. Psychiatry 379 (2012).

[14] Faraone, *The World Federation of ADHD International Consensus Statement: 208 Evidence-Based Conclusions About the Disorder*, 128 Neurosci. Biobehav. Rev. 789 (2021).

[15] *Id.*

[16] Information regarding the fundamental principles of epidemiology relevant to the issues set forth herein are set forth in more detail in defendants' ASD *Daubert* brief. (*See* ASD Mem. Section II.A-H.)

[17] Thapar, *What Have We Learnt About the Causes of ADHD?*, 54(1) J. Child Psychol. Psychiatry 3 (2013); Faraone, *Molecular Genetics of Attention-Deficit/Hyperactivity Disorder*, 57(11) Biol. Psychiatry 1313 (2005); Nikolas & Burt, *Genetic and Environmental Influences on ADHD Symptom Dimensions of Inattention and Hyperactivity: A Meta-Analysis*, 119(1) J. Abnorm. Psychol. 1 (2010); Thapar, *Genetic Basis of Attention Deficit and Hyperactivity*, 174(2) British J. Psychiatry 105 (1999).

[18] Demontis, *Genome-Wide Analyses of ADHD Identify 27 Risk Loci, Refine the Genetic Architecture and Implicate Several Cognitive Domains*, 55(2) Nat. Genet. 198 (2023).

for genetic and familial confounding often attenuates or eliminates the association.

For example, a large cohort study from Sweden found that the observed association between ADHD and prenatal exposure to heavy smoking, RR 2.50 (95% CI 2.40-2.61), was attenuated to RR 1.69 (95% CI 1.40-2.04) when controlling for genetics by comparing cousins—and became an inverse association of RR 0.84 (95% CI 0.65-1.06) when using a sibling-control analysis.[19] Chen 2014 observed a similar attenuation of the purported ADHD risk associated with maternal obesity after performing a sibling-control analysis.[20] There, the hazard ratio dropped from HR 1.64 (95% CI 1.57-1.73) to a non-statistically significant HR 1.15 (95% CI 0.85-1.56) after a sibling-control analysis.[21] Additionally, Wiggs 2017 initially observed a hazard ratio of 1.23 (95% CI 1.19-1.28) for oxytocin-induced labor induction and ADHD in children,[22] but the association was a null 0.99 (95% CI 0.91-1.07) after a sibling-control analysis was performed.[23] In short, researchers have proposed many possible causes for ADHD over the years—and time and again, those causes are ruled out with genetic controls.

B. The State Of The Science On The Purported Association Between Prenatal Acetaminophen Use And ADHD

A number of studies over the last decade have assessed the potential association between prenatal acetaminophen exposure and the development of ADHD. Eight of those studies (utilizing data from five cohorts) found a weak association with a diagnosis of ADHD,[24] but

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[19] Skoglund, *Familial Confounding of the Association Between Maternal Smoking During Pregnancy and ADHD in Offspring*, 55(1) J. Child Psychol. Psychiatry 61, 65 (2014).

[20] Chen, *Maternal Pre-Pregnancy Body Mass Index and Offspring Attention Deficit Hyperactivity Disorder: A Population-Based Cohort Study Using A Sibling-Comparison Design*, 43(1) Int'l J. Epidemiol. 83 (2014).

[21] *Id.*

[22] Wiggs, *A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement*, 47(4) Behav. Genet. 383 (2017).

[23] *Id.*

[24] Ten studies have investigated the association between prenatal acetaminophen exposure and an ADHD

those studies are highly limited because they did not adjust properly (or at all) for genetic and other potential confounders. Only one study evaluating the association between acetaminophen use during pregnancy and an ADHD diagnosis in children included a sibling analysis to address potential genetic confounders by assessing ADHD outcomes for exposed and unexposed siblings. That study, Gustavson 2021,[25] initially observed an association in cases where mothers took acetaminophen for 29 days or more (adjusted OR = 2.02, 95% CI 1.17-3.25). But when the authors controlled for potential genetic confounding by comparing ADHD outcomes in children who were exposed to acetaminophen during pregnancy versus their siblings who were not, the association disappeared (OR = 1.06, 95% CI 0.51-2.05).

Sibling analysis or sibling-controlled designs typically involve comparing pairs of matched siblings where one sibling was exposed to the variable of interest but the other was not (and/or where one of the matched siblings exhibits the outcome of interest but the other does not).[26] If the results show that the outcome of interest occurs with similar frequency in siblings regardless of exposure, then any association is likely caused by shared confounding factors rather than the exposure variable being examined. Because siblings are naturally matched on many potential confounders (including several factors in the early environment or upbringing as well as genetics), these comparisons implicitly adjust for myriad shared confounders and reduce the

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diagnosis in children, nine of which are cohort studies that analyzed data from only four cohorts. Ystrom 2017, Gustavson 2019, and Gustavson 2021 utilized data from the Norwegian Mother and Child Cohort. Three other studies, Ji 2018, Ji 2020, and Anand 2021 utilize data from the Boston Birth Cohort. Liew 2014 and Liew 2019 utilized data from the Danish National Birth Cohort—and Baker 2020 utilized data from the GEST cohort. One retrospective case-control study, Chen 2019, utilized data from the Taiwan Longitudinal Health Insurance Database.

[25] Gustavson, *Acetaminophen Use During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder – A Longitudinal Sibling Control Study*, 1(2) JCPP Advances 1 (2021) ("Gustavson 2021").

[26] *See* Sjölander, *Sibling Comparison Studies*, 9 Annu. Rev. Stat. Appl. 71 (2022).

possibility of unmeasured confounding.[27]

Other so-called "negative-control" studies have considered whether maternal use of acetaminophen before or after pregnancy or paternal use of acetaminophen has an association with the development of ADHD. The design of these studies is called "negative control" because, by analyzing exposures that are ***not*** expected to be associated with the observed outcome (i.e., the negative control), these studies can help reveal whether a confounding factor is driving the hypothesized association between the exposure and outcome analyzed. Unmeasured confounding is likely to be present if there is an observed association between the negative control and the outcome in the study population.[28] For example, Ystrom 2017[29] and Stergiakouli 2016[30] both observed an association between ***paternal*** use of acetaminophen during pregnancy and the development of ADHD, suggesting that the medicine itself is not driving the association.

While negative control designs can be informative, it is important to identify a proper negative control that is time-invariant. Paternal use of acetaminophen fits that requirement because there is no reason to believe that fathers who take acetaminophen before or during their partner's pregnancy differ from fathers who do not. Another type of negative control used in acetaminophen studies is problematic, however, because it compares women who take acetaminophen during pregnancy to women who take it before or after pregnancy. The problem

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[27] *See* Gustavson 2021, *supra* note 25, at 2.

[28] *See* Shi, *A Selective Review of Negative Control Methods in Epidemiology*, 7(4) Curr. Epidemiol. Rep. 190 (2020) ("[T]he presence of an association between the NCE and the outcome (or between the NCO and the exposure) constitutes compelling evidence of residual confounding bias.").

[29] (Baccarelli Am. Rep. at 115-16; Am. Rep. of Robert Cabrera ("Cabrera Am. Rep.") at 145-46, June 22, 2023 (Ex. 6); Rebuttal Rep. of Eric Hollander ("Hollander Rebuttal Rep.") at 13, 17, July 28, 2023 (Ex. 12); Am. Rep. of Stan Louie ("Louie Am. Rep.") ¶¶ 69, 74, June 21, 2023 (Ex. 9).)

[30] *See* Stergiakouli, *Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding*, 170(10) JAMA Pediatrics 964, at Supplementary eTable 3 (2016) ("Stergiakouli 2016") (aRR = 1.41, 95% CI 1.02-1.97).

with this negative control is that those two groups of women vary in potentially relevant ways. For one thing, acetaminophen is recommended for use during pregnancy as an alternative to other pain-relief medications such as ibuprofen or prescription medications that are not indicated for pregnant women.[31] As a result, the population of women who take acetaminophen during pregnancy is likely different, and potentially larger, than the population of women who take the medication outside pregnancy. This is borne out by data from the Copenhagen Pregnancy Cohort, which indicate that approximately 25% of women who took acetaminophen three months before pregnancy had chronic medical diseases, compared to 36% of women who took acetaminophen during the first trimester of pregnancy.[32] Women in the Copenhagen Pregnancy Cohort with mental health disorders were also more likely to use acetaminophen during pregnancy (mental diseases aOR = 2.74, CI 95% 1.67-4.49).[33] Data from the Norwegian Birth Cohort similarly revealed differences between women who take acetaminophen during pregnancy and women who take acetaminophen after pregnancy.[34] And Stergiakouli 2016 found that women in the Avon Longitudinal Study of Parents and Children birth cohort who took acetaminophen during pregnancy had higher rates of psychiatric illness than women who took acetaminophen postnatally (10.2% v. 8.1%, respectively).[35]

There are also approximately 20 studies that assess potential associations between

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31 Taagaard, *Paracetamol Use Prior to and in Early Pregnancy: Prevalence and Patterns Among Women With and Without Chronic Medical Diseases*, 89(8) Br. J. Clin. Pharmacol. 2583 (2023) ("Taagaard 2023") ("Paracetamol is the first choice of analgesic during pregnancy, probably due to the assumed low teratogenicity in addition to the antipyretic properties and since non-steroidal anti-inflammatory drugs (NSAIDs) should be cautiously used during the first and second trimesters and avoided in the third.").

32 *Id*. at 2582.

33 *Id.*

34 Ystrom, *Prenatal Exposure to Acetaminophen and Risk of ADHD*, 140(5) Pediatrics 1 (2017) ("Ystrom 2017").

35 Stergiakouli 2016, *supra* note 30, at 966.

prenatal acetaminophen use and screening tests that plaintiffs' experts claim can be used as proxies for an ADHD diagnosis. These include the CBCL, SDQ and ASQ, as well as IQ tests and other reports of certain behavioral issues.[36] Some have no relevance at all to ADHD (e.g., IQ tests), but even the proxy studies that evaluate behaviors found among individuals with ADHD are of limited value because the screening tests are deliberately overbroad, as discussed above. Moreover, the results of the proxy studies are mixed and inconsistent. A number of the proxy studies evaluated the effect of acetaminophen exposure at different levels on multiple different outcomes, generating up to 20-75 different risk ratios per study. (*See* Section I.C, *infra*.) These individual risk ratios vary from study to study and within studies, with positive findings for a particular subgroup in one article contradicted by null or negative findings from another.[37] For example, while the authors of Tovo-Rodrigues (2018) reported adjusted ORs of 1.47 (95% CI 1.02-2.02) and 1.42 (95% CI 1.06-1.92) for emotional symptoms and hyperactivity/inattention among six-year-old boys on the SDQ, there was no association among the same boys when scoring conduct problems (adjusted OR. 0.93, 95% CI 0.68-1.27).[38]

While plaintiffs' experts also cite a so-called "consensus" statement titled "Paracetamol use during pregnancy—a call for precautionary action,"[39] published by Bauer in 2021, that

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[36] *See, e.g.*, Thompson, *Association between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years*, 9(9) PLoS One 1 (2014) ("Thompson 2014") (using SDQ and Conners' Behavioural Rating Scale: Revised—Long Format); Sznajder 2022, *supra* note 10 (using CBCL); *see also* Trønnes 2020, *supra* note 10 (using ASQ, CBCL and Emotionality, Activity and Shyness Temperament Questionnaire); Liew, *Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study*, 27(6) Epidemiology 912 (2016) (using IQ testing).

[37] *See, e.g.*, Vlenterie 2016, *supra* note 9 (neither short nor long-term (greater than 28 days) use of acetaminophen was significantly associated with attention outcomes in adjusted cohort); Parker, *Maternal Acetaminophen Use During Pregnancy and Childhood Behavioural Problems: Discrepancies Between Mother- and Teacher-Reported Outcomes*, 34(3) Paediatr. Perinat. Epidemiol. 299 (2020) (authors did not observe attention-related behavior problems according to parent or teacher report).

[38] *See* Tovo-Rodrigues 2018, *supra* note 8, at Table 3.

[39] Bauer, *Consensus Statement: Paracetamol Use During Pregnancy—A Call for Precautionary Action*, 17

article is neither a systematic review nor a pooled study. Moreover, the authors acknowledge that all 26 studies that have "identified positive associations with APAP exposure during pregnancy and . . . parent-reported neurodevelopmental outcomes, primarily [ADHD]," suffered from potential confounding based on "indication," "genetic factors," "bias introduced by exposure and outcome misclassification" and "study participant loss to follow-up."[40] And although the authors point to Baker 2020 and Ji 2020 as overcoming many of these limitations, they also note that those "biomarker studies are not without limitations in the assessment of exposure."[41] In a follow-up statement, the authors expressly disclaimed the notion that a causal relationship has been established between prenatal acetaminophen exposure and ADHD, explaining that because "limitations and uncertainties remain despite the large body of available data . . . we avoided any inference of causality in our [c]onsensus [s]tatement."[42]

C. Plaintiffs' Experts' General Causation Opinions

1. Dr. Andrea Baccarelli

Dr. Baccarelli, an epidemiologist, seeks to testify that "[s]ubstantial evidence supports a strong, positive, causal association between acetaminophen and Neurodevelopmental Disorders (NDDs)—particularly [ADHD], Autism Spectrum Disorder (ASD), and their related symptoms." (Baccarelli Am. Rep. at 2.) Dr. Baccarelli claims to have conducted "an extensive review of the scientific evidence" that involved grading the strength of the studies he reviewed with "expert opinion scores." (*Id.* at 2, 22-23.) Dr. Baccarelli subjectively classifies many of the studies

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Nature Revs. Endocrinology 757 (2021).

