UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation	22MD3043 (DLC) 22MC3043 (DLC) OPINION AND ORDER

APPEARANCES:

For plaintiffs:
Keller Postman LLC
Ashley C. Keller
Ashley Barriere
150 N. Riverside Plaza, Ste. 4100
Chicago, IL 60606

Bernstein Liebhard LLP
Daniel C. Burke
10 East 40th St
New York, NY 10016

Wagstaff & Cartmell, LLP
Lindsey Scarcello
4740 Grand Avenue, Ste 300
Kansas City, MO 64112

For defendants:
Barnes & Thornburg LLP
Kristin L. Richer
Jessica L. Brennan
2029 Century Park East, Suite 300
Los Angeles, CA 90067

King & Spalding LLP
Kristen R. Fournier
1185 Avenue of the Americas, 34th Floor
New York, New York 10036

Skadden, Arps, Slate, Meagher & Flom LLP
Jessica Davidson
One Manhattan West
New York, NY 10001

DENISE COTE, District Judge:

This Opinion addresses the Rule 702 motion filed on March 29, 2024 by the defendants in this multidistrict products liability litigation ("MDL"). A prior Opinion excluded the testimony of the five expert witnesses on whom the plaintiffs had previously relied, each of whom opined that prenatal exposure to acetaminophen causes attention deficit hyperactivity disorder ("ADHD") and autism spectrum disorder ("ASD"). In re

Acetaminophen - ASD-ADHD Prods. Liab. Litig., --- F. Supp. 3d. ---, No. 22md3043 (DLC), 2023 WL 8711617 (S.D.N.Y. Dec. 18, 2023) ("First Daubert Opinion").

Plaintiffs in more recently filed actions rely on another expert, Dr. Roberta Ness. Dr. Ness opines that prenatal exposure to acetaminophen causes ADHD. For the following reasons, the defendants' motion to preclude the testimony of Dr. Ness is granted.

Procedural Background

Familiarity with prior Opinions in this MDL, particularly the First Daubert Opinion, is assumed. This Opinion summarizes only those facts relevant to this motion. Nevertheless, much of the factual and procedural background in this Opinion is drawn from the First Daubert Opinion.

I. MDL Consolidation, Motions to Dismiss

This litigation began in 2022, when plaintiffs -- children, parents, and guardians who alleged injuries from the development in children of ASD and ADHD due to a mother's prenatal use of acetaminophen -- began to file products liability lawsuits in federal courts. Plaintiffs sued the manufacturer of Tylenol (Johnson & Johnson Consumer Inc.) and retailers of store-branded acetaminophen products, alleging that the defendants' labeling

practices for acetaminophen were deficient under various state laws.

In October of 2022, the Judicial Panel on Multidistrict Litigation consolidated plaintiffs' cases and transferred the cases to this Court under 28 U.S.C. § 1407. This MDL has included hundreds of cases. Motions to dismiss individual actions on the ground of preemption were denied in November 2022 and April 2023.[1] Additional motions to dismiss were addressed in April and May of 2023.[2]

II. Proposed Label Change & FDA Involvement

On April 7, 2023, in response to a request from the Court, the plaintiffs submitted proposed language for a label change for the acetaminophen products then at issue in this litigation ("Plaintiffs' Proposed Warning"). The Plaintiffs' Proposed Warning was:

> **Autism/ADHD**: Some studies show that frequent use of this product during pregnancy may increase your child's risk of autism and attention deficit hyperactivity disorder. If you use this product during pregnancy to treat your pain and/or fever, use

[1] In re Acetaminophen – ASD-ADHD Prods. Liab. Litig., No 22md3043 (DLC), 2022 WL 17348351 (S.D.N.Y. Nov. 14, 2022) ("Preemption Opinion I"); In re Acetaminophen – ASD-ADHD Pros. Liab. Litig., No 22md3043 (DLC), 2023 WL 3026412 (S.D.N.Y. Apr. 20, 2023).

[2] In re Acetaminophen – ASD-ADHD Prods. Liab. Litig., No. 22md3043 (DLC), 2023 WL 3045802 (S.D.N.Y. Apr. 21, 2023); 2023 WL 3126589 (S.D.N.Y. Apr. 27, 2023); 2023 WL 3126636 (S.D.N.Y. Apr. 27, 2023); 2023 WL 3162623 (S.D.N.Y. Apr. 28, 2023); and 2023 WL 3467057 (S.D.N.Y. May 15, 2023).

> the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Because this MDL raises important issues related to public health and drug safety for pregnant women and their offspring, the Court invited the United States, including the Food and Drug Administration ("FDA"), to submit its views on the Plaintiffs' Proposed Warning. On September 8, as the parties were about to file their initial Rule 702 motions, the United States responded to the invitation. The Government declined to submit a Statement of Interest but noted in its letter the FDA's independent 2023 conclusion (discussed in more detail infra) that the scientific evidence on this topic is as of yet "unable to support a determination of causality."

III. General Causation Discovery

All fifty states require some evidence of general causation in products liability cases involving medical issues. See In re Mirena IUS Levonorgestrel-Related Products Liability Litigation, 982 F.3d 113, 124 (2d. Cir. 2020) ("Mirena II"). At a pretrial conference on December 2, 2022, the Court proposed, and the parties agreed, to conduct discovery related to general causation first; if the plaintiffs' experts on the issue of general causation survived Rule 702 motions, the remainder of discovery would proceed. The initial Rule 702 motions were fully submitted on October 20, 2023. Oral argument on the

defendants' motions to strike the plaintiffs' expert reports was held on December 7, 2023.[3]

On December 18, 2023, the First Daubert Opinion was issued. It excluded the proposed testimony of five experts: Drs. Andrea Baccarelli, Robert Cabrera, Eric Hollander, Brandon Pearson, and Stan Louie, each of whom was tendered in support of a transdiagnostic opinion that prenatal exposure to acetaminophen causes both ASD and ADHD.[4] Pursuant to an Order to Show Cause process, final judgment was entered in approximately 550 cases in the MDL, specifically those cases in which a Short Form Complaint was served on or before January 11, 2024. Those plaintiffs have appealed.

On February 1, the plaintiffs in several newly-filed actions advised the Court that they had retained their own

[3] The Court did not require testimony from any of the expert witnesses. See Kumho Tire Company, Ltd. v. Carmichael, 526 U.S. 137, 152 (1999) (noting trial court has "latitude in deciding how to test an expert's reliability, and to decide whether or when special briefing or other proceedings are needed to investigate reliability").

[4] Dr. Hollander defined a transdiagnostic process as a "mechanism that underlies and connects a group of disorders that transcends traditional diagnostic boundaries" and opined that "it is appropriate to review the body of evidence that measures symptoms of neurodevelopmental disorders and to not limit the analysis to studies that focus on ASD and ADHD as specified outcomes when evaluating the potential causal association between prenatal [acetaminophen] exposure and ASD and ADHD in offspring."

expert, Dr. Roberta Ness, who offers opinion testimony on general causation as to ADHD only. Over the objection of the defendants, the Court permitted these plaintiffs to substitute Dr. Ness as their general causation expert. Defendants' Rule 702 motion to exclude opinions offered by Dr. Ness was fully submitted on June 11, 2024.