[40] *Id.* at 762.

[41] *Id.* at 763.

[42] Bauer, *Reply to "Paracetamol Use in Pregnancy—Caution over Causal Inference from Available Data": "Handle with Care—Interpretation, Synthesis and Dissemination of Data on Paracetamol in Pregnancy,"* 18 Nature Revs. Endocrinology 192, 192 (2022).

showing no relationship between acetaminophen exposure and adverse ADHD-related outcomes as "weak," including, Laue 2019, ***a study Dr. Baccarelli co-authored***, which found no statistically significant association between in utero exposure to acetaminophen and decreased scores on any of the examined WISC-IV domains (which test IQ).[43] Meanwhile, with the exception of one 36-year-old study, every study that Dr. Baccarelli cites as reporting a positive association between acetaminophen use and ADHD or other adverse neurodevelopmental defects received a grade from "moderate" to "very strong." (Baccarelli Am. Rep., App. 1.)

Dr. Baccarelli's biased grading is evident in other ways as well. He praises studies with positive associations even though they involve limitations that are similar or identical to those in studies he criticizes because of their null associations. For instance, Dr. Baccarelli notes that a limitation in his own study, Laue 2019 (which did not find an association between in utero exposure and adverse neurodevelopmental outcomes), was the fact that it measured "an outcome—intelligence score—that does not directly bear on ADHD or ASD." (Baccarelli Am. Rep. at 108.) As the authors (including Dr. Baccarelli) explain, "behavior and intelligence are different neuropsychological constructs," meaning that the results "cannot be directly compared to other studies." (*Id.*) Nevertheless, Dr. Baccarelli relies for his ADHD opinion on Liew 2016, which measured "IQ in 5-year olds" (i.e., an intelligence score like the one used in Laue 2019), going so far as to give the study a "strong" grade. (*Id.* at 106; *see also id.* at App. 1, at 15.)

Dr. Baccarelli also discounts Parker 2020, which found that acetaminophen use during pregnancy was weakly associated with mother-reported behavior problems but not associated with teacher-reported problems. (*See id.* at 109-10.) Dr. Baccarelli dismisses the teacher-

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[43] *See* Laue, *Association Between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian Cohort Study*, 167(1) Toxicol. Sci. 138 (2019) ("Laue 2019").

reports' finding of no association as a potential "misclassification" (*id.* at 110), even though he admits elsewhere in his report that studies have found that "teacher ratings ***better*** predicted" "how children with ADHD, Combined Type and ADHD, Inattentive Type, would be differentiated from each other" than parent ratings (*id.* at 77 (emphasis added)).

Similarly, Dr. Baccarelli states that the negative-control analysis in Trønnes 2020 was not "as persuasive" as the more favorable Ystrom 2017 study in part because Trønnes 2020 "did not have ADHD as an endpoint and was forced to rely on less clearly defined child outcomes." (*Id.* at 116.) But the endpoint used in Trønnes 2020 was the CBCL, the same screening tool used in other studies that Dr. Baccarelli considers persuasive. (*See, e.g.*, *id.* at 91-92 (highlighting Sznajder 2022's use of the CBCL and "noting that the CBCL attention scale has been shown to be well correlated with ADHD diagnosis in children"); *id.* at 105-06 (noting that a strength of Vlenterie 2016, which used the CBCL, was its "ability to examine a range of outcomes potentially related with neurodevelopmental difficulties"); *id.* at 105 (discussing Brandlistuen 2013, which relies in part on the CBCL).)

2. Dr. Robert Cabrera

Dr. Cabrera, a teratologist, opines that "[t]herapeutic dosages of acetaminophen taken by pregnant wom[e]n are sufficient to cause neurotoxicity, neurodevelopmental disorder, ASD, and ADHD in exposed offspring." (Cabrera Am. Rep. at 6.) His report addresses, *inter alia*, human epidemiological studies (*see id.* at 128-68), animal behavioral studies (*see id.* at 73-95), mechanistic studies (*see id.* at 38-73), and acetaminophen toxicity studies (*see id.* at 29-31). In reaching his opinions on general causation, Dr. Cabrera says he performed a "systematic review" of the relevant literature (*see id.* at 7), used a "Weight of the Evidence" analysis for "examining study quality," and assessed the Bradford Hill factors (*id.*).

Like Dr. Baccarelli, Dr. Cabrera examines the literature surrounding human exposure to

acetaminophen and the purported association with ADHD. (*See id.* at 136-46.) Reviewing much of the same literature as Dr. Baccarelli, Dr. Cabrera comes to the conclusion that "[t]here is a moderate association between APAP use during pregnancy and ADHD in children." (*See id.* at 147.) Dr. Cabrera also purports to have conducted a causation analysis using the criteria set forth by Bradford Hill and concludes that all the considerations identified by Hill, except specificity, support a finding of causation. (*See id.* at 189-95.)

Finally, Dr. Cabrera considers multiple rat and mouse studies that he claims "show 'clear evidence' that perinatal APAP exposure results in learning deficits and impaired social behavior." (*Id.* at 126-27.) A number of those studies, however, involve experiments that dosed adult—not developing—rodents (Ishida 2007, Gould 2012, Zhao 2017), and several of the studies found no change in—or even reduced—the purported ADHD-like behaviors in the rodents that were studied (*see, e.g.*, Klein 2020, Saad 2016, Harshaw 2022). Moreover, such studies only looked at small facets of potential ADHD-like behaviors, not actual ADHD diagnoses in animals, since, as Dr. Cabrera concedes, "you can't diagnose a mouse with ADHD." (Dep. of Robert Cabrera ("Cabrera Dep.") 192:4-12, Aug. 2, 2023 (Ex. 7).)

3. Dr. Brandon Pearson

Dr. Pearson is a toxicologist who primarily opines that "preclinical studies strengthen the association seen in epidemiological studies between in utero exposure to APAP and neurodevelopmental disorders including ASD and ADHD in humans." (Am. Rep. of Brandon Pearson ("Pearson Rep.") at 4, June 21, 2023 (Ex. 8).) Dr. Pearson employs a "weight of evidence" methodology in evaluating causation, which he describes as (1) "develop[ing] [a] hypothesis," (2) "establish[ing] lines of evidence and knowledge gaps," (3) "determin[ing] data reliability, uncertainty and relevance," (4) "assign[ing] weight of evidence," and (5) "examin[ing] evidence coherence and impact of uncertainty," ultimately resulting in Dr. Pearson

weighing the results of the studies to come to his conclusions. (*See id.* at 66-82.)

Dr. Pearson evaluates in vivo, in vitro and in silico (i.e., computer modeling) studies, from which he concludes that "APAP increases the risk of adverse neurodevelopmental outcomes in humans when used in accordance with the dosing information on the product label." (*Id.* at 127.) With respect to in vivo studies examining a purported link between acetaminophen and ADHD, Dr. Pearson relies on many of the same animal studies as Dr. Cabrera that examine how acetaminophen exposure affects certain rodent behaviors. (*See id.* at 82-115.) Remarkably, Dr. Pearson is not bothered by studies that contradict his hypothesis. To the contrary, he states that "findings that are in the opposite direction of the prediction"—i.e., studies that would tend to suggest less hyperactivity or impulsivity in rodents exposed to acetaminophen—"nevertheless demonstrate that the sensitive neurobehavioral system is perturbed by the developmental exposure to the medication," and "[a] directional concordance is not required." (Rebuttal Rep. of Brandon Pearson ("Pearson Rebuttal Rep.") at 4, July 28, 2023 (Ex. 18).) Needless to say, this "heads I'm right, tails you're wrong" approach is not supported by valid scientific principles.

4. Dr. Stan Louie

Dr. Louie is a pharmacologist retained by plaintiffs to investigate whether and at what exposure level acetaminophen purportedly "increases the risk of developing autism spectrum disorder" and ADHD. (Louie Am. Rep. ¶ 15.) His core opinion is that "prenatal exposure to acetaminophen increases the risk of developing ASD and ADHD in offspring when acetaminophen is taken by the pregnant mother in the therapeutic dose range . . . for at least 28 cumulative days during pregnancy, or a total of between 18.2 grams (18,200 mg [a single 650 mg dose for 28 days) to 112 grams (112,000 mg [the maximum approved daily dosage of 4,000 mg for 28 days])." (*Id.* ¶ 27.) As support for this opinion, Dr. Louie relies on studies similar to those cited by Drs. Baccarelli and Cabrera, conflates ADHD and ASD-related studies, and

chiefly focuses on seven epidemiological studies that "collected . . . time of exposure data" on the number of days or weeks the studied women took acetaminophen. (*Id.* ¶ 69.) As explained more fully in defendants' ASD *Daubert* brief, none of these seven studies stratified usage beyond 29 days of use; instead, they lumped together all women who took acetaminophen anywhere from one to nine months of pregnancy. (ASD Mem. at 71-72.) Notably, Dr. Louie does not offer any opinions on how the distribution of those 28 days—i.e., consecutively or throughout the pregnancy—affects the risk of ADHD; nor does he take that information into consideration in forming his opinions. (*See* Dep. of Stan Louie ("Louie Dep.") 90:7-15, Aug. 7, 2023 (Ex. 10) (Dr. Louie noting that he "didn't talk about how you spread [the days of use] out"); *id.* 88:6-12 (Dr. Louie noting that he did not consider "whether it's 28 consecutive days or whether . . . the 28 days are spaced out evenly over the entire pregnancy").)

5. Dr. Eric Hollander

Plaintiffs' expert psychiatrist, Dr. Hollander, opines that, in light of the purported "interconnectedness of neurodevelopmental disorders, including ADHD and ASD, it is appropriate to review" evidence measuring "symptoms of neurodevelopmental disorders . . . when evaluating the potential causal association between prenatal APAP exposure and ASD and ADHD in offspring." (Am. Rep. of Eric Hollander ("Hollander Am. Rep.") at 4, June 22, 2023 (Ex. 11).) As set forth more fully in defendants' ASD *Daubert* brief, Dr. Hollander's novel "transdiagnostic" approach is not based on any generally accepted methodology or scientific literature, but rather on his supposed "experience." (ASD Mem. at 45-47.)

Although Dr. Hollander did not undertake "a Bradford Hill analysis in [his] initial report," he conducted one for his rebuttal report. (Dep. of Eric Hollander ("Hollander Dep.") 71:15-21, Aug. 9, 2023 (Ex. 13); *see also* Hollander Rebuttal Rep. at 5-10, 14-21.) In his Bradford Hill analysis, Dr. Hollander simultaneously assesses whether acetaminophen use causes

ASD and ADHD and repeatedly conflates the two distinct disorders. While Dr. Hollander claims that he undertook his own, independent analysis (*see* Hollander Dep. 162:17-21, 163:2-8), he conceded at his deposition that he expressly "rel[ied] on [Dr. Baccarelli's] weighting of each of the individual studies" (*id.* 162:9-13) since he "did not have time to weight each study on a number of different metrics" (*id.* 174:9-18). In fact, Dr. Hollander brought to his deposition a copy of Dr. Baccarelli's "summary table of the different individual articles" and referred to it when answering questions about the individual studies. (*Id.* 194:10-195:11; *see also id.* 204:15-25; *id.* 286:13-19; Hollander Dep. Ex. 54 (Ex. 19).)

ARGUMENT

The standards for the admission of expert testimony are set forth in detail in defendants ASD *Daubert* brief, which is incorporated herein. Plaintiffs' experts' general causation opinions with respect to ADHD are inadmissible under these standards for several reasons.

I. DRS. BACCARELLI, CABRERA, HOLLANDER, LOUIE AND PEARSON MISREAD THE RELEVANT SCIENCE IN AN ATTEMPT TO CREATE A CAUSAL NARRATIVE.

Plaintiffs' experts assert that a causal association exists between maternal acetaminophen use during pregnancy and ADHD in children, based on a misreading of the science that: (1) places inappropriate emphasis on studies that have significant limitations while disregarding better evidence demonstrating that the associations observed are the result of confounding; and (2) improperly relies on studies that do not involve individuals diagnosed with ADHD, have inconsistent findings, and/or did not produce statistically significant results.

A. Plaintiffs' Experts Rely On Studies That Did Not Properly Adjust For Genetic Confounders, While Ignoring Better-Conducted Research.

"[S]ound scientific methodology requires that a scientist consider all of the scientific evidence when making causation determinations." *In re Zoloft (Sertraline Hydrochloride)*

Prods. Liab. Litig., 26 F. Supp. 3d 449, 463 (E.D. Pa. 2014). Accordingly, in developing a causation opinion, an expert may not rely only on "selectively favorable data," "unjustifiably disregard[] inconsistent data," or "ignore[] categories of relevant evidence." *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17-4188, 2021 WL 4037820, at *7 (S.D.N.Y. Sept. 3, 2021), *aff'd*, No. 22-146, 2023 WL 4837521 (2d Cir. July 28, 2023). In addition, an expert may not disregard "the express limitations" placed by the authors of the studies on which he or she relies. *Id.* at *9.