Factual Background

Before addressing the defendants' Rule 702 motion, this Opinion sets out background information relevant to the motion. This background information describes 1) acetaminophen and its regulation; 2) ADHD and its characteristics; 3) the basics of epidemiological evidence; 4) the types of scientific research and the principal studies on which Dr. Ness has relied; and 5) the assessments, statements and conclusions of various medical and governmental bodies on the issue at stake in this motion.

I. Acetaminophen and its Regulation

Acetaminophen (sometimes referred to as "APAP" in the literature) is the active ingredient marketed for the relief of fever and pain in Tylenol and certain other over-the-counter pain relievers. Untreated fever during pregnancy is associated with poor pregnancy outcomes, and untreated pain can result in depression, anxiety, and high blood pressure in the mother. See

FDA 2022[5] at 33; see U.S. Food and Drug Administration, FDA has reviewed possible risks of pain medicine use during pregnancy (Jan. 9, 2015), at perma.cc/4JY6-CN6V. Acetaminophen is considered the only pain reliever and fever reducer indicated for use during pregnancy because of the risks of miscarriage or birth defects associated with other analgesics like NSAIDS. About 60% of pregnant women in the U.S. are estimated to use acetaminophen. FDA 2022 at 5. Acetaminophen can cross the placental barrier and can thus enter fetal circulation. Ricci et al., In Utero Acetaminophen Exposure and Child Neurodevelopmental Outcomes: Systematic Review and Meta-

[5] As will be discussed in detail infra, the FDA has reviewed scientific literature pertinent to this litigation several times. The FDA's internal reviews include: Taylor & Wang, Review of Study of Acetaminophen Use in Pregnancy and Risks of ADHD in Offspring, U.S. Food and Drug Administration (May 15, 2014) ("FDA 2014"); Mosholder et al., Acetaminophen Use in Pregnancy and ADHD in Offspring, U.S. Food and Drug Administration (Mar. 18, 2015) ("FDA 2015"); Mosholder, Neurodevelopmental Outcomes Following Prenatal Acetaminophen Exposure, U.S. Food and Drug Administration (Oct. 14, 2016)("FDA 2016"); Nguyen & Gassman, Memorandum of Consultation: Public Communication About In Utero Acetaminophen Exposure And The Potential For Adverse Neurodevelopmental Outcomes, U.S. Food and Drug Administration (Feb. 10, 2017) ("FDA 2017"); Abraham et al., Functional Neurobehavioral Outcomes and Urogenital Outcomes Associated with Prenatal Acetaminophen Exposure, U.S. Food and Drug Administration (Jul. 15, 2022) ("FDA 2022"); Abraham et al., Updated Literature Review of Studies that Examine the Association Between Acetaminophen Exposure During Pregnancy and Neurobehavioral or Urogenital Outcomes, U.S. Food and Drug Administration (Mar. 10, 2023) ("FDA 2023").

Analysis, 37 Paediatr. Perinat. Epidemiol. 473, 474 (2023) ("Ricci 2023").

Since 1982, all over-the-counter drugs intended for systemic absorption must include a general pregnancy warning: "**If pregnant or breast-feeding**, ask a health professional before use." 21 C.F.R. § 201.63; see Preemption Opinion I, 2022 WL 17348351, at *6 (noting requirement that first four words be in bold type). Acetaminophen, which is systemically absorbed, is among the drugs whose labelling must include this warning. The governing regulations require no additional warning related to pregnancy for acetaminophen products. See U.S. Food and Drug Administration, Over-the-Counter (OTC) Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (Oct. 14, 2022).

II. ADHD

ADHD is a neurodevelopmental disorder ("NDD"). Diagnostic and Statistical Manual of Mental Disorders (5th ed., Text Revision, 2022) ("DSM") at 70. Its essential feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. Id. Inattention typically manifests as wandering off task, failing to follow through on instructions or finishing work or chores, having difficulty sustaining focus, and being

disorganized. Id. Hyperactivity refers to excessive motor activity when it is not appropriate. Id. Impulsivity refers to hasty actions that occur in the moment without forethought; impulsive behaviors may manifest as social intrusiveness or making decisions without consideration of long-term consequences. Id.

ADHD begins in childhood, and several symptoms must be present by age 12 for diagnosis. Id. at 70. Further, children must show symptoms in more than one setting (e.g., home and school or home and work), and confirmation of substantial symptoms across settings typically cannot be done accurately without consulting informants who have seen the individual in those settings. Id. The prevalence of ADHD is estimated to be about 7.2% of children worldwide, although prevalence ranges widely from country to country (from 0.1% to 10.2%). Id. at 71.

According to the DSM, the precise cause of ADHD is unknown. There is no biological marker for diagnosing ADHD. Id. at 72. While some neuroimaging studies have shown differences in children with ADHD compared with control subjects, meta-analyses of all neuroimaging studies do not show differences, likely due to differences in diagnostic criteria as well as technical aspects of the neuroimaging technique. Id. Heritability, a measure of how much variation in a trait at the population level

is due to genetic influence, rather than environmental factors, is estimated to be about 74%. Id. at 71. While there is no single gene for ADHD, studies have identified a number of genes that may be associated with ADHD, as well as several environmental risk factors, including low birthweight, prenatal exposure to smoking, and possibly diet. Id.

III. Epidemiology

Epidemiology is the study of the causes, incidence, and distribution of diseases. Epidemiological studies attempt to determine whether an agent is related to the risk of developing a certain disease. Reference Manual on Scientific Evidence (3d ed. 2011) ("RMSE") at 555. Due to ethical constraints, most epidemiological studies are observational, rather than experimental. In an observational study, the authors compare the rate of disease among a group of subjects who have been exposed to the agent of interest and compare that rate with that of an unexposed control group. Id. at 556.

Two major types of observational studies are cohort studies and case control studies. In cohort studies, researchers define a study population without regard to the participants' disease status, then classify the study participants into groups based on whether they were exposed to the agent of interest. Id. at 557. Cohort studies can be prospective (the cohort is defined

in the present and followed forward into the future, and the proportions of individuals in each group who develop the disease of interest are compared) or retrospective (the researcher determines the proportion of individuals in the exposed group who developed the disease from available records or evidence and compares that proportion with the proportion of another group that was not exposed). Id.

In case-control studies, the researcher begins with a group of individuals who have a disease ("cases") and then selects a similar group of individuals who do not have the disease ("controls"). Id. at 559. The researcher then compares the groups in terms of past exposures.

A. Interpreting Observational Study Results

Because observational studies do not control for exposure to other risk factors for disease, their results must be interpreted with some caution. "[T]he first question an epidemiologist addresses is whether an association exists between exposure to the agent and disease." Id. at 566. If an association is found, its strength can be stated in several ways, including risk ratios ("RR") or odds ratios ("OR"), which represent the ratio of the incidence rate of disease in exposed individuals to the incidence rate in unexposed individuals. If the risk ratio equals 1.0, the risk in exposed individuals is

the same as the risk in unexposed individuals. Id. at 567. If it is greater than 1.0, the risk in exposed individuals is greater than the risk in unexposed individuals; in other words, there is a positive association between exposure to the agent and the disease, which may or may not be causal. Id. If it is less than 1.0, there is a negative association between exposure and disease, which may or may not reflect a protective effect of the agent on risk of disease. Id. An association (negative or positive), without more, should be interpreted with caution; further analysis must be conducted to assess whether the association is real or is instead a result of chance, confounding, or bias. Id. at 567-68.

1. Chance

Chance, or random error, is evaluated through measures of statistical significance, which is usually reported using a range of values referred to as the "95% confidence interval" ("CI"). The CI encompasses the results we would expect 95% of the time if samples for new studies were repeatedly drawn from the same population. All other things being equal, the larger the sample size, the narrower the confidence interval. Id. at 581. The narrower the CI, the more statistically stable the results of the study. Id. at 580. If a CI crosses 1.00, the result is not considered statistically significant. For

example, if a study found a risk ratio of 1.5 with a 95% CI of 0.08-3.4, the result is not statistically significant because the CI includes 1.0. Id. at 581. If a study found a risk ratio of 1.5 with a 95% CI of 1.1-2.2, the results are statistically significant because the CI does not include an RR of 1.0. Id.[6]

2. Bias

Bias is a systematic, non-random error. Two types of relevant bias are selection bias (where the population of the study is not representative of the general population), and information bias (where inaccurate information about either the disease or the exposure status of the study participants is recorded). Id. at 583. Many studies have shown that individuals who participate in studies differ significantly from those who do not; thus, if a significant number of subjects drop out of a study before completion, the remaining subjects may not be representative of the original study population. Id. at 584. Research has also shown that individuals with diseases tend to recall past exposures more readily than individuals with no disease, which creates a potential for recall bias in studies that rely on retroactive interviews of subjects to determine exposure, such as retroactive case control studies. Id. at 585.

[6] In this Opinion, risk ratios will be stated in the following format: 1.50 (0.95-1.80) or (1.50; 0.95-1.80), indicating a risk ratio of 1.50 with a 95% CI of 0.95-1.80.

3. Confounding

Confounding, which occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and outcome of interest, is another major cause for error in epidemiological studies. Id. at 591. For example, researchers may conduct a study that finds individuals with gray hair have a higher rate of death than those with hair of another color. Instead of hair color having an impact on rate of death, the results are probably explained by the confounding factor of age. Id.

Two major potential confounders are at issue in this litigation: confounding by indication and confounding by genetics. Confounding by indication may be at issue if the reason a pregnant person takes acetaminophen itself causes ADHD. If, for example, fever during pregnancy is associated with development of ADHD, and fever is also related to whether a pregnant person takes acetaminophen, it will be critical to determine whether an association between prenatal exposure to acetaminophen and ADHD is causal or the result of confounding. As for genetic confounding, there could be genetic factors that make pregnant people more likely to take acetaminophen during pregnancy, and also make it more likely that their offspring will have ADHD.

Although there is always a chance that an unknown confounder contributes to a study's finding, there are choices researchers can make in designing a study that prevent, limit, or account for confounding. For confounding by indication, a study design could track both the potential confounder (e.g., fever) and the exposure of interest (prenatal use of acetaminophen), and then control for fever in the data analysis.

Researchers can attempt to control for genetic confounders by gathering data on parental ADHD diagnoses, using negative control exposures, or conducting sibling control studies. Negative control exposures should be time-invariant and should not be expected to have a causal relationship to the outcome of interest. For example, there is no reason to expect that paternal use of acetaminophen during pregnancy varies compared to paternal use of acetaminophen before pregnancy (time-invariance), or that it could cause a neurodevelopmental disorder in offspring (because conception has already occurred).[7]

In sibling control studies, researchers compare the rate of the outcome in siblings who were exposed to the agent to that of siblings who were not exposed. If the association is causal,

[7] See, e.g., Sanderson et al., Negative Control Exposure Studies in the Presence of Measurement Error: Implications for Attempted Effect Estimate Calibration, 47(2) Int. J. Epidemiol. 587 (2018); Brew & Gong, Modelling Paternal Exposure as a Negative Control, 49(3) Int. J. Epidemiol. 1053 (2020).

the exposed sibling is expected to have a higher risk of the outcome than the non-exposed sibling. Gustavson et al., Acetaminophen Use During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder -- A Longitudinal Sibling Control Study, 1(2) JCPP Advances 1, 2 (2021) ("Gustavson 2021"). If the association is mainly explained by familial confounding factors, such as genetics or shared environmental factors, the risk should be similar for the two siblings. Id.

B. Causation

Once an association has been found between exposure to an agent and development of a disease, researchers then consider whether the association reflects a true cause-effect relationship. It is important to note that epidemiology cannot prove causation; rather, causation is a judgment to be made by epidemiologists and others interpreting the epidemiological data. RMSE at 598. There is no objective formula or algorithm that can be used to determine whether a causal inference can be made. Thus, although the drawing of causal inferences is informed by scientific expertise, courts must scrutinize proposed expert opinions on causation to ensure the experts conducted a review of available studies using a reliable methodology. Id. Pertinent to this MDL is whether it is reliable to draw a causal inference from the associations that

researchers have observed between prenatal acetaminophen exposure and ADHD.

IV. Types of Evidence at Issue Here

Since at least 1987,[8] scientists have been examining whether the prenatal use of acetaminophen may be associated with adverse neurodevelopmental outcomes. To date, however, no medical organization or regulatory body has concluded that prenatal exposure to acetaminophen causes ADHD. Before reviewing the relevant literature from medical organizations and regulatory bodies, some of the studies that have been undertaken are described.

A. Published Studies

1. Exposure Measurement Methods

Because acetaminophen is available without a prescription and used widely by both non-pregnant and pregnant individuals, it is particularly hard for researchers to come by objective and precise data about its use. While a few studies have assessed acetaminophen exposure using biomarkers, which are objective measures, and one study used prescription data from maternal medical records, the majority of the studies have assessed

[8] Streissguth et al., Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements, 35 Teratology 211 (1987).

exposure using maternal self-reports at varying times during or after pregnancy.