Plaintiffs' experts' approach to the ADHD literature violates these principles. They build their opinions on what they view as the most favorable findings, while disregarding the express limitations of the studies on which they rely—limitations that are echoed in review articles, meta-analyses and statements of scientific organizations. They also fail to properly account for the most important consideration in reviewing the relevant literature: genetic confounding.

1. **Plaintiffs' Experts Ignore The Limitations In The Studies On Which They Rely.**

Plaintiffs' experts seize on studies with odds ratios, hazard ratios, or relative risks above 1.0, but fail to acknowledge the likelihood—recognized in the very same studies—that confounding or bias may be driving those associations.

"Where a positive association is observed, its validity is assessed by evaluating the role of possible alternative explanations, such as chance, bias, or confounding." *Daniels-Feasel*, 2021 WL 4037820, at *2. "Confounding refers to '[a] factor that is both a risk factor for the disease and a factor associated with the exposure of interest.'" *Id.* at *3 (quoting *Reference Manual on Scientific Evidence* ("*RMSE*") (3d ed. 2011), at 621). "Bias is a systematic, non-random error, that may appear, for example, in the case of information bias, where the available records for one group are more likely to include relevant information than another." *Id.* (citing *RMSE*, at 249). Where a study's results could be explained by confounding or bias that cannot

be ruled out, that result cannot form the basis of a reliable causation opinion—especially where the expert "fail[s] to mention" or unjustifiably "dismiss[es]" express admonitions by a study's authors that such confounding or bias might explain the result. *Id.* at *8; *see also id.* at *10, *17 (similar); *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 387 F. Supp. 323, 353 (S.D.N.Y. 2019) (a study that reports an association but "reach[es] no conclusion" as to causation and notes "identifiable confounders" is "insufficient to support an expert conclusion" of causation), *aff'd*, 982 F.3d 113 (2d Cir. 2020); *Daniels-Feasel*, 2021 WL 4037820, at *8 (expert opinion that SSRIs cause autism was unreliable where, among other things, the expert "d[id] not mention" a study's limitations in his report and asserted, without "any explanation," that the limitation was an "overstatement" in his deposition).

Plaintiffs' experts' opinions violate these principles. The two studies cited by plaintiffs' experts as reporting the strongest associations between in utero acetaminophen exposure and ADHD—Baker 2020 and Ji 2020—do not adjust for genetic confounders and have additional, significant limitations that plaintiffs' experts ignore. All five of plaintiffs' experts rely on Baker 2020, which reports an association between ADHD diagnoses and prenatal exposure to acetaminophen, as measured by the presence of acetaminophen in meconium samples taken from newborns.[44] In that study, among the 345 children included in the analysis, detection of acetaminophen in meconium was associated with increased odds of ADHD (OR = 2.43, 95% CI 1.41-4.21).[45] Baker 2020 also purports to identify a "dose-response association," whereby each

[44] Baccarelli Am. Rep. at 88; Cabrera Am. Rep. at 137-38; Hollander Rebuttal Rep. at 11; Louie Am. Rep. ¶ 89; Pearson Rep. at 30.

[45] Baker, *Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity*, 174(11) JAMA Pediatrics 1073 (2020) ("Baker 2020").

doubling of acetaminophen exposure (as measured by the amount of acetaminophen in the meconium) increased the odds of ADHD by 10% (OR = 1.10, 95% CI 1.02-1.19).

But Baker 2020 did not reach a causal inference. To the contrary, the authors acknowledged the possibility of "confounding by unknown genetic, social, and other familial factors," noting that the study lacked information from a sufficient number of test participants to control for genetic confounding.[46] Nor did Baker 2020 attempt to adjust for confounding by indication, e.g., for maternal fever or infection.[47] This is especially problematic because studies have shown that maternal fever while pregnant is associated with the risk of a child developing ADHD, increasing the chances that the use of acetaminophen to treat fever is a significant confounder that could affect study results.[48] The study authors also cautioned that no work was done in the study to "correlate maternal acetaminophen use with acetaminophen concentrations in meconium," which the authors stressed "should be the subject of future work."[49] Plaintiffs' experts all but ignore these shortcomings, with Dr. Baccarelli dismissing the "theoretical possibility of unmeasured residual confounding" out of hand (Baccarelli Am. Rep. at 88) and Dr. Cabrera vaguely referencing the "potential for residual confounding" as a limitation of the study without explaining why that concern does not affect his own opinion (Cabrera Am. Rep. at 138).

Drs. Baccarelli, Cabrera, Hollander and Louie also rely heavily on Ji 2020, which measured cord plasma metabolites of acetaminophen present in umbilical cord plasma samples collected at birth and separated them into tertiles based on the amount of acetaminophen

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46 *Id.*

47 *Id.* at 1079.

48 Baccarelli Am. Rep. at 86 (noting Gustavson 2019 found statistically significant increases in risk for diagnosed ADHD from maternal febrile episodes).

49 Baker 2020, *supra* note 45, at 1079.

identified in the plasma. According to Ji 2020, individuals with cord blood acetaminophen levels in the second and third tertiles had an increased risk of ADHD diagnosis (second tertile OR = 2.26, 95% CI 1.40-3.69; third tertile OR = 2.86, 95% CI 1.77-4.67). But, like Baker 2020, the authors of Ji 2020 acknowledged that the study was subject to a variety of limitations.[50] Among them, the study was "unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors."[51] Further, as explained in the ASD *Daubert* brief, the Ji 2020 authors found that ***all*** tested cord plasma samples had detectable amounts of acetaminophen, suggesting some non-medicinal environmental exposure to acetaminophen or a laboratory error because it is unlikely that all 966 women in the study had recently taken acetaminophen. (*See* ASD Mem. at 12.) Only Dr. Baccarelli addresses this potential error in the study, asserting, without support, that the study authors "***may*** have protected against bias" caused by the clearly faulty discovery of acetaminophen in every sample of cord blood by "perform[ing] a tertile analysis." (Baccarelli Am. Rep. at 102 (emphasis added).) And even if the acetaminophen levels recorded for the cord blood were valid, the Ji 2020 authors acknowledge that "[g]iven that the half-life of acetaminophen in adults is less than three hours, the cord plasma measurement may at most reflect maternal use of acetaminophen at or near childbirth." As a result, the study does not provide any information regarding the potential effect of acetaminophen use during pregnancy (as opposed to during or immediately prior to labor).

The other studies on which plaintiffs' experts rely similarly fail to adjust for genetic

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[50] Ji, *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood*, 77(2) JAMA Psychiatry 180, 187-88 (2020) ("Ji 2020") ("[B]ecause of our observational study design, we were unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors.").

[51] *Id.*

confounding or confounding by indication and/or have other express limitations that plaintiffs' experts fail to address. For example:

- ***Liew 2014***: Drs. Baccarelli, Cabrera, Hollander and Louie cite Liew 2014 as finding that prenatal exposures to acetaminophen may increase the risk of being diagnosed with hyperkinetic disorder ("HKD") (HR = 1.37, 95% CI 1.19-1.59), receiving ADHD medications (HR = 1.29, 95% CI 1.15-1.44), or exhibiting ADHD-like behaviors at age seven (RR = 1.13, 95% CI 1.01-1.27)—and also showing an increased risk of these outcomes with increased reported duration of exposure.[52] But the authors of Liew 2014 explicitly concede that "the possibility of unmeasured residual confounding by indication for drug use, ADHD-related genetic factors, or co-exposures to other medications cannot be dismissed."[53]

- ***Chen 2019***: Drs. Baccarelli and Cabrera rely on Chen 2019 as evidence that "exposure to acetaminophen in the second trimester (OR = 1.19, 95% CI 1.00-1.40), both the first and second trimesters (OR = 1.28, 95% CI 1.00-1.64), or in any trimester (OR = 1.20, 95% CI 1.01-1.42) is associated with an increased risk of ADHD in offspring."[54] But the confidence intervals for all 24 associations observed include, or are just over, 1.0, rendering them statistically insignificant (or barely significant) and therefore indicating that it is possible no association exists at all. In addition, cumulative doses of acetaminophen calculated by regression analysis were not related to increased ADHD risk (second trimester OR = 1.13, 95% CI 0.76-1.69; both first and second trimesters OR = 0.98, 95% CI 0.50-1.91), which led the authors of the study to conclude that it showed ***no*** "dose-dependent relationship between prenatal acetaminophen use and the offspring's ADHD risk."[55] The authors of Chen 2019 also acknowledge that it is possible that some of the mothers involved in the study had undiagnosed "ADHD and substance use disorders," potentially skewing the study's results. Accordingly, the authors recommend further research "to investigate the potential roles of maternal ADHD and substance use disorders in the association of prenatal exposure to acetaminophen and ADHD risk in offspring."[56]

- ***Liew 2019***: The authors of Liew 2019, cited by Dr. Baccarelli, observed an association between maternal use of acetaminophen during pregnancy and ADHD in children (OR = 1.34, 95% CI 1.05-1.72). But the underlying cohort study was

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[52] Baccarelli Am. Rep. at 80-81; Cabrera Am. Rep. at 141-42; Hollander Rebuttal Rep. at 13, 17; Louie Am. Rep. ¶¶ 69, 77.

[53] Liew 2014, *supra* note 8, at 319.

[54] Baccarelli Am. Rep. at 86; *see also* Cabrera Am. Rep. at 138-39.

[55] Chen, *Prenatal Exposure to Acetaminophen and the Risk of Attention- Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan*, 80(5) J. Clin. Psychiatry e1, e3-e4 (2019) ("Chen 2019").

[56] *Id.* at e6.

> not limited to pregnant women, and the authors simply assumed that if the mothers gave birth in the same year they filled out the survey, the regular usage would have continued throughout pregnancy. This is not a logical assumption because many women change their medication choices during pregnancy. In addition, plaintiffs' experts fail to note that the authors produced adjusted odds ratios that purported to control for maternal age, child's birth year, child's birth order, gestational diabetes, preeclampsia, and regular maternal use of aspirin or other nonsteroidal anti-inflammatory drugs at the time of the pregnancy (aOR = 1.39, 95% CI 0.99-1.95 and aOR = 1.46, 95% CI 1.01-2.09),[57] and one of those point estimates was not statistically significant, while the other barely was. Further, the Liew 2019 authors concede that they could not "rule out the possibility of other uncontrolled risk factors for ADHD that are uniquely correlated with the use of acetaminophen during the pregnancy period," such as "conditions like fever, infections, or mild pain."[58] The authors also acknowledge that they did not "have data with which to evaluate possible confounding by prescription medication use in pregnancy," and that "[f]uture investigations are still needed, especially studies with improved exposure and outcome assessment and studies with the ability to address known and possibly unknown confounding factors in the analyses."[59]

In short, plaintiffs' experts misrepresent the state of the science by basing their causation opinions on studies that make clear that genetic and other possible confounders (e.g., confounding by indication), cannot be ruled out as the reason for the associations observed and/or have other serious limitations acknowledged by the authors. In so doing, plaintiffs' experts "draw[] impermissibly speculative conclusions . . . that 'exceed the limitations the authors themselves place[d] on the[se] stud[ies]." *In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 431 (S.D.N.Y. 2016) (quoting *In re Accutane Prods. Liab.*, No. 04-2523, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009), *aff'd*, 378 F. App'x 929 (11th Cir. 2010)).

2. Plaintiffs' Experts Fail To Properly Account For The Elephant In The Room: Genetic Confounding

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[57] Liew, *Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II*, 188(4) Am. J. Epidemiol. 768, 773 (2019) ("Liew 2019").

[58] *Id.* at 772.

[59] *Id.* at 773.

Plaintiffs' experts' causation opinions are also unreliable because they fail to grapple with a central issue raised by scientists regarding the ADHD literature: that genetic confounders are likely driving the positive associations in those studies. This is driven home by plaintiffs' experts' rejection of Gustavson 2021, the one study that properly addressed genetic confounding, while relying on other studies that do not properly control for genetic factors.

First, plaintiffs' experts improperly disregard Gustavson 2021, which used a sibling analysis to control for genetic confounders, because it "do[es] not support [their] conclusion[s]." *Daniels-Feasel*, 2021 WL 4037820, at *9-10; *see also id.* at *17 (similar); *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 262 (S.D.N.Y. 2018) ("*Mirena II*") (expert's failure to grapple with evidence concerning confounding factors rendered her causation opinion unreliable), *aff'd*, 982 F.3d 113 (2d Cir. 2020). The Gustavson 2021 paper is a de facto continuation of the analysis conducted by the same authors and published in Ystrom 2017, on which plaintiffs' experts heavily rely.[60] While both Ystrom 2017 and Gustavson 2021 utilized data from the Norwegian Mother and Child Cohort, Gustavson 2021 benefited from a more mature dataset[61] because the children were older and more had been diagnosed with ADHD.[62] As a result, Gustavson 2021 had the power to conduct two separate analyses on the relationship between prenatal exposure to acetaminophen and ADHD diagnosis in children—one

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[60] *See* Baccarelli Am. Rep. at 83-85, 115-16; Cabrera Am. Rep. at 145-46; Hollander Rebuttal Rep. at 13, 17, 18; Louie Am. Rep. ¶¶ 69, 74. Gustavson 2021 is also co-authored by a number of the same researchers involved in Brandlistuen 2013, on which plaintiffs' experts rely.