For example, mothers in the Norwegian Mother and Child Cohort Study ("MoBa"), the data from which has been the basis of several studies, completed questionnaires at weeks 17 and 30 of gestation and 6 months after giving birth. The mothers reported fever and medication use per month leading up to each questionnaire. Mothers in the Danish National Birth Cohort ("DNBC"), another large cohort, were interviewed over the telephone at weeks 12 and 30 of gestation and 6 months after giving birth. They were asked if they had ever taken painkillers during the preceding period; if they said yes, they were given a list of the 44 most common pain medications and were asked to report the number of weeks during which they had taken such medication in the preceding period. One study used biennial questionnaires (Nurses Health Study II) and inferred exposure from use reported the year of the pregnancy; another used interviews ranging from a few days to up to 10 years after birth. Some studies asked mothers to remember how many days they had used acetaminophen in a given period, others asked simply whether the mother had ever used acetaminophen during the pregnancy, and others asked for weeks of use without discriminating between, e.g., daily use during that week or use

just once. The studies discussed below should thus be interpreted with this heterogeneity in mind.

2. Individual Studies

Dr. Ness relies principally on eight studies. Six of those studies are original studies that examined data from five cohorts and the connection between prenatal acetaminophen exposure and an ADHD diagnosis. Two of those studies are original studies that examine data from one cohort and the connection between perinatal or postnatal acetaminophen exposure and an ADHD diagnosis.

The designs of these studies reflect the challenges scientists have encountered in assessing whether an important and widely used over-the-counter drug has caused ADHD, a condition known to be highly heritable. Some studies have used biomarkers instead of relying on maternal recall. Some have controlled for indications of use during pregnancy, such as fever or pain. Others have attempted to adjust for genetic confounding.

A very recent study, Ahlqvist 2024,[9] examined the issue of genetic confounding and is also discussed here even though it

[9] Ahlqvist et al., Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability, 331(14) JAMA 1205 (2024).

was published after Dr. Ness delivered her expert report in this litigation.[10] Its results "indicate that the association between acetaminophen use during pregnancy and neurodevelopmental disorders is a noncausal association." Id. at 1212.

The oldest study on which Dr. Ness principally relies is Liew 2014.[11] Liew 2014 drew data from the DNBC, which assessed exposure to acetaminophen using maternal interviews at weeks 12 and 30 of gestation. This study had a sample size of 64,322 children. The authors found statistically significant associations between a diagnosis of hyperkinetic disorder ("HKD")[12] and first trimester use (1.35; 1.07-1.72), use in both the first and third trimesters (1.41; 1.08-1.84), and use in all three trimesters (1.61; 1.30-2.01), id. at 318, but no such associations for second or third trimester use, for use in both the first and second trimesters, or for use in both the second and third trimesters. Id. The authors cautioned that "the possibility of unmeasured residual confounding by indication for

[10] Ahlqvist 2024 was published the day of Dr. Ness's deposition.

[11] Liew et al., Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders, 168(4) JAMA Pediatrics 313 (2014).

[12] HKD is the analogue for ADHD used by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision ("ICD-10"), a medical classification list published by the World Health Organization.

drug use, ADHD-related genetic factors, or co-exposures to other medications cannot be dismissed." Id. at 319.

Liew 2019[13] gathered data from 8,856 children born to women enrolled in the Nurses' Health Study II cohort. Data was collected in biennial questionnaires that asked women whether they had regularly used a variety of medications in the past two years.[14] Regular maternal use during the year of the child's birth was analyzed as the exposure variable. The authors also attempted to perform a negative control exposure analysis using the mother's responses from four years before and four years after the child's birth. They found that ADHD was associated with regular use during the child's birth year (1.35; 1.07-1.71), but not with use four years before (1.12; 0.91-1.38) or after (1.05; 0.88-1.26). Id. at 773. In the subset of women

[13] Liew et al., 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 (2019).

[14] In 1993, women were asked to "mark if used regularly" the box next to acetaminophen if they used it 2+ times per week in a section titled "Current Medication". In 1995, the questionnaires asked recipients how many days each month, on average, they took acetaminophen, with 0, 1-4, 5-14, 15-21, and 22+ days as options. The 1996 study instructed women to "mark if used regularly in past 2 years" acetaminophen if use was 2+ times per week. In 2001, they were directed to "mark if used regularly in past 2 years" both days per week (1, 2-3, 4-5, 6+) and total tabs per week (1-2, 3-5, 6-14, 15+). See https://nurseshealthstudy.org/participants/questionnaires.

who indicated they were pregnant at the time they completed the questionnaire, there was a statistically insignificant association (1.39; 0.99-1.95), although in the model with acetaminophen use in all exposure periods included together, the association was statistically significant (1.46; 1.01-2.09). Id. The authors concluded that their results provided evidence that the association is "unlikely to be explained by [] time-invariant factors" such as genetics. Id. at 774.

Baker 2020,[15] a study of 345 children, is the only study that showed an association between an objective biological measure of prenatal exposure and a child's ADHD diagnosis. The authors found that detection of acetaminophen in meconium -- an infant's first feces, which may reflect exposure during the final two-thirds of pregnancy -- was associated with ADHD (2.43; 1.41-4.21). Id. at 1077. The authors conducted a sensitivity analysis to determine whether the results would be different if they excluded mothers who were given acetaminophen during delivery, and the association persisted (2.38; 1.35-4.21). Id. Self-reported maternal ADHD data was available for 155 individuals. Id. at 1075. The authors stated that controlling

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

for maternal ADHD in this subset increased the risk ratio by .02; however, that data is not presented in the main report or supplemental tables and the authors do not indicate whether the resulting risk ratio was statistically significant. Id. The authors did not control for indication for use. The authors concluded that the association between prenatal acetaminophen and ADHD may be even stronger than previously estimated because prior studies may have been biased toward the null by inaccurate maternal recall, and that the FDA and the Society for Maternal Fetal Medicine ("SMFM") should "consider re-evaluating the evidence regarding the safety of fetal acetaminophen exposure." Id. at 1080.

Two studies, Ji 2018[16] and Ji 2020,[17] used objective measures of biomarkers to assess acetaminophen exposure during the postpartum (Ji 2018) and peripartum (Ji 2020) periods. Both studies used data from the Boston Birth Cohort, which consists of a predominantly urban low-income minority population. Ji 2018 measured acetaminophen and its metabolites in maternal

[16] Ji et al., Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder, 8(127) Brain Sci. 1 (2018).

[17] Ji et al., Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder & Autism Spectrum Disorder in Childhood, 77(2) JAMA Psychiatry 180 (2020).

blood plasma from 1,180 samples taken 1-3 days postpartum. Looking at the total acetaminophen burden, the authors found associations of 1.58 (1.02-2.46) for below median and 1.88 (1.18-3.00) for above median compared to "not detected." Id. at 8. The authors controlled for maternal fever during pregnancy and intrauterine infection, but were unable to adjust for several familial factors. Id. at 11. Because the blood samples were taken post-partum and the half-life of acetaminophen is only 1.5-3 hours, the samples do not reflect prenatal use of acetaminophen.

Ji 2020 measured acetaminophen metabolites in umbilical cord plasma in 996 mother/child pairs. The authors found unchanged acetaminophen in 100% of the cord blood samples. They thus broke down the samples into thirds ("tertiles") based on the total level of acetaminophen detected (including unchanged acetaminophen and its metabolites). They found statistically significant increases in ADHD for both the second tertile compared to the first (2.26; 1.40-3.69) and the third tertile compared to the first (2.86; 1.77-4.67). As with Ji 2018, the authors adjusted for maternal fever but did not adjust for genetic factors. Id. at 188. Again, because of the short half-life of acetaminophen, the samples only reflected use during the period shortly before, during, and immediately after giving

birth, rather than the prenatal period. The relevance of the Ji studies to this litigation is disputed by the parties.

Chen 2019,[18] a case-control study with 950 mother-and-child case pairs and 3,800 control pairs, analyzed data from medical records and found an association between prenatal acetaminophen prescriptions in Taiwan and a child's ADHD diagnosis. After controlling for maternal infections during the pregnancy and maternal mental health disorders, such as major depressive disorder and bipolar disorder, Chen 2019 found an association between use in "any" trimester and an ADHD diagnosis (1.20; 1.01-1.42).[19] Id. at e5. Chen 2019 also found significant associations between ADHD risk and maternal mental health disorders, such as major depressive disorder (1.57; 1.10-2.24) and bipolar disorder (2.25; 1.19-4.27). Id. Its authors noted several limitations in the study, including that unreported ADHD may exist in the control group and the fact that none of the mothers in either the study pairs or control group had been

[18] Chen et al., Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan, 80(5) J. Clin. Psychiatry (2019).

[19] The associations for the second trimester and for the first and second trimesters combined had a 95% CI that included 1.00. The associations for the first trimester, the third trimester, and for the third trimester combined with the first or second trimester had a 95% CI that spanned above and below 1.00.

identified with either ADHD or a substance use disorder. Id. at e6.

Two studies -- Ystrom 2017[20] and Gustavson 2021 -- used data from the MoBa cohort. The authors of Ystrom 2017 attempted to control for confounding due to indications for use of acetaminophen and parental symptoms of ADHD. In the partially adjusted model, Ystrom 2017 found associations between use for greater than 29 days (2.20; 1.50-3.24) and an HKD diagnosis. Id. at 6. In fully adjusted models, the study found associations between ever use (that is, any use during pregnancy) (1.12; 1.02-1.24), use in both first and second trimesters (1.21; 1.06-1.39) and in any two trimesters (1.22; 1.07-1.38) and an ADHD diagnosis. Id. at 5. The study also found that paternal preconceptional use of acetaminophen for 29 days or more was also associated with ADHD (2.06; 1.36-3.13). Id. at 4. Given that paternal use of acetaminophen is also associated with ADHD, the authors reported that "the causal role of acetaminophen in the etiology of ADHD can be questioned." Id. at 7. The authors cautioned that they "d[id] not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD." Id.

[20] Ystrom et al., Prenatal Exposure to Acetaminophen and Risk of ADHD, 140(5) Pediatrics 1 (2017).

Gustavson 2021 used more recent data from the same cohort to conduct a sibling-control analysis with the goal of assessing the role of familial confounding. The authors found no association between use for less than 29 days and HKD but did initially find an association between HKD and use for more than 29 days over the course of the pregnancy (2.02; 1.17-3.25). Id. at 7. That association was attenuated to non-significance using a sibling-control analysis (1.06; 0.51-2.05). Id. The authors concluded that the association between acetaminophen use and ADHD "may at least partly be due to familial confounding." Id. at 8.

Finally, Ahlqvist 2024 collected data from all singleton liveborn children in Sweden from July 1, 1995 to December 31, 2019, with follow-up until December 31, 2021, with a sample size of 2,480,797 children born to 1,387,240 mothers. The authors measured exposure based on antenatal records collected at around 8-10 weeks gestation and later in pregnancy. They found a slightly elevated risk of ADHD for ever-use of acetaminophen compared to never-use in the full population (1.07; 1.05-1.10). Id. at 1205. As in Gustavson 2021, however, when the authors performed a sibling analysis (N=1,773,747 full siblings), the association attenuated to non-significance (0.98; 0.94-1.02). Id. The authors performed statistical analyses to determine the

possible impact of exposure measurement error on their results and found that "complete nullification of the acetaminophen-neurodevelopment disorder associations going from the population-based to sibling control models is unlikely to result from even extreme levels of measurement error." Id. at eAppendix 2. The authors noted that "[b]irthing parents with higher acetaminophen use differed in many aspects from those with lower use or no use." Id. at 1212. They concluded that the results of their study "indicate that the association between acetaminophen use during pregnancy and neurodevelopmental disorders is a noncausal association." Id. While the study did not identify specific confounding factors, it mentioned as likely candidates the pregnant individuals' genetics and indications for use of acetaminophen such as infection or fever. Id.

3. Questionnaire Studies

Several studies, on which Dr. Ness relies "for context," used the results of screening questionnaires as outcome measurements as opposed to a diagnosis of ADHD. These screening questionnaires included, inter alia, the Strength and Difficulties Questionnaire ("SDQ"), the Ages and Stages Questionnaire ("ASQ"), the Child Behavior Checklist ("CBCL"), the Childhood Autism Spectrum Test ("CAST"), and the

Emotionality, Activity, and Sociability Temperament Questionnaire ("EAS"). As noted in the First Daubert Opinion, it is challenging to assess consistency and make comparisons among studies that rely on questionnaires that have multiple endpoints and contain no diagnosis of ADHD. First Daubert Opinion, 2023 WL 8711617, at *25. There is an increased risk that an investigator or expert will cherry pick results or fail to address inconsistencies. Id. Dr. Ness relied on non-diagnostic studies to a lesser extent than the plaintiffs' first set of experts.

4. Meta-Analyses

Finally, there have been several meta-analyses attempting to pool data from existing studies on the association between acetaminophen and ADHD. The most recent meta-analysis, Ricci 2023, is the only meta-analysis that conducted a subgroup analysis limited to studies with diagnostic outcome measurements. Ricci 2023 conducted an ADHD subgroup analysis using data from Baker 2020, Ji 2020, Liew 2019, and Ystrom 2017. The authors concluded that their analysis suggests "a small increase in risk of child ADHD associated with in utero acetaminophen exposure," but noted that "[t]he certainty of the evidence on this topic is low," and their findings "should be further explored in future high-quality research on a range of

neurodevelopmental outcomes, with adequate control for confounding by indication." Id. at 483.