[61] In the interim, Gustavson 2019 conducted an analysis to determine whether the association between maternal fever and ADHD diagnosis in offspring was affected by acetaminophen use to treat fever during pregnancy. Maternal fever was associated with an increased risk of ADHD (aOR = 1.30, 95% CI 1.15-1.47). This association persisted regardless of acetaminophen usage (with acetaminophen OR = 1.35, 95% CI 0.96-1.90; without acetaminophen OR = 1.32, 95% CI 1.01-1.71). *See* Gustavson, *Maternal Fever During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder*, 9(1) Sci. Rep. 1, 4 (2019).

[62] Gustavson 2021, *supra* note 25, at 2.

that did not control for genetic factors and another with data from siblings that were not exposed to acetaminophen in utero. Prior to the sibling-control analysis, Gustavson 2021 observed a two-fold increase in the risk of ADHD diagnosis in children with long-term (29 days or more) prenatal exposure to acetaminophen (aHR = 2.02, 95% CI 1.17-3.25), but this purported increase in risk was ***attenuated to a statistically insignificant association*** of 1.06 (95% CI 0.51-2.05) after the sibling-control analysis. Thus, Gustavson 2021 suggests that, like previously observed associations between other prenatal exposures and ADHD, any association between in utero exposure to acetaminophen and ADHD in children is driven by unmeasured confounding—namely genetics. As the authors explained, their findings "highlight the importance of using designs that allow accounting for unmeasured confounding factors when examining prenatal risk factors for neurodevelopmental disorders"[63]—a design that the studies on which plaintiffs' experts rely did not employ.

The results of Gustavson 2021's sibling-control analysis are consistent with other scientific literature suggesting that genetics play an important confounding role in the alleged associations between maternal acetaminophen use and ADHD. For example, Leppert 2019 determined that mothers with a higher genetic risk for developing ADHD were significantly more likely to take acetaminophen during late pregnancy (OR = 1.11, 95% CI 1.04-1.18).[64] This led the authors to state: "our findings add to the increasing evidence that the observational associations between many prenatal factors and neurodevelopmental disorders in offspring may be at least partially genetically confounded."[65]

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63 *Id.* at 8.

64 *See* Leppert, *Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures*, 76(8) JAMA Psychiatry 834, 838 (2019).

65 *Id.* at 840.

Gustavson is also consistent with studies using paternal use of acetaminophen as a negative control, including studies on which plaintiffs' own experts rely. For example, as noted above, Drs. Baccarelli, Cabrera, Hollander and Louie rely on Ystrom 2017 as evidence that maternal use of acetaminophen during pregnancy is associated with a 12% increased risk of ADHD in children (CI 1.02-1.24).[66] But that study found that ***paternal use*** of acetaminophen before pregnancy was "as strongly associated with ADHD . . . as the corresponding maternal prenatal use" (8 to 28 days aHR = 1.81, 95% CI 1.26-2.60; and 29 or more days aHR = 2.06, 95% CI 1.36-3.13).[67] As the authors note, "[i]f the association is due to unobserved familial factors (e.g., genetic factors), paternal use of acetaminophen may also be associated with ADHD in a way similar to maternal use of acetaminophen."[68] Ultimately the authors stated, "[w]e do not provide definitive evidence for or against a causal relationship between maternal use of acetaminophen and ADHD."[69]

Plaintiffs' experts offer no sound reason to reject Gustavson 2021's sibling-control findings or the role of genetic confounding more generally in the observed associations that they tout as establishing causation. Drs. Hollander and Pearson do not address Gustavson 2021 at all, and while Dr. Louie asserts that he "gave weight" to Gustavson 2021 "based on its strong study design" and claims that the study "revealed a two-fold increase in risk of ADHD diagnosis (aHR

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[66] Baccarelli Am. Rep. at 83; Cabrera Am. Rep. at 145; Hollander Am. Rep., Materials Considered at 90; Louie Am. Rep. ¶¶ 69, 74.

[67] Ystrom 2017, *supra* note 34, at 4, 7.

[68] *Id.* at 2. In addition, Ystrom 2017 found that maternal use of acetaminophen for less than eight days was negatively associated with ADHD (aHR = 0.90, 95% CI 0.81-1.00), suggesting that acetaminophen "could be ***beneficial*** with regard to fetal development" in certain circumstances. *Id.* at 6-7 (emphasis added). *See also id.* at 7 (because "paternal use of acetaminophen is also associated with ADHD, the causal role of acetaminophen in the etiology of ADHD can be questioned").

[69] *Id.* at 7. The Ystrom 2017 authors speculate that there may be some mechanism by which acetaminophen use affects the male reproductive system in a way that would increase the risk of ADHD in children conceived after paternal use of acetaminophen, but concede there is no scientific support for this hypothesis.

= 2.02, 95% CI = 1.17-3.25)," he does not even mention the result of the study's sibling-control analysis. This approach of adopting only the less analytically rigorous half of a study—that is negated by its more rigorous approach—"strongly suggests outcome bias" that negates the reliability of an expert opinion. *Mirena II*, 341 F. Supp. 3d at 277.

Dr. Louie's omission is particularly egregious given his praise of other sibling-control studies. According to Dr. Louie's report, he assigned "the greatest weight" to Brandlistuen 2013, a sibling-control study that did not involve an ADHD diagnosis but found that siblings exposed to acetaminophen had some adverse developmental outcomes at three years of age relative to unexposed siblings. Dr. Louie claims that Brandlistuen 2013 "employed the strongest study design" and "allowed [the authors] to adjust for familial and genetic factors." (Louie Am. Rep. ¶¶ 71-72; *see also* Louie Dep. 114:19-25 (studies using sibling control analyses generally should be given greater weight than ones that do not).) Yet, Dr. Louie conveniently ignores the sibling-control results from Gustavson 2021, presumably because they do not support plaintiffs' causation theory. Dr. Louie's failure "to consider the most important scholarship bearing on th[e] point" in the form of a study that looked directly at the diagnosis at issue is "at odds with principles of sound science." *Mirena II*, 341 F. Supp. 3d at 296.

While Drs. Baccarelli and Cabrera address Gustavson 2021 in their analyses, both improperly dismiss the sibling-control design as a source of "bias" that could lead to an under-estimation of the true association. (Baccarelli Am. Rep. at 118; *see also* Cabrera Am. Rep. at 140.) Dr. Baccarelli agrees it is "desirable" to control for confounders, but asserts that the "sibling-control design eliminates not only the impact of family factors that operate as confounders but also that of family factors that operate as mediators" by "play[ing] a role in the causal pathway between an exposure and an outcome." (Baccarelli Am. Rep. at 118, 120.) To

Dr. Baccarelli, this means that Gustavson 2021's sibling-control analysis "biased" the association toward the null by eliminating family factors that may facilitate or increase the "effect of acetaminophen on ADHD." (*Id*. at 120.) For that to be true, however, maternal use of acetaminophen would somehow have to permanently alter the mother's genes to increase ADHD risk for all her future children. None of plaintiffs' experts takes such a radical position.

The only support Dr. Baccarelli provides for this critique is Sjölander & Zetterqvist 2017,[70] which notes as a general matter that sibling-control designs can control for mediators as well as confounders. But that paper also clarifies that "[c]ontrolling for mediators may or may not lead to bias, depending on the research question,"[71] and it does not discourage the use of sibling controls; instead, the paper recommends that researchers employ study-specific analyses of mediators. Thus, Dr. Baccarelli's stated concerns about sibling-controlled studies are inapplicable. *See Daniels-Feasel*, 2021 WL 4037820, at *8 (excluding general causation expert where the rationale he gave for "dismissing" studies that went against his conclusion lacked a sound basis); *see also In re Zoloft*, 26 F. Supp. 3d at 459 (expert failed to provide "a detailed, scientific critique" of study suggesting "the statistical association observed . . . may result from an unmeasured confounding factor") Further, Gustavson 2021 employed several rigorous sensitivity analyses to account for potential forms of bias that may occur in sibling-controlled studies and determined that the attenuation was not due to any such biases.[72]

Dr. Baccarelli also criticizes Gustavson 2021's sibling-control analysis on the ground that it was underpowered because it is purportedly "based on only approximately 2-3 cases of

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[70] Sjölander & Zetterqvist, *Confounders, Mediators, or Colliders: What Types of Shared Covariates Does a Sibling Comparison Design Control For?*, 28(4) Epidemiology 540 (2017).

[71] *Id.* at 540.

[72] Gustavson 2021, *supra* note 25, at Appendix S1 and S2, Tables S4-S5, Figures S1, S2.

ADHD." (Rebuttal Rep. of Andrea Baccarelli ("Baccarelli Rebuttal Rep.") at 7, July 28, 2023 (Ex. 16).) This is inaccurate. Gustavson 2021's sibling-control analysis of prenatal exposure to acetaminophen longer than 29 days utilized data from at least 34 cases of ADHD (and potentially more depending on whether families with more than two children had multiple children with ADHD diagnoses), not just "2-3" cases as Dr. Baccarelli falsely claims.[73]

In any event, Dr. Baccarelli's insistence that Gustavson 2021's sibling-control analysis may have masked hypothetical family mediators of ADHD or would have benefitted from a larger sample size would not be a basis for disregarding its results even if these critiques were legitimate. Gustavson 2021 is the ***only*** diagnostic ADHD study to control for genetics using the sibling design that plaintiffs' own expert, Dr. Louie, praises. At the very least, it confirms that genetic confounding must be explored before a causation determination can be made. In these circumstances, plaintiffs cannot meet their burden to prove, by a "preponderance of the evidence," that their experts' causation opinions are based on "sufficient data" and are "the product of reliable methods reliably applied." *Mirena II*, 341 F. Supp. 3d at 239-40; *see also James v. Coloplast Corp.*, No. 20-654, 2022 WL 4465956, at *5 (D. Minn. Sept. 26, 2022) (excluding causation opinion because plaintiff had not "established by a preponderance of the evidence on the record before the [c]ourt that [the expert's] causation opinion [was] reliable"), *appeal dismissed*, No. 22-3185, 2023 WL 3444873 (8th Cir. Jan. 26, 2023).

Second, plaintiffs' experts' reliance on other supposed negative control studies is also

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[73] Dr. Baccarelli appears to have arrived at his conclusion that Gustavson 2021's sibling-control analysis involved only two or three ADHD cases by erroneously applying the Norwegian Patient Registry's 2.8% ADHD diagnosis rate to the already-discordant set of 34 families. But in describing its sibling-control population, Gustavson 2021 states that "[s]iblings were discordant on exposure for 29 days or more in 380 families, and 34 of these were also discordant on the outcome." Gustavson 2021, *supra* note 25, at 5. Of those families, 30 included two children and four included three children.

unreliable because there are significant differences between women who take acetaminophen during pregnancy and women who take acetaminophen when they are not pregnant. As noted above, women who take acetaminophen during pregnancy are significantly more likely to have chronic medical conditions, mental diseases and psychiatric conditions that are potential confounding causes of the associations observed.[74] Given these discrepancies, the negative control studies relied on by plaintiffs' experts do not reliably control for genetics and are certainly no substitute for a sibling-control analysis like the one performed by Gustavson 2021.

In sum, plaintiffs' experts' causation opinions are inherently unreliable because they improperly ignore or dismiss the recognized role of genetics in ADHD. By relying on studies that fail to properly account for potential genetic confounders—while dismissing the fact that the only sibling-control study demonstrates that the association between in utero acetaminophen exposure and ADHD in children disappears when researchers control for genetics—plaintiffs' experts employ a results-oriented approach that distorts the findings in the relevant body of literature. *See Daniels-Feasel*, 2021 WL 4037820, at *8 (excluding general causation expert who "dismiss[ed] . . . [a] study that reported no statistically significant association between antidepressants and ASD after all adjustments").

B. Plaintiffs' Experts Improperly Rely On Studies That Did Not Evaluate An Association With A Clinical Diagnosis Of ADHD.

Drs. Baccarelli, Cabrera, Hollander and Louie also rely heavily on so-called "proxy" studies, and certain meta-analyses of those studies, that use various screening tools and questionnaires to measure, *inter alia*, behavior, cognition, temperament, psychomotor

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[74] *See* Taagaard 2023, *supra* note 31 (women with chronic medical disorders are more likely to use acetaminophen during pregnancy, including women with mental diseases (mental diseases aOR = 2.74, CI 95% 1.67-4.49)); Stergiakouli 2016, *supra* note 30, at 966 (finding higher rates of psychiatric illness among women who took acetaminophen during pregnancy versus women who took it postnatally (10.2% v. 8.1%, respectively)).

development, IQ, attention and language. (*See* Cabrera Am. Rep. at 149-63; *see also* Baccarelli Am. Rep. at 104-12; Hollander Rebuttal Rep. at 11-13; Louie Am. Rep. ¶¶ 69-73.) As explained in detail in the ASD *Daubert* brief, relying on screening tests to formulate a general causation opinion is scientifically unsound because mere symptoms are not reliable proxies for actual clinical diagnoses of the disorders in question (*see* ASD Mem. at 38-40). This principle applies with equal force to ADHD because having some symptoms that may be found in people with ADHD is very different from having the actual disorder. *Rochkind*, 164 A.3d at 262.