B. Statements by Governmental Bodies, Medical Societies, and other Associations

1. FDA Oversight

Following the publication of Liew 2014, the FDA opened a Tracked Safety Issue ("TSI") for prenatal acetaminophen exposure on May 15, 2014; it has been conducting periodic reviews of the evidence ever since. The 2014 review recommended that "no regulatory action be taken at this time based on available data" but that, given the TSI, "DEPI [the Division of Epidemiology] and DNDP [the Division of Nonprescription Drug Products] stay current on the published safety literature related to [acetaminophen] use in pregnancy." FDA 2014 at 3. The 2015 review concluded that "[w]hether the association [between prenatal exposure to APAP and behavioral difficulties] is causal in nature remains uncertain." FDA 2015 at 8. In 2016, the FDA noted that "in utero exposure to APAP was associated with a spectrum of adverse neurodevelopmental outcomes, though findings with respect to specific outcomes varied somewhat across studies, and positive findings were generally modest." FDA 2016 at 15. It further stated that "a causal relationship [between prenatal exposure to APAP and adverse neurodevelopmental outcomes] is not certain because of the possibility of

confounding, particularly by conditions such as maternal fever and infection that may prompt pregnant women to take APAP but which may also be risk factors for neurocognitive problems." Id.

In 2015, the FDA issued a public Drug Safety Communication about prenatal use of NSAIDs, opioids, and acetaminophen. See FDA, FDA has reviewed possible risks of pain medicine use during pregnancy (Jan. 9, 2015), at perma.cc/4JY6-CN6V. The safety announcement noted the recent reports questioning the safety of pain medications when used during pregnancy, but stated that the FDA had evaluated the scientific literature and determined it was too limited to make any recommendations. Id. at 1. Regarding ADHD specifically, the announcement noted that the "weight of evidence is inconclusive regarding a possible connection between acetaminophen use in pregnancy and ADHD in children." Id. at 5.

In 2016, the FDA reviewed published preclinical literature (i.e., animal studies). It concluded that the animal studies were not adequately designed to address the question of causation, and that behavioral responses in animals predictive of ADHD in humans are uncertain. FDA 2017 at 2.

A 2017 review noted that all of the observational studies reviewed "had significant limitations that question the causal

effect of [acetaminophen] on adverse neurodevelopmental outcomes." FDA 2017 at 10. Thus, the FDA was "unable to draw any conclusion about the causal association between prenatal [acetaminophen] exposure and the different adverse neurodevelopmental outcomes, based on the available evidence." Id. at 12. That review recommended informing the public that the FDA had evaluated additional studies but retaining the 2015 conclusion about the inability to draw causality conclusions. Id.

The FDA conducted further reviews in 2022 and 2023. The 2022 review looked at 24 additional studies. FDA 2022 at 7. It concluded that "there are still study limitations and inconsistent study findings that prohibit causal interpretations of the association between APAP exposure and functional neurobehavioral outcomes." Id. at 33. The 2023 review looked at three additional studies, only one of which assessed attention, and concluded that "findings on the associations between APAP use during pregnancy and neurobehavioral . . . outcomes remain mixed." FDA 2023 at 17. It noted that the three studies reviewed "do not change DEPI-I's conclusions from its most recent review -- the limitations and inconsistent findings of current observational studies of APAP and

neurobehavioral and urogenital outcomes are unable to support a determination of causality." Id. at 17-18.

2. Other Organizations

The FDA's conclusions are in line with the conclusions reached by medical societies both in this country and in Europe. For example, the U.S.-based SMFM examined studies on acetaminophen and neurodevelopmental outcomes in 2017. SMFM found that "the weight of the evidence is inconclusive regarding the possible causal relationship between acetaminophen use and neurobehavioral disorders in the [children]" and that acetaminophen use during pregnancy is "reasonable and appropriate."[21] The Royal College of Obstetricians and Gynaecologists, a professional association based in the United Kingdom, noted in 2018 that "[c]urrent advice is that [acetaminophen] remains safe for use during pregnancy and breastfeeding." Bisson, Antenatal and postnatal analgesia: Scientific Impact Paper No. 59, BJOG (2018), at e117-118.

The first major statement suggesting that pregnant women receive a more specific warning about the risk of developmental disorders in their offspring came just three years ago. In 2021, a group of 13 authors (joined by 78 signees) -- consisting

[21] SMFM, SMFM Statement: Prenatal Acetaminophen Use and Outcomes in Children, 216(3) Am. J. Obstetrics & Gynecology B14, B15 (2017).

of scientists, clinicians, and epidemiologists -- published a "Consensus Statement" reviewing literature concerning prenatal acetaminophen use and adverse developmental outcomes, including ADHD. Bauer et al., Consensus Statement: Paracetamol Use During Pregnancy — A Call for Precautionary Action, 17 Nature Revs. Endocrinology 757, 758, 762 (2021) ("Consensus Statement"). The Consensus Statement called for the prioritization of research initiatives and evidence-based medical guidance for acetaminophen use by pregnant women. The authors of the Consensus Statement stated that "the combined weight of animal and human scientific evidence is strong enough for pregnant women to be cautioned by health professionals against its indiscriminate use . . . . We recommend that APAP should be used by pregnant women cautiously at the lowest effective does for the shortest possible time." Id. at 764.

The Consensus Statement prompted a "Consensus Counterstatement" by another group of 60 scientists and clinicians (comprising 10 authors and 50 signees) affiliated with the Organization of Teratology Information Specialists ("OTIS"). See Alwan et al., Paracetamol Use In Pregnancy -- Caution Over Causal Inference From Available Data, 18 Nature Revs. Endocrinology 190 (2022) ("Counterstatement"). The authors of the Counterstatement reviewed literature and

concluded that the studies were "limited by serious methodological problems, including failure to account for confounding, and elements of bias that make interpretation of the data challenging." Id. Although the authors agreed with the Consensus Statement's call for further investigation, they "urge[d] against recommending [] precautionary measures for [acetaminophen] use in pregnancy and against the dissemination of information based on inconclusive and insufficient evidence." Id.

In a reply, the authors of the Consensus Statement pointed out that "we avoided any inference of causality in our Consensus Statement." Bauer et al., 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 Rev. Endocrinology 192 (2022). They reiterated, however, their belief that "available data provide sufficient evidence for concern and a recommendation of precautionary action." They also noted that "[o]ur recommendations should not increase maternal anxiety, as they only suggest adherence to current guidelines." Id.

Another response to the initial Consensus Statement, signed by 63 researchers and clinicians and 16 organizations, "argue[d]

that the available evidence supports neither a change in clinical practice (minimal use when necessary), restricting APAP availabilities to pharmacies, nor additional warning labels on packaging." O'Sullivan 2022.[22] The authors of the O'Sullivan 2022 statement noted that "[t]he overarching societal message that has been drawn from [the] Consensus Statement is that APAP use in pregnancy is unsafe and should be restricted in both use and access." Id. The authors stated that "[w]e, and others, believe this interpretation is exaggerated." Id. The organizations that signed this letter included the International Federation of Gynecology and Obstetrics, the European Association of Perinatal Medicine, the British Maternal and Fetal Medicine Society, the U.K. Teratology Information Service, as well as American, Angolan, Brazilian, Canadian, Finnish, and Portuguese obstetric and gynecological associations.