In *Rochkind*, for example, an expert opined that the plaintiff's exposure to lead paint and resulting "lead poisoning" was "'a significant contributing factor' to her neuropsychological problems, including her ADHD." *Id.* at 257. The Maryland Court of Appeals ultimately reversed a verdict in favor of the plaintiff, reasoning that the science relied on by the expert only showed that lead may cause certain symptoms that are found in ADHD (and other conditions as well), such as attention deficits and hyperactivity, but not necessarily ADHD itself. According to the court, "[a]lthough research shows that lead exposure can cause general attention deficits and hyperactivity, these lead-caused behaviors do not necessarily indicate that an individual has ADHD because these behaviors are also symptoms of a variety of other disorders and learning disabilities." *Id*. at 262. By "equating attention deficits and hyperactivity with a clinical ADHD diagnosis, [the expert] painted an inaccurate picture of the scientific research regarding lead poisoning," requiring exclusion of her opinion. *Id*.

Drs. Hollander, Cabrera and Louie generally agree that screening tools are not a valid substitute for clinical diagnoses (*see* Hollander Dep. 307:20-308:21; Cabrera Dep. 186:6-16 (agreeing that screening results are merely "informative"); *see also* Louie Dep. 71:5-12 (clinical

diagnoses are "stronger[] information")), as do the authors of the studies they cite.[75] And prior to becoming an expert in this litigation, Dr. Baccarelli—in Laue 2019—criticized non-diagnostic studies for precisely this reason, stating: "the lack of an objective, clinical measurement of neurodevelopment in these studies may have caused overestimation of the adverse effects of acetaminophen—parents of children with some symptoms may overreport those traits—leading to unnecessary concern about the safety of acetaminophen."[76]

Nonetheless, plaintiffs' experts now rely on behavioral assessment tools that imprecisely measure such disparate outcomes as "drawing scores," "gross motor development," "language delay in girls," "performance IQ" and "conduct problems" as proxies for clinical ADHD diagnoses. (*See* Cabrera Am. Rep. at 160-63; *see also* Baccarelli Am. Rep. at 157-58 (relying on studies involving "a broad spectrum of conditions and symptoms").) This is particularly troubling because some of these outcomes (e.g., child IQ or language difficulties) are not even part of an ADHD diagnosis and thus would not be part of appropriate ADHD screening. (Baccarelli Am. Rep. at 108 (noting that intelligence score "does not directly bear on ADHD" and agreeing that "behavior and intelligence are different neuropsychological constructs"); *see also* Hollander Dep. 351:5-14 (IQ is not a symptom for ASD or ADHD).)

Moreover, to the extent certain behaviors are relevant to an ADHD evaluation (e.g., compulsive behavior or attention difficulties), they are not specific to ADHD; rather, they are also associated with a host of "other psychiatric disorders, including depression, bipolar disorder,

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[75] *See, e.g.*, Vlenterie 2016, *supra* note 9, at 2006 (authors of study using the ASQ, CBCL and short-form Emotionality, Activity and Shyness Temperament Questionnaire to measure behavioral outcomes noting that "[t]he use of parent-reported behaviour outcomes can also be prone to differential misclassification and do not have simple clinical interpretation" and calling for "more objective neurocognitive and neurobehavioural measures" in future studies).

[76] Laue 2019, *supra* note 43, at 139.

ASD, anxiety disorders, oppositional defiant disorder, conduct disorder, eating disorder, and substance use disorders." (Hollander Am. Rep. at 44; *see also* Baccarelli Am. Rep. at 36 ("[D]ifferent NDDs often have shared/overlapping symptomology . . . ."); Hollander Dep. 347:21-348:15 (hyperactivity "can be a symptom in other conditions").) In addition, many of the cited studies are based on behaviors reported by a single observer (e.g., parents but not teachers or clinicians) (*see, e.g.*, Stergiakouli 2016 (maternal behavioral reports)), whereas an ADHD diagnosis requires multiple symptoms to be present in multiple different settings. And other studies relied on by plaintiffs' experts reported outcomes that explicitly failed to meet the purportedly relevant diagnostic cut-off for ADHD (*see* Avella-Garcia 2016 ("Since we did not use cut-off points to evaluate the outcomes, a strength of our study is that it links prenatal exposure to acetaminophen to ADHD and ASC symptoms in a manner that goes ***beyond*** examining only disorders, to include milder dysfunctions that are more widespread in the population.")).[77] As a result, these tests not only lack specificity with regard to ADHD, but they are also inherently over-inclusive.

The specific screening tools used by the studies relied upon by plaintiffs' experts are emblematic of this problem. For example, multiple studies[78] use the SDQ, which Dr. Hollander describes as "a valid tool for discriminating cases with ADHD from those without ADHD or with other mental health diagnoses." (Hollander Rebuttal Rep. at 26.) As noted above, however, the SDQ is intentionally sensitive and non-specific to identify a broad set of individuals who

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[77] Avella-Garcia, *Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function and Autism Spectrum Symptoms*, 45(6) Int'l J. of Epidemiol. 1987, 1993 (2016) ("Avella-Garcia 2016") (emphasis added).

[78] *See, e.g.*, Liew 2014, *supra* note 8 (cited in Baccarelli Am. Rep. at 80-81; Cabrera Am. Rep. at 141-42; Hollander Rebuttal Rep. at 13, 17; Louie Am. Rep. ¶¶ 69, 77); Thompson 2014, *supra* note 36 (cited in Baccarelli Am. Rep. at 80; Cabrera Am. Rep. at 144-45, 146-49); Stergiakouli 2016, *supra* note 30 (cited in Baccarelli Am. Rep. at 115; Baccarelli Rebuttal Rep. at 4; Cabrera Am. Rep. at 157); Tovo-Rodrigues 2018, *supra* note 8 (Baccarelli Am. Rep. at 85).

may have ADHD and need further clinical evaluation. As a consequence, the SDQ has a high false-positive rate. One study, Russell 2013, reported that the SDQ's "positive predictive value (PPV) was low at 12%, which is to be expected in a population-based sample screening for rare disorders comprising young children."[79] The FDA, too, has questioned the reliability of the SDQ as a viable research tool, noting its low predictive validity of a psychiatric diagnosis as a "limitation for research purposes."[80] And while Dr. Hollander touts the Child Behavior Checklist as a reliable proxy for ADHD diagnoses (*see* Hollander Rebuttal Rep. at 25), that scale has a positive predictive value of only 57% and has been described as merely "a useful screening instrument for ADHD"—i.e., ***not*** a substitute for an actual clinical diagnosis.[81]

The ASQ screening tool—used in Brandlistuen 2013—is similarly non-specific to ADHD, despite the experts' claims that it is a "strong" study. (*See, e.g.*, Louie Am. Rep. ¶ 71 ("assign[ing] the greatest weight" to Brandlistuen 2013 because it "employed the strongest study design"); *see also* Baccarelli Am. Rep., App. 1, at 15 (rating Brandlistuen 2013 as a "strong" study); Cabrera Am. Rep. 151-52 (citing Brandlistuen 2013 as evidence that APAP leads to negative neurodevelopmental outcomes).) As explained above, the ASQ asks parents to rate their children's communication and gross motor skills[82]—an imprecise exercise that, as noted above, prompted Dr. Baccarelli to dismiss the conclusion of another study using the same questionnaire. (*See* Baccarelli Am. Rep. at 116 (dismissing finding in Trønnes 2020 that acetaminophen does ***not*** have a negative impact on child communication, behavior or

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79 Russell 2013, *supra* note 11.

80 *See* Dkt. No. 483-1 at FDACDER000017.

81 Aebi, *Accuracy of the DSM-Oriented Attention Problem Scale of the Child Behavior Checklist in Diagnosing Attention-Deficit Hyperactivity Disorder*, 13(5) J. Atten. Disord. 454 (2010).

82 Brandlistuen 2013, *supra* note 9.

temperament as not "persuasive" because it "did not have ADHD as an endpoint and was forced to rely on less clearly defined child outcomes," such as "internalizing behavior" and "externalizing behavior").) In any event, studies relying on the ASQ have inconsistent results. For example, although Brandlistuen 2013 reports a statistically significant association between long-term acetaminophen use and communication difficulties,[83] another study using the same ASQ screening questionnaire found no statistically significant association with communication problems after adjusting for confounders.[84]

Plaintiffs' experts' reliance on several meta-analyses pooling data from non-diagnostic studies is inappropriate and unreliable for similar reasons. All but one of the meta-analyses plaintiffs' experts cite include underlying studies that did not limit the outcome being investigated to an ADHD diagnosis. Only Ricci 2023,[85] which found a weak association between prenatal acetaminophen exposure and ADHD and is cited by Drs. Baccarelli, Cabrera and Hollander (*see, e.g.*, Baccarelli Am. Rep. at 96-97; Cabrera Am. Rep. at 165-66; Hollander Rebuttal Rep. at 15), performed a subgroup analysis that was limited to studies involving diagnosed ADHD. Notably, the authors of that study acknowledge several limitations in the underlying data used in the meta-analysis, including the fact that exposures and outcomes were self-reported by caregivers, introducing bias, and that there was incomplete controlling for confounding by indication. The authors also note variability across studies in terms of what indications were measured and point out that very few studies measured parental ADHD, which increases the likelihood of residual confounding by genetic factors, as noted above.

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83 *Id.* at 1704, 1708.

84 Vlenterie 2016, *supra* note 9.

85 Ricci, *In Utero Acetaminophen Exposure and Child Neurodevelopmental Outcomes: Systematic Review and Meta-Analysis*, 37 Paediatr. Perinat. Epidemiol. 473 (2023).

In short, by "equating" ill-defined behavioral outcomes in children "with a clinical ADHD diagnosis," plaintiffs' experts "paint[] an inaccurate picture of the scientific research." *Rochkind*, 164 A.3d at 262. And even the results of the non-diagnostic studies indicate that bias and/or confounding is responsible for at least some of the observed associations.

C. Plaintiffs' Experts Improperly Rely On Cherry-Picked Outcomes From Studies With Numerous Endpoints.

Plaintiffs' causation opinions are also unreliable because they cherry-pick isolated findings from epidemiological studies that tested numerous endpoints. This raises methodological concerns for two reasons.

First, plaintiffs' experts rely only on the positive associations identified in these studies, while ignoring null or negative associations, to paint a picture of a consistent association where none exists. Federal courts regularly exclude causation opinions offered by experts who "select[] data from studies that fit with [their] ultimate opinion[s] while simultaneously ignoring data in the very same studies that do not fit with [those] opinions." *In re Zantac (Ranitidine) Prods. Liab. Litig.*, No. 20-2924, --- F. Supp. 3d ----, 2022 WL 17480906, at *139 (S.D. Fla. Dec. 6, 2022) (excluding expert who ignored data that "contradict[ed] her opinion and, at the very least, d[id] not support her opinion"), *appeal dismissed*, No. 23-10090, 2023 WL 2849068 (11th Cir. Mar. 22, 2023); *Konrick v. Exxon Mobil Corp.*, No. 14-524, 2016 WL 439361, at *10 (E.D. La. Feb. 4, 2016) (excluding expert who "[i]n several instances . . . cite[d] studies selectively, highlighting only data that support[ed] his position in a way that undermine[d] the reliability of his methodology"), *aff'd*, 670 F. App'x 222 (5th Cir. 2016) (per curiam).

Here, as noted above, nearly all of plaintiffs' causation experts cite to Liew 2014 in support of their ADHD causation opinions, with Dr. Baccarelli stating that the study "demonstrate[s] a clear dose response" between in utero acetaminophen exposure and ADHD

symptoms because "[s]tronger associations were observed with use in more than one trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes."[86] But the Liew 2014 findings relevant to dose response are inherently inconsistent. Only one combination of trimesters (the second and third) yielded a significant association (OR = 1.44, 95% CI 1.12-1.87), whereas use in the first and second trimesters (OR = 1.03) and first and third trimesters (OR = 1.23) were ***not*** associated with a statistically significant increased risk. Moreover, the association observed for use in all three trimesters combined (OR = 1.24, 95% CI 1.03-1.48) was ***lower*** than use in just the second and third trimesters and barely achieved statistical significance, suggesting that the association observed for the second and third trimesters was spurious.

In addition, Dr. Baccarelli and other plaintiffs' experts cite Tovo-Rodrigues at al. 2018 as reporting that intrauterine exposure to acetaminophen increased the odds of hyperactivity/inattention (OR = 1.42, 95% CI 1.06-1.92) in boys at age six. But the same study shows that the association was attenuated and did not reach statistical significance when participants were screened again at age eleven (OR = 1.25, 95% CI 0.95-1.65), and ***no association was observed for girls*** at either age (OR = 0.76, 95% CI 0.51-1.12 at age six; OR = 1.14, 95% CI 0.79-1.64 at age eleven). None of plaintiffs' experts provides any justification for relying on the data for boys at age six, despite the null results for boys at age eleven and for girls of any age.