Medical bodies also responded to the Consensus Statement. The American College of Obstetricians and Gynecologists ("ACOG") reviewed the literature and noted that the studies "show no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any trimester and fetal developmental issues." ACOG, ACOG Response to Consensus

[22] O'Sullivan et al., Paracetamol Use in Pregnancy -- Neglecting Context Promotes Misinterpretation, 18 Nat. Rev. Endocrinology 385 (2022).

Statement on Paracetamol Use During Pregnancy (Sept. 29, 2021).[23] The European Network of Teratology Information Services ("ENTIS") issued a position statement that the Consensus Statement "reflects the views of the authors and is not endorsed by regulatory authorities or medical specialty organizations." European Network of Teratology Information Services, Position Statement on Acetaminophen (Paracetamol) in Pregnancy, at 1 (Oct. 3, 2021). It noted several problems with the underlying studies, including the use of unvalidated outcome measurements, which "are neither developed nor validated for the purpose and context in which they are used." Id. It specifically pointed to Ji 2020, which it stated has "severe issues with external and internal validity." Id. at 2. ENTIS noted that the Consensus Statement "and the ensuing reaction w[ould] promote unwarranted uncertainty, fear, and guilt among pregnant women" and would "also likely result in use of less safe alternatives during pregnancy." Id.

In November 2021, the Society of Obstetricians and Gynaecologists of Canada ("SOGC") weighed in. It noted that "[t]he position of the SOGC, and a number of other international societies, is that the evidence for causality for this claim is

[23] https://www.acog.org/news/news-articles/2021/09/response-to-consensus-statement-on-paracetamol-use-during-pregnancy.

weak and has many fundamental flaws." SOGC, Statement on the Use of Acetaminophen for Analgesia and Fever in Pregnancy (Nov. 8, 2021).[24]

Finally, after the publication of Ahlqvist 2024, which was funded in part by the National Institutes of Health ("NIH"), the NIH issued a news release regarding the study.[25] The NIH stated that, according to the study, "[a]cetaminophen exposure during pregnancy is not linked to the risk of autism, ADHD, or intellectual disability." Id.

Discussion

As in all tort cases, plaintiffs in this MDL must prove by a preponderance of the evidence that defendants' breach of a duty owed to plaintiffs caused plaintiffs' injuries. Causation in pharmaceutical products liability cases such as those in this litigation has two components, general and specific. Daniels-Feasel v. Forest Pharmaceuticals, Inc., 2021 WL 4037820, at *5 (S.D.N.Y. 2021), aff'd, 2023 WL 4837521 (2d Cir. 2023) (citation omitted). "General causation is whether a substance is capable of causing a particular injury or condition in the general

[24] https://sogc.org/en/en/content/featured-news/Statement_on_the_use_of_acetaminophen.aspx.

[25] https://www.nih.gov/news-events/news-releases/study-reveals-no-causal-link-between-neurodevelopmental-disorders-acetaminophen-exposure-before-birth.

population, while specific causation is whether a substance caused a particular individual's injury." Id. (citation omitted).

As the above discussion reflects, the state of scientific evidence on prenatal use of acetaminophen presents a challenge for any expert witness offering the opinion that such use causes ADHD. Major medical organizations and regulators have cautioned against drawing causal inferences from the existing body of scientific literature. Nevertheless, Dr. Ness draws such an inference. Dr. Ness opines that within a reasonable degree of scientific certainty, prenatal use of acetaminophen causes ADHD. Defendants argue that Dr. Ness's opinions are inadmissible under the Federal Rules of Evidence and the standards set by the Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), and its progeny. Before addressing this motion, the relevant legal standards are set forth.

I. Standard: Daubert and Rule 702

Federal Rule of Evidence 702 ("Rule 702") governs the admission of expert testimony in federal court. The Supreme Court has made clear that the district court has a "gatekeeping" function under Rule 702: it is charged with the "task of ensuring that an expert's testimony both rests on a reliable

foundation and is relevant to the task at hand." Daubert, 509 U.S. at 597.

Testimony is relevant where it has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Bustamonte v. KIND, LLC, 100 F.4th 419, 427 (2d Cir. 2024) (citation omitted). Next, to determine whether expert testimony has a sufficiently reliable foundation to be admissible at trial, a court must consider the "indicia of reliability identified in [Rule] 702." Clerveaux v. East Ramapo Central School District, 984 F.3d 213, 233 (2d Cir. 2021) (citation omitted).

Rule 702 allows a "witness who is qualified as an expert by knowledge, skill, experience, training, or education" to testify, "in the form of an opinion or otherwise if the proponent demonstrates to the court that it is more likely than not that":

> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
> (b) the testimony is based on sufficient facts or data;
> (c) the testimony is the product of reliable principles and methods; and
> (d) the expert's opinion reflects a reliable application of the principles and methods to the facts of the case.

Fed. R. Evid. 702.[26] An expert can fail to meet the Rule 702 and Daubert standards "for various reasons, relating to the expert's qualifications and/or methodology." Mirena II, 341 F. Supp. 3d at 240.

1. Qualification

To determine whether a witness qualifies as an expert, courts "compare the area in which the witness has superior knowledge, education, experience, or skill with the subject matter of the proffered testimony." Id. (citing United States v. Tin Yat Chin, 371 F.3d 31, 40 (2d Cir. 2004)). In determining whether the witness has the relevant experience, courts consider "the degree to which that experience was developed for litigation." Id.; see also In re Mirena IUD Products Liability Litigation, 169 F. Supp. 3d 396, 440 (S.D.N.Y. 2016), aff'd, 713 Fed. Appx. 11, 15 (2d Cir 2017) ("Mirena I") (affirming exclusion of experts who "lacked pre-

[26] Rule 702 was amended effective December 1, 2023. "Nothing in the amendment imposes any new, specific procedures." Fed. R. Evid. 702, Advisory Committee Notes, 2023 Amendments. Instead, one purpose of the amendment was to emphasize that

> [j]udicial gatekeeping is essential because just as jurors may be unable, due to lack of specialized knowledge, to evaluate meaningfully the reliability of scientific and other methods underlying expert opinion, jurors may also lack the specialized knowledge to determine whether the conclusions of an expert go beyond what the expert's basis and methodology may reliably support.

Id.

litigation expertise" and "developed their theories for the purposes of this litigation"). If the witness does not possess superior knowledge, education, experience or skill in the relevant area, the court must exclude her testimony. Mirena II, 341 F. Supp. 3d at 240-41.

2. Reliability

In addition to the indicia of reliability identified in Rule 702, a trial court may consider the criteria enumerated in Daubert, "some or all of which might prove helpful in determining the reliability of a particular scientific theory or technique." Clerveaux, 984 F.3d at 233 (citation omitted). The Daubert factors are: (1) whether the methodology or theory has been or can be tested; (2) whether the methodology or theory has been subjected to peer review and publication; (3) the methodology's error rate and the existence and maintenance of standards controlling the technique's operation; and (4) whether the methodology or technique has gained general acceptance in the relevant scientific community. Daubert, 509 U.S. at 593-94. "[W]hile a court need not consider the Daubert factors, it does not abuse its discretion in doing so." Mirena II, 982 F.3d at 124.