Other publications cited by plaintiffs' experts as supporting their causation opinions have similarly inconsistent results. For example:

- **Vlenterie 2016**, cited by Drs. Baccarelli and Cabrera, evaluated neurobehavioral

[86] Baccarelli Am. Rep. at 80-81.

outcomes using the ASQ (psychomotor skills) and CBCL (externalizing problems, including attention). Dr. Baccarelli grades Vlenterie as a "1" or a "strong" study. While both experts note that the authors found a single significant association between acetaminophen use and motor milestone delay (*see* Baccarelli Am. Rep. at 105-06; *see* Cabrera Am. Rep. at 159-60), they gloss over the fact that neither short-term nor long-term (> 28 days) use of acetaminophen was significantly associated with other outcomes in the adjusted cohort, including ***inattention***, a core feature of ADHD.[87]

- **Parker 2020** is cited by plaintiffs' experts as evidence of an association between prenatal acetaminophen exposure and parent-reported behavioral problems. (*See* Cabrera Am. Rep. at 155-56; Baccarelli Am. Rep. at 109-10.) But plaintiffs' experts fail to grapple with the fact that the authors did not observe increases in attention-related behavior problems according to parent or teacher report.

- **Inoue 2021** is described by Dr. Baccarelli as "corroborat[ing] published associations between prenatal exposures to acetaminophen and behavioral problems" by using parent-reported and child-reported responses to the SDQ to evaluate associations between prenatal and postnatal exposure to acetaminophen and behavioral problems in children at the age of eleven years.[88] Specifically, Dr. Baccarelli cites the study as reporting that "maternal acetaminophen use during pregnancy was consistently associated with increased risks for offspring developing behavioral and emotional problems at 11 years of age, using outcome measures reported by the parent ***or*** the child."[89] But Inoue 2019 reports different results for different "behavior problems" depending on the reporter (parent versus child), with many results showing no statistically significant association with acetaminophen exposure. This includes parent reports of problems with "internalizing" (aRR = 1.09 (1.00, 1.19)), parent reports of problems with "externalizing" (aRR = 1.07 (0.99, 1.15)), parent reports of "conduct problems" (aRR = 1.05 (0.94, 1.17)), and parent reports of "peer problems" (aRR = 1.05 (0.94, 1.17)).

Plaintiffs' experts' reliance on selected findings in studies that consider numerous potential endpoints is also methodologically improper because they do not account for what is known as "multiplicity bias." As explained in defendants' Biological Plausibility brief, studies involving multiple endpoints suffer from "multiplicity" problems because there is a higher likelihood that any one statistically significant positive association is the result of chance. (*See* Bio. Plaus. Mem. at 35-36.) Specifically, "if one conducted an examination of a large number of

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87 Vlenterie 2016, *supra* note 9, at 2004.

88 Baccarelli Am. Rep. at 111-12.

89 *Id*. (emphasis added).

associations in which the true RR equals 1," i.e., no association, "on average 1 in 20 associations found to be statistically significant at a .05 level would be spurious."[90] In these circumstances, epidemiologists typically employ a correction known as the Bonferroni (or multiplicity) adjustment, which alters the acceptable confidence interval from 95% to a stricter 97.5%.[91] But neither plaintiffs' experts nor the multiple-endpoint studies on which they rely have addressed the probability of false positives introduced by multiple comparisons. For example:

- **Ji 2018** computed 144 risk ratios without adjusting for the fact that multiple comparisons were being made.
- **Ji 2020** and **Anand 2021** used the same dataset as Ji 2018 and each computed 32 different risk ratios.
- **Liew 2016(b)** reports results for 34 different comparisons, without an adjustment to address multiplicity issues.
- **Liew 2014** tested multiple different hypotheses based on exposure level and trimester of acetaminophen usage (with the study's supplemental data demonstrating that the authors calculated at least 79 hazard ratios) without conducting a multiplicity analysis.
- **Tovo-Rodrigues 2018** produced 48 different risk ratios with no controls for errors relating to multiplicity.
- **Chen 2019** produced 23 different risk ratios, many of which were not statistically significant. (*See* Section I.D, *supra*.) While plaintiffs' experts claim that various sensitivity analyses conducted by the Chen 2019 authors to "exclud[e] gestational infections and maternal mental health disorders confirmed [an] association (OR = 1.33, 95% CI 1.04-1.69),"[92] the confidence intervals for even those adjusted ratios all fall just above 1.0, exacerbating the risk that at least some of the associations observed were the result of chance.

Because these studies tested multiple—in some cases dozens—of outcomes without addressing the potential for multiplicity bias, plaintiffs' experts cannot reliably testify that the

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90 *RMSE*, at 577 n.82.

91 *See* VanderWeele & Mathur, *Some Desirable Properties Of The Bonferroni Correction: Is The Bonferroni Correction Really So Bad?*, 188(3) Am. J. Epidemiol. 617 (2019).

92 Baccarelli Am. Rep. at 86.

isolated positive associations observed in these studies actually reflect increased risks.

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In short, plaintiffs' experts attempt to manufacture a causal association between in utero acetaminophen exposure and ADHD by ignoring established genetic causes for this disorder and picking and choosing positive associations within the literature, while ignoring findings that do not support their theories. Cobbling together weak associations from cherry-picked data is not a reliable scientific method. For this reason alone, their ADHD causation opinions should be excluded under *Daubert*.

II. PLAINTIFFS' EXPERTS' BRADFORD HILL ANALYSES ARE UNRELIABLE.

Three of plaintiffs' experts—Drs. Baccarelli, Cabrera and Hollander—purport to perform Bradford Hill analyses with respect to the ADHD literature, a process that "involves examin[ing] nine 'metrics that epidemiologists use to distinguish a causal connection from a mere association.'" *Daniels-Feasel*, 2021 WL 4037820, at *6 (quoting *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795 (3d Cir. 2017)); *see also Mirena II*, 341 F. Supp. 3d at 242. For many of the same reasons discussed in defendants' ASD *Daubert* brief, these experts' Bradford Hill analyses are unreliable.

A. Plaintiffs' Experts Engage In Non-Scientific Approaches To Reach The Conclusion That There Is Strength Of Association.

Strength of association "is a necessary, or gating, factor for any Bradford Hill analysis to proceed" because "[a] strong association (large in magnitude) is more likely to represent causation than a weak association (small in magnitude)," *Mirena II*, 341 F. Supp. 3d at 242, 258, which is more likely to reflect uncontrolled confounding or bias, *LeBlanc v. Chevron USA, Inc.*, 513 F. Supp. 2d 641, 648 (E.D. La. 2007), *vacated and remanded on other non-relevant grounds*, 275 F. App'x 319 (5th Cir. 2008) (per curiam).

Dr. Baccarelli concedes that many of the studies reporting a positive association between acetaminophen exposure and an ADHD diagnosis found an association "between 1.0 and 2.0,"[93] and Dr. Cabrera acknowledges that "an odds ratio between 1 and 2 is deemed low."[94] As a result, they attempt to minimize the importance of this consideration, stating that: (1) the low risk ratios identified are as strong as other, known causal associations; (2) the associations observed may have been "dampened" by limitations in the studies; and (3) the number of studies observing a small risk increases the strength of the association. (*See, e.g.*, Baccarelli Am. Rep. at 159-60; Cabrera Am. Rep. 189-90; Hollander Rebuttal Rep. at 15.) This effort to redefine Bradford Hill's first consideration highlights the unreliability of their opinions.

While the experts are correct that some small associations have been determined to be causal in specific circumstances—such as the examples of "smoking and heart disease" or exposure to second-hand smoke and lung cancer cited by Dr. Baccarelli (Baccarelli Am. Rep. at 159)—those associations involved exceptional circumstances. With respect to second-hand smoke and cancer, for example, there was evidence of an obvious causal mechanism, clear support by analogy to smoking and cancer, and more than 50 consistent epidemiological studies from over 20 countries,[95] all of which are missing here.

Dr. Baccarelli also posits that "the magnitude of the risk in many of these studies has been dampened due to . . . the inability to directly measure acetaminophen exposure in many of the studies," which requires researchers to rely on mothers' self-reports regarding exposure.

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93 Baccarelli Am. Rep. at 159.

94 Cabrera Am. Rep. at 134, 189.

95 U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*, Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health (2004), https://www.ncbi.nlm.nih.gov/books/NBK44695/pdf/Bookshelf_NBK44695.pdf.

(Baccarelli Am. Rep. at 159; *see also* Cabrera Am. Rep. at 190 (asserting that there are "factors that bias studies towards the null, which makes the association weaker").) But this argument is backwards. If anything, inaccuracies in maternal self-reports regarding acetaminophen use during pregnancy are likely to bias study results in favor of an association. The strong genetic etiology of ADHD makes it more likely that mothers of children diagnosed with ADHD are themselves affected by the symptoms of the disorder, including anxiety, neuroticism, and impulsivity, compared to mothers of neurotypical children. This would lead to differential reporting of acetaminophen use, as anxiety is known to lead to both increased retention in longitudinal studies[96] and greater recall and reporting of past events.[97] As the authors of Masarwa 2020,[98] a meta-analysis on which Dr. Baccarelli relies, recognize, "a healthy mother who experienced an uneventful pregnancy will be less likely to report medication use during and after pregnancy than a mother with co-morbidities and an eventful pregnancy." Thus, the limitations identified by plaintiffs' experts are more likely to have resulted in over-estimates of any association between prenatal acetaminophen exposure and the development of ADHD.

Finally, Drs. Baccarelli and Hollander take the position that "the number of studies that have consistently found a statistically significant association weighs heavily in support of this factor."[99] As explained in the ASD *Daubert* brief, this contention erroneously conflates strength

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[96] Dupuis, *Mental Disorders, Attrition at Follow-Up, and Questionnaire Non-Completion in Epidemiologic Research*, 28 Int'l J. Methods Psychiatr. Res. 1 (2019); de Graaf, *Psychiatric and Sociodemographic Predictors of Attrition in a Longitudinal Study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS)*, 152(11) Am. J. Epidemiol. 1039 (2000), https://doi.org/10.1093/aje/152.11.1039.

[97] Bekkhus, *Re-Examining the Link Between Prenatal Maternal Anxiety and Child Emotional Difficulties, Using a Sibling Design*, 47(1) Int'l J. Epidemiol. 156 (2018).

[98] Masarwa, *Acetaminophen Use During Pregnancy and the Risk of Attention Deficit Hyperactivity Disorder: A Causal Association or Bias?*, 34(3) Paediatr. Perinat. Epidemiol. 309, 314 (2020).

[99] Baccarelli Am. Rep. at 159; *see also* Hollander Rebuttal Rep. at 15 (asserting that "[i]mportantly, the association between APAP exposure and . . . ADHD has been found consistently in meta-analyses and systematic reviews," supporting a finding of a sufficiently strong association).

of association with consistency, which are analytically distinct. (ASD Mem. at 51.) In any event, the ADHD studies are far from consistent, as set forth below.

For all of these reasons, Drs. Baccarelli, Cabrera and Hollander do not apply a reliable methodology in determining that the "strength criterion is satisfied."[100]

B. Drs. Baccarelli, Cabrera And Hollander Pretend That An Inconsistent Body Of Literature Is Consistent.

Dr. Baccarelli claims (contrary to the FDA) that the "consistency element is strongly satisfied here" because "[t]here are at least ten (10) studies showing a statistically significant association between prenatal acetaminophen use and ADHD."[101] But this oversimplification of the science ignores the critical fact that Gustavson 2021 is one of those 10 studies—and, after finding a statistically significant association, it determined, using a sibling analysis, that the association ***was not significant*** when properly controlling for genetic factors. The fact that one of the largest, most recent and best designed diagnostic studies did not report a statistically significant association when controlling for genetics puts the lie to plaintiffs' experts' claim that the existing science demonstrates a consistent association across study designs. *See Daniels-Feasel*, 2021 WL 4037820, at *9 (consistency factor not met where expert "cherry-pick[ed]" data and "fail[ed] to note" studies with contrary findings); *see also In re Zoloft*, 858 F.3d at 799-800 (consistency not met where expert "[c]laim[ed] a consistent result without meaningfully addressing" studies supporting "no association").

Plaintiffs' experts' insistence that the science is consistent is also belied by Dr. Cabrera's own admission that the "association between prenatal APAP exposure and adverse

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100 Baccarelli Am. Rep. at 160; *see also* Cabrera Am. Rep. at 190-91; Hollander Am. Rep. at 16.

101 Baccarelli Am. Rep. at 161-62.

neurodevelopmental outcomes in children . . . is not consistent across all studies, and some studies did not find significant associations or found mixed results."[102] Indeed, even those studies that report a statistically significant increased risk are inconsistent with one another. For example, Liew 2014 and Ystrom 2017 both analyzed rates of ADHD/HKD diagnosis according to maternal acetaminophen use by trimester, and the adjusted results were inconsistent:

- ***Liew 2014*** reported a statistically significant association for exposure in the first trimester only (HR = 1.35, 95% CI 1.07-1.72), while Ystrom 2017 did not (HR = 1.12, 95% CI 0.94-1.32).
- ***Ystrom 2017*** reported a statistically significant association for exposure in the first and second trimesters combined (HR = 1.21, 95% CI 1.06-1.39), while Liew 2014 did not (HR = 1.31, 95% CI 0.93-1.85).
- ***Liew 2014*** reported a statistically significant association for exposure in the first and third trimesters combined (HR = 1.41, 95% CI 1.08-1.84), while Ystrom 2017 did not (HR = 1.34, 95% CI 0.77-2.34).

In addition, both Liew 2014 and Ystrom 2017, which reported no statistically significant association between acetaminophen use in the third trimester and the development of ADHD, are arguably inconsistent with the statistically significant results from Ji 2018 and Ji 2020, which measured maternal acetaminophen levels shortly before or during labor and therefore would have captured third trimester use.