Although "Rule 702 sets forth specific criteria for the district court's consideration, the Daubert inquiry is fluid and

will necessarily vary from case to case." Id. at 123 (citation omitted). The Daubert factors do not constitute a definitive checklist or test. For example, courts also consider whether the proffered expert opinions were developed for the purpose of litigation. Daniels-Feasel, 2021 WL 4037820, at *4 (citation omitted). Further, proffered expert testimony can fail all four Daubert factors and still be admitted; however, in those circumstances, a court must "carefully scrutinize, pause, and take a hard look at the expert's methodology." Mirena II, 341 F. Supp. 3d at 240. So long as an expert's analysis is reliable "at every step," it is admissible. Mirena II, 982 F.3d at 123 (citation omitted). But "any step that renders the analysis unreliable ... renders the expert's testimony inadmissible." Amorgianos v. National R.R. Passenger Corp., 303 F.3d 256, 267 (2d Cir. 2002) (citation omitted). Thus, it may not only be appropriate for a district court "to take a hard look at plaintiffs' experts' reports," it may be "required to do so to ensure reliability." Mirena II, 982 F.3d at 123. "[I]n deciding whether a step in an expert's analysis is unreliable, the district court should undertake a rigorous examination of the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert applies the facts and methods to the case at hand." Id.

(citation omitted). Ultimately, a court must "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." Kumho Tire Co., 526 U.S. at 152.

Although the Supreme Court in Daubert emphasized that the court's inquiry under Rule 702 must focus "solely on principles and methodology, not on the conclusions they generate," 509 U.S. at 595, it later clarified that "conclusions and methodology are not entirely distinct from one another." General Electric Company v. Joiner, 522 U.S. 136, 146 (1997). Thus, although

> [t]rained experts commonly extrapolate from existing data[,] nothing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.

Id.

Where, however, an expert "otherwise reliably utilizes scientific methods to reach a conclusion, lack of textual support [for an expert's opinion] may go to the weight, not the admissibility of the expert's testimony." Mirena II, 982 F.3d at 124. A "minor flaw in an expert's reasoning or a slight modification of an otherwise reliable method will not render an expert's opinion per se inadmissible." Amorgianos, 303 F.3d at

267. "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 596.

II. Epidemiology Cases

Several additional considerations are important when experts offer general causation opinions in pharmaceutical cases. For instance, "if an expert applies certain techniques to a subset of the body of evidence and other techniques to another subset without explanation, this raises an inference of unreliable application of methodology." In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation, 858 F.3d 787, 797 (3d Cir. 2017) ("Zoloft"). Additionally, when experts rely on the studies of others, they must not exceed the limitations the authors themselves place on the study. Daniels-Feasel, 2021 WL 4037820, at *4.

Further, "an expert must not cherry-pick from the scientific landscape and present the Court with what he believes the final picture looks like." Id. at *5 (citation omitted). Instead, "[s]ound scientific methodology in assessing general causation requires an expert to evaluate all of the scientific evidence when making causation determinations." Id. (citation omitted). Cherry-picking is a form of "result-driven analysis

which undermines principles of the scientific method by applying methodologies (valid or otherwise) in an unreliable fashion." Id. (citing In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prod. Liab. Litig. (No II) MDL 2502, 892 F.3d 624, 634 (4th Cir. 2018)). "Therefore, exclusion of the proffered testimony is warranted where the expert fails to address evidence that is highly relevant to his or her conclusion." Id.

Dr. Ness, like plaintiffs' prior experts, has employed a "Bradford Hill" analysis, which is a generally accepted methodology for determining causation among epidemiologists. See Zoloft, 858 F.3d at 795; see also RMSE at 599-606; Daniels-Feasel, 2021 WL 4037820, at *6-*7. The Bradford Hill criteria are "metrics that epidemiologists use to distinguish a causal connection from a mere association." Zoloft, 858 F.3d at 795.

The nine Bradford Hill criteria are:

1) Strength of Association. This criterion is represented by the risk ratio discussed above. The higher the relative risk, the higher the likelihood that the relationship is causal. Lower relative risks can also reflect causality, but such associations should be scrutinized more carefully because there is a greater chance that they are the result of uncontrolled confounding or biases. RMSE at 602.

2) Consistency. Because no single study can prove causation, it is important to replicate study results before drawing an inference of causation. Consistent findings observed in multiple studies across different populations tend to support causation. Id. at 604.

3) Dose-Response. A dose-response relationship exists where studies show that the greater the exposure, the greater the risk of disease. Id. at 603. Generally, higher exposures should increase the incidence or severity of disease; however, some causal agents do not exhibit a dose-response relationship. Id. For example, some agents do not cause disease until the exposure exceeds a certain threshold dose. Id. Thus, a dose-response relationship is strong but not essential evidence of causation.

4) Biological Plausibility. Causal relationships should be consistent with existing knowledge about the mechanism by which the outcome develops. The importance of this factor depends on the degree of existing knowledge about how a disease develops.

5) Temporality. Causes must precede effects.

6) Coherence. A causal relationship should be consistent with other information and knowledge about the disease or harm.

7) Specificity. When the exposure is only associated with a single disease or type of disease, such specificity strengthens the case for a causal inference. Lack of specificity does not undermine causal inferences where there is a good explanation for its absence. Id. at 605-606.

8) Analogy. A causal inference is supported where relationships similar to the putative causal relationships have been substantiated.

9) Experimental Evidence. Causation is more likely if there is experimental evidence showing that removing the exposure results in a decrease of the occurrence of a disease.

The Bradford Hill analysis has been found to be a "generally reliable" methodology. Zoloft, 858 F.3d at 796. No single Bradford Hill factor is required to infer causation; the criteria "are neither an exhaustive nor a necessary list." Id.

Rule 702 requires, however, that an expert not only use "reliable principles and methods" but also that "the expert's opinion reflects a reliable application of the principles and methods to the facts of the case." Fed. R. Evid. 702. "Flexible methodologies . . . can be implemented in multiple ways; despite the fact that the methodology is generally reliable, each application is distinct and should be analyzed

for reliability." Zoloft, 858 F.3d at 795. Experts must "rigorously explain how they have weighted the criteria considered." Daniels-Feasel, 2021 WL 4037820, at *6.

Because the Bradford Hill factors are "neither an exhaustive nor a necessary list[,] [a]n expert can theoretically assign the most weight to only a few factors, or draw conclusions about one factor based on a particular combination of evidence." Zoloft, 858 F.3d at 796. "No algorithm exists for applying the [Bradford] Hill guidelines to determine whether an association truly reflects a causal relationship or is spurious." Milward v. Acuity Specialty Prods