C. Drs. Baccarelli, Cabrera And Hollander Downplay The Specificity Requirement Without Any Scientific Basis.

Drs. Baccarelli, Cabrera and Hollander expressly concede that the association between acetaminophen exposure and ADHD is not specific, but take the position that specificity is essentially irrelevant to the causation inquiry. As explained in defendants' ASD *Daubert* brief, this argument is baseless. (ASD Mem. at 54-55.) Rather, courts have recognized that the degree

[102] Cabrera Am. Rep. at 160.

of specificity of an alleged association remains highly relevant because "the vast majority of agents do not cause a wide variety of effects." *Davis v. McKesson Corp.*, No. 18-1157, 2019 WL 3532179, at *34 (D. Ariz. Aug. 2, 2019) (citation omitted).

D. Drs. Baccarelli, Cabrera And Hollander Lack Reliable Evidence Of A Dose Response.

Biological gradient, the next Bradford Hill criterion, asks whether "a dose-response relationship has been established, i.e., does the magnitude of the response increase as the magnitude of the dose increases?" *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001). This consideration is essential because "[t]he toxicity of any substance depends critically on the dose to which a human being is exposed and for what duration." *Id.* at 168-69, 188 (excluding general causation expert who cited literature in which "[f]ew, if any, dose-response relationships were reported"); *see also, e.g.*, *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1242 (11th Cir. 2005) (dose response is considered by some to be the "single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect") (citation omitted). As explained below, Drs. Baccarelli, Cabrera and Hollander misrepresent the scientific literature on the fundamental question of dose response.

Drs. Baccarelli and Hollander claim that Baker 2020, Ji 2020, Ystrom 2017, Liew 2016, Avella-Garcia 2016 and Liew 2014 all "assessed a dose response for ADHD" and found "evidence of a dose-response gradient of increased risk with increasing exposure." (Baccarelli Am. Rep. at 163; *see also* Hollander Rebuttal Rep. at 17-19 (citing the same studies as supportive of coherence).)[103] But this assertion vastly overstates both the strength of those

[103] Dr. Baccarelli's citation to Baker 2022 was likely a typo given that Baker 2022 does not purport to find a dose-response relationship, while Baker 2020 (cited by Dr. Hollander) does. *See also* Dep. of Andrea Baccarelli ("Baccarelli Dep.") 423:21-23, Aug. 14, 2023 (Ex. 3) ("So [Baker 2022] has very little—very little to do with what we are discussing today.").) Dr. Baccarelli often conflates the two throughout his report. *See* Baccarelli Dep. 40:14-

studies and their actual findings. As noted above, Baker 2020 does not support a dose-response relationship. Although the authors examine the purported relationship between "acetaminophen detected ***in meconium***" and ADHD, they explicitly note that they did ***not*** "correlate maternal acetaminophen use with acetaminophen concentrations in meconium"—i.e., the authors did not link the level of acetaminophen in meconium with the amount of acetaminophen taken by the mothers. Nor do Ji 2020 and Ystrom 2017 provide persuasive evidence of a dose-response trend. Like Baker 2020, Ji 2020 lacked any method to calculate the dose of acetaminophen taken by the subjects' mothers (and Ystrom 2017 only inquired about the number of days on which subjects' mothers used acetaminophen during pregnancy, not the dose consumed). Moreover, as explained above, both studies failed to control for a number of significant confounders that have been shown to be associated with the risk of developing ADHD.[104]

Further, Liew 2014 does not support a dose response because only one combination of trimesters (second and third) yielded a significant association, and use in all three trimesters resulted in a ***lower*** association than use in just the second and third trimesters, which is the opposite of a dose response.[105] In addition, Liew 2014 calculated different hazard ratios based on the number of weeks of reported acetaminophen exposure——and the results undermine plaintiffs' experts' finding that there is a dose response. While the association between acetaminophen use and prescriptions for ADHD medications increased from adjusted HR 1.18 (95% CI 1.00-1.40) at one week of exposure to an adjusted HR 1.49 (95% CI 1.15-1.93) at 6-10 weeks of exposure, the association ***decreased*** for longer exposures to adjusted HR 1.24 (95% CI

17 ("I think I wrote Baker 2022 a few times when I meant Baker 2020 . . . .").

104 *See supra* Section I.A.1, I.A.2.

105 Liew 2014, *supra* note 8.

0.94-1.65) at 11-20 weeks of exposure. Similarly, although the adjusted HR between acetaminophen use and parent-reported ADHD-like behaviors on the SDQ was 0.95 (95% CI 0.69-1.14) at one week and 1.30 (95% CI 1.99-1.70) at 6-10 weeks of exposure, it dropped to 1.09 (95% CI 0.81-1.47) at 11-20 weeks. This same lack of dose-response can be seen in hospital-diagnosed HKD as well because the association ***decreased*** from an adjusted HR of 1.30 (95% CI 1.05-1.61) at one week of use to an adjusted HR of 1.19 (95% CI 0.95-1.48) for 2-5 weeks of use. And Chen 2019—ignored by Drs. Baccarelli and Hollander in their discussions of biological gradient—found that cumulative doses of acetaminophen calculated by regression analysis were not related to increased ADHD risk (second trimester OR = 1.13, 95% CI 0.76-1.69; both first and second trimesters OR = 0.98, 95% CI 0.50-1.91), leading the authors to conclude that their study showed ***no*** "dose-dependent relationship between prenatal acetaminophen use and the offspring's ADHD risk."[106]

As to the remaining studies, Avella-Garcia 2016 does not support a dose-response relationship because there was no precision in ascertainment of dose; instead, participants were categorized based on never use, sporadic use (defined as "any dose in one or two trimesters") or persistent use (defined as "use of any dose in all three trimesters").[107] Accordingly, that study shows, at best, a purported relationship based on when acetaminophen was taken during pregnancy, not how the actual dosage of acetaminophen affected adverse outcomes. And the results of Liew 2016 fail to tip the scale since, while the authors note a "dose-response-***like*** relation," they also conceded that their findings with respect to dose response were limited

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106 Chen 2019, *supra* note 55, at e3-e4.

107 Avella-Garcia 2016, *supra* note 77.

because "[m]any women (***>80%***) did not recall the[ir] exact number or doses of paracetamol."[108]

Dr. Cabrera's cursory analysis similarly does not support his conclusion that "[t]he biological gradient criterion is supported." (Cabrera Am. Rep. at 191.) Dr. Cabrera concedes that the "[m]eta-analyses did not explicitly report a dose-response relationship between APAP exposure levels and the risk of ADHD." (*Id.*) Moreover, Dr. Cabrera seemingly relies on two of the same flawed studies as Drs. Baccarelli and Hollander (Baker 2020 and Ji 2020), vaguely noting that "[t]wo studies looked at APAP in meconium, one supporting a dose-response interaction between APAP and ADHD" and that "[a]nother study looked at cord blood and supported a dose-response interaction." (*Id.*) Nor does Dr. Cabrera explain how any conclusions can be drawn from studies of meconium in light of the limitation expressly acknowledged in Baker 2020 that no work has been done to "correlate maternal acetaminophen use with acetaminophen concentrations in meconium."

Accordingly, plaintiffs' experts lack a reliable basis for their opinions on the biological gradient criterion.

E. Drs. Baccarelli, Cabrera And Hollander Do Not Offer Reliable Opinions About Biological Plausibility.

Plaintiffs' experts' opinions regarding biological plausibility are unreliable and inadmissible for all the reasons set forth in defendants' Biological Plausibility brief and in defendants' ASD *Daubert* brief. As a threshold matter, scientists do not understand the anatomical or biomechanical mechanism that gives rise to ADHD. *See Mirena II*, 341 F. Supp. 3d at 285 (expert must explain "the threshold issue of what [the disease] is and how this

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[108] Liew, *Paracetamol Use During Pregnancy and Attention and Executive Function in Offspring at Age 5 Years*, 45 Int'l J. of Epidemiol. 2009, 2013, 2016 (2016) (emphases added).

condition comes about"). Because none of plaintiffs' experts has identified the actual physiological processes that cause the development of ADHD (or when in pregnancy they occur), they cannot possibly demonstrate any "plausible" mechanism by which acetaminophen leads to those unknown processes. Moreover, even if it were theoretically possible to identify an environmental cause for ADHD, plaintiffs' experts have not reliably done so here because: (1) their opinions are based on cherry-picking favorable studies, while ignoring those that reach contrary results; and (2) that cherry-picked literature shows only scattered neurochemical changes that the experts cannot link to ADHD. At most, plaintiffs' experts have generated hypotheses about how acetaminophen exposure might theoretically cause ADHD. Rule 702 requires more. *See In re Accutane Prods. Liab. Litig.*, 511 F. Supp. 2d 1288, 1296 (M.D. Fla. 2007) (excluding expert with mechanistic hypotheses that was "merely plausible, not proven").

F. Drs. Baccarelli, Cabrera And Hollander's Opinions That The Literature Is Coherent Is Unsupported And Incorrect.

Coherence means that "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease."[109] Dr. Cabrera considers this criterion to be satisfied in large part because "[i]f APAP exposure at therapeutic doses can generate sufficient oxidative stress to result in neurodevelopmental toxicity, then we expect that it would also cause parallel damage on reproductive development and DNA oxidation damage," and "[t]he association between APAP exposure and ASD and ADHD is coherent with the existing knowledge of oxidative stress and potential for hepatotoxicity and neurotoxicity with APAP exposures." (Cabrera Am. Rep. at 192-93.) But as explained more fully in the Biological Plausibility brief, plaintiffs' experts have

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[109] Hill, *The Environment and Disease: Association or Causation?* 295, 298 (1965).

vastly overstated the science linking both therapeutic doses of acetaminophen to those outcomes and those outcomes to the development of ADHD.[110]

In addition, nearly every study Dr. Baccarelli cites as evidence that the science is coherent is unrelated to ADHD. Two of the four studies Dr. Baccarelli cites supporting his claim that "a causal association is coherent with the sudden and significant rise in the rates of NDDs seen over the past several decades," Bauer & Kriebel 2013 and Becker & Schultz 2010, examine proposed links between "[a] country's average prenatal paracetamol consumption" and "its ***autism/ASD*** prevalence"[111] and "acetaminophen's link to ***asthma*** and . . . immune anomalies in ***autism***."[112] This says nothing about ADHD. Another study, Shaw 2013, primarily studied the link between acetaminophen and autism, with the authors explicitly acknowledging that the data regarding the overall incidence of ADHD "are not available to the same depth as the [incidence] data for autism and asthma."[113] And while the authors of Liew 2014 do state that an association "'might explain some of the increasing incidence in HDK/ADHD' over the past decades" (Baccarelli Am. Rep. at 165), Dr. Baccarelli conveniently omits the immediately-following, qualifying statement from the authors that "further studies are needed" to make that claim.[114] Dr. Hollander's argument for coherence is even weaker than Dr. Baccarelli's, as he relies entirely on

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[110] Alemany, *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 Euro. J. Epidemiol. 993 (2021), cited by Dr. Baccarelli in support of coherence, similarly relied on these flawed findings regarding the proposed biological mechanisms.

[111] Bauer & Kriebel, *Prenatal and Perinatal Analgesic Exposure and Autism: An Ecological Link*, 12(41) Environmental Health 1, 4 (2013) (emphasis added).

[112] Becker & Schultz, *Similarities in Features of Autism and Asthma and a Possible Link to Acetaminophen Use*, 74 Med. Hypotheses 7, 7 (2010) ("Becker & Schultz 2010") (emphases added).

[113] Shaw, *Evidence that Increased Acetaminophen use in Genetically Vulnerable Children Appears to be a Major Cause of the Epidemics of Autism, Attention Deficit with Hyperactivity, and Asthma*, 2(1) J. Restor. Med. 14, 17 (2013).

[114] Liew 2014, *supra* note 8, at 319.

the Becker & Schultz 2010 study, which, as explained above, only examined the purported association between acetaminophen and autism/asthma.[115]

Acetaminophen as a causal agent of ADHD is also incoherent with current understandings of the disorder and acetaminophen usage given that the prevalence of ADHD does not line up with differing worldwide use of acetaminophen during pregnancy. If acetaminophen use were causally related to ADHD, one would expect to see higher rates of ADHD in countries where more pregnant women report taking acetaminophen. Statistics do not bear that out. As plaintiffs' experts concede, the prevalence of ADHD does not differ by country,[116] but the reported rates of acetaminophen use during pregnancy do. One 2021 study, for example, found that acetaminophen use during pregnancy differs dramatically by country, with countries like the United States reporting use anywhere from 55.8%-65.5%, compared to countries like Denmark and Saudi Arabia, which reported use at 39.9% and 4%, respectively.[117] In other words, the use of acetaminophen during pregnancy varies dramatically by geography, with some countries reporting usage rates 20 or more percentage points higher than other countries, without any corresponding difference in the rates of ADHD.

Accordingly, plaintiffs' experts' belief that coherence is satisfied is entirely unsupported.

G. The Opinions Offered By Drs. Baccarelli, Cabrera And Hollander On Temporality Are Speculative.

As explained in defendants' ASD *Daubert* brief, plaintiffs' experts lack a reliable basis

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115 Becker & Schultz 2010, *supra* note 112.

116 *See* Hollander Am. Rep. at 39 ("Point prevalence rates for ADHD are similar across the globe, including North America, Europe, Oceania, South America, Asia, Africa, and the Middle East. . . . Prevalence rates do not differ between North America and Europe . . . .").

117 Zafeiri, *Over-the-Counter Analgesics During Pregnancy: A Comprehensive Review of Global Prevalence and Offspring Safety*, 27(1) Hum. Reprod. Update 67, 69 (2021).

on which to opine that there is a temporal relationship between in utero exposure to acetaminophen and ADHD, because Drs. Baccarelli, Cabrera and Hollander fundamentally disagree on when the most vulnerable period for fetal development occurs, making it impossible for them to know whether maternal exposure to acetaminophen in various studies actually preceded the biological changes that lead to ADHD. (*See* ASD Mem. at 60.)

H. Plaintiffs' Experts' Opinions On Analogy And Experiment Are Illogical And Unsupported.

The assertions by Drs. Baccarelli, Cabrera and Hollander that the "analogy" and "experiment" considerations support a finding of causation with respect to in utero acetaminophen exposure and the development of ADHD are unreliable for the reasons set forth in defendants' ASD *Daubert* brief and Biological Plausibility brief. With respect to analogy, plaintiffs' experts attempt to analogize acetaminophen to valproic acid, which they claim similarly increases oxidative stress levels, but they offer no scientific basis for such a comparison. (*See* ASD Mem. at 60-61.) And with respect to experiment, plaintiffs' experts agree that randomized clinical trials—the primary type of experimental evidence—have not been conducted on acetaminophen and ADHD, and the other experimental evidence they point to (i.e., animal and in vitro studies) does not support a finding of causation, as further elaborated in the next section. (*See also* ASD Mem. at 61-66; Bio. Plaus. Mem. at 18-21.)

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Because the Bradford Hill analyses offered by Drs. Baccarelli, Cabrera and Hollander are unreliable at virtually every step, those opinions should be excluded under *Daubert*.

III. PLAINTIFFS' EXPERTS CANNOT FILL ANALYTICAL GAPS IN THEIR OPINIONS WITH ANIMAL STUDIES.

"[E]xpert opinions relying on animal studies may only be admitted where 'the gap between what [they] reasonably imply and more definitive scientific proof of causality is not too

great,' and the 'inferences are of a kind that physicians and scientists reasonably make from good but inconclusive science.'" *Daniels-Feasel*, 2021 WL 4037820, at *13-14 (citation omitted). Here, Drs. Cabrera and Pearson cannot bridge the analytical gap in plaintiffs' theories with animal study evidence because: (1) the behavioral assays employed by animal researchers are too simplistic to accurately model or predict ADHD in humans; (2) the studies on which they rely examine outcomes wholly unrelated to an ADHD diagnosis in humans; and (3) the studies come to entirely inconsistent results even when examining arguably relevant behavior.

First, the animal studies cited by plaintiffs' experts do not reliably support their causation opinions because rodent behavior has little, if any, correlation to the complex human behaviors necessary for a diagnosis of ADHD. As explained by the authors of Philippot 2017, on which both Drs. Cabrera and Pearson rely, "rodent models cannot fully recapitulate complex human neuropsychiatric disorders," including ADHD.[118] For example, studies cannot examine whether rodents have "difficulty organizing tasks and activities," fail to "give close attention to details," make "careless mistakes in schoolwork" or have "difficulty waiting [their] turn."[119] As Dr. Cabrera plainly put it, "you can't diagnose a mouse with ADHD." (Cabrera Dep. 192:4-12; *see also* Dep. of Brandon Pearson ("Pearson Dep.") 76:19-21, Aug. 11, 2023 (Ex. 17) ("We're not measuring ADHD in these animals. They are animals, not people.").)

In short, concluding that certain exhibited behaviors in rodents after they are exposed to acetaminophen is evidence that acetaminophen causes a complex disorder like ADHD in humans requires "giant analytical leaps between the data and the opinions proffered." *Caraker v. Sandoz*

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[118] Philippot, *Adult Neurobehavioral Alterations in Male and Female Mice Following Developmental Exposure to Paracetamol (Acetaminophen): Characterization of a Critical Period*, 37(10) J. Appl. Toxicol. 117 (2017).

[119] *Id.*

Pharms. Corp., 188 F. Supp. 2d 1026, 1036-37 (S.D. Ill. 2001). That is not proper under *Daubert*.

Second, many of the studies relied on by Drs. Cabrera and Pearson are not even relevant to plaintiffs' theory that acetaminophen increases the risk of ADHD because, as explained in the ASD *Daubert* brief, they examined outcomes that have nothing to do with neurodevelopment and/or involved very different levels and types of exposures.

For example, a number of the studies cited by Drs. Cabrera and Pearson examined the effect of acetaminophen exposure on rodent sexual behavior (*see* Cabrera Am. Rep. at 85, 125 (discussing Hay-Schmidt 2017); *see also* Pearson Rep. at 106-07), or dosed adult mice with acetaminophen (*see* Cabrera Am. Rep. at 126-27 (discussing Ishida 2017, Gould 2012 and Zhao 2017)), which is very different from in utero exposure (*see* ASD Mem. at 64-65). Because such studies are too "far-removed" from plaintiffs' theory of general causation, they do not provide valid support for their experts' opinions. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144-46 (1997) (rejecting extrapolation from animal studies involving significant amounts of exposure "far-removed" from the circumstances of the plaintiff's exposure to PCBs).

Third, the studies that examine behaviors arguably relevant to an ADHD diagnosis do not present consistent results. For example, while Dr. Cabrera claims that a number of studies illustrate how "[e]xposing mice and rats during development to APAP . . . causes significantly altered learning, locomotor, and social behavior consistent with . . . ADHD" by demonstrating results such as "clear evidence of locomotor activity" or "ambulation" (Cabrera Am. Rep. at 126-27), he ignores that other findings in the same studies are to the contrary. For example, Saeedan 2018 and Baker 2023—which Dr. Cabrera cites to support his opinion that perinatal exposure to acetaminophen results in "impair[ed] learning or social behavior" (Cabrera Am. Rep. at 126-

27)—actually found ***reduced*** locomotor activity in the open field assay.[120] Notably, Dr. Baker refused to accept Dr. Pearson's suggested title for what became Baker 2023 ("Developmental acetaminophen exposure produces ADHD-like behavioral alterations in mice), going so far as to state, "I don't think we can say ADHD-like" behaviors. (*See* Pearson Dep. 57:4-10, 57:14-58:6; *see also* Pearson Dep. Ex. 69 (Ex. 20).) Further, while Dr. Cabrera relies on Klein 2020, Saad 2016 and Harshaw 2022 (*see* Cabrera Am. Rep. at 126-27), each of those studies found no change in locomotor activity in the open field assay. And although Dr. Pearson asserts that "increased number of arm entries" in a Y-maze test "indicates hyperactivity" in rodents (Pearson Rep. at 45), three of the studies Dr. Pearson relies on—Klein 2020, Herrington 2022, and Baker 2023[121]—found no difference in the similarly elevated maze test results for acetaminophen-exposed and non-exposed mice (*see* Pearson Rep. at 94, 98-99, 112-14), while another study he cites—Saeedan 2018[122] (*see* Pearson Rep. at 91-92)—actually found a ***decrease*** in such purported animal "hyperactivity."

Dr. Pearson tries to explain away these inconsistent results in his rebuttal report by claiming that "findings that are in the opposite direction of the prediction nevertheless demonstrate that the sensitive neurobehavioral system is perturbed by the developmental exposure to the medication" and that "[a] directional concordance is not required." (Pearson Rebuttal Rep. at 4; *see also* Pearson Dep. 76:8-21.) This position contradicts Dr. Pearson's own

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[120] Saeedan, *Effect of Early Natal Supplementation of Paracetamol on Attenuation of Exotoxin/Endotoxin Induced Pyrexia and Precipitation of Autistic Like Features in Albino Rats*, 26 Inflammopharmacology 951 (2018) ("Saeedan 2018"); Baker, *Sex-Specific Neurobehavioral and Prefrontal Cortex Gene Expression Alterations Following Developmental Acetaminophen Exposure in Mice*, 177 Neurobiol. Dis. 1 (2023) ("Baker 2023").

[121] Klein, *Gestational Exposure to Paracetamol in Rats Induces Neurofunctional Alterations in the Progeny*, 77 Neurotoxicol. Teratol. 1 (2020); Herrington, *Elevated Ghrelin Alters the Behavioral Effects of Perinatal Acetaminophen Exposure in Rats*, 64(3) Dev. Psychobiol. 1 (2022); Baker 2023, *supra* note 120.

[122] Saeedan 2018, *supra* note 120.

report. In explaining the open field assay, Dr. Pearson specifically notes that "[i]ncreased"—***not*** decreased—"activity in the open field apparatus may indicate hyperactivity which is linked with ADHD in humans." (Pearson Rep. at 44.) Similarly, Dr. Pearson explains that, in the Y-maze test, "[a]n ***increased*** number of arm entries indicates hyperactivity (ADHD factor II)." (*Id.* at 45 (emphasis added).) Dr. Pearson's sudden about-face on this issue further underscores his rudderless and results-oriented approach to interpreting the animal studies.

In short, plaintiffs' experts cannot reliably fill the gaps in the human science with animal studies, and their efforts to do so are thus inadmissible under *Daubert*.

IV. DR. HOLLANDER'S OPINIONS SHOULD BE EXCLUDED BECAUSE HE LACKS THE REQUISITE FAMILIARITY WITH BOTH THE SCIENCE AND HIS OWN OPINIONS.

Dr. Hollander's opinions are separately inadmissible because his "deposition testimony reveal[s] critical gaps in h[is] knowledge" of the studies he purportedly relies on and highlights his lack of familiarity with his own report. *Caruso v. Bon Secours Charity Health Sys. Inc.*, No. 14-4447, 2016 WL 8711396, at *6 (S.D.N.Y. Aug. 5, 2016), *aff'd*, 703 F. App'x 31 (2d Cir. 2017); *see also In re Vioxx Prods. Liab. Litig.*, No. 05-4046, 2005 WL 3541045, at *3 (E.D. La. Dec. 6, 2005) (excluding expert who "displayed a fundamental lack of understanding of the relevant scientific literature").

Dr. Hollander's testimony is replete with examples illustrating his lack of familiarity with the studies on which he claims to have relied in his report. For example, when questioned about the authors' methods in the meta-analysis Masarwa 2018—a study that Dr. Hollander has cited repeatedly (*see* Hollander Am. Rep., Materials Considered at 56; Hollander Rebuttal Rep. at 15-16)—Dr. Hollander struggled to answer basic questions about the study (*see* Hollander Dep. 196:14-198:2, 199:11-200:12, 200:13-201:11) and was ultimately forced to refer to the "summary table of the different individual articles that was prepared by [Dr.] Baccarelli,"

plaintiffs' epidemiology expert, to determine whether the Masarwa 2018 authors "controlled for genetic factors" (Hollander Dep. 194:6-17). Dr. Hollander also repeatedly contradicted the Masarwa 2018 authors' own statements that the results of their analysis "indicated significant heterogeneity" (Hollander Dep. 208:13-209:12), asserting to the contrary that "there's not a lot of heterogeneity" in the study (Hollander Dep. 204:3-14).

Dr. Hollander also demonstrated a complete lack of understanding of the basic epidemiological principles necessary to interpret the results of the studies on which he purportedly relied, claiming that it was "not necessarily" the case that for "a point estimate to be statistically significant, the confidence interval has to be entirely over 1." (*Compare* Hollander Dep. 141:16-19, *with RMSE*, at 581 ("[T]he boundaries of the confidence interval with alpha set at .05 encompass a relative risk of 1.0, and the result would be said to be not statistically significant at the .05 level.") and ASD Mem. at 8-9 & n.16.) Put simply, Dr. Hollander's inability "to explain or recount the results and implications of the numerous tests and studies" he cites demonstrates the inadequacy of his review. *In re Vioxx*, 2005 WL 3541045, at *3; *see also Pac. Life Ins. Co. v. Bank of N.Y. Mellon*, 571 F. Supp. 3d 106, 117 (S.D.N.Y. 2021) (excluding opinion of expert whose deposition testimony illustrated that he did not conduct an "independent analysis" of the assumptions underlying his opinions).

In addition, as detailed in Defendants' ASD *Daubert* brief, Dr. Hollander lacked basic familiarity with ***his own report***, at his deposition, disclaiming reliance on studies specifically discussed in his report and testifying that he disagreed with statements quoted to him directly from it. (*See* ASD Mem. at 24-25.) These confused and contradictory statements strongly suggest that he was not the primary drafter of his report and further highlight the unreliability of his opinions. *See Richman v. Respironics, Inc.*, No. 08-9407, 2012 WL 13102265, at *13

(S.D.N.Y. Mar. 13, 2012) (excluding expert whose opinions "contradict[ed] his own deposition testimony"). For these reasons, too, Dr. Hollander's opinions should be excluded.

CONCLUSION

For the reasons set forth above, the Court should exclude the opinions offered by Drs. Baccarelli, Cabrera, Hollander, Louie and Pearson that in utero exposure to acetaminophen is capable of causing, or increases the risk of, ADHD.

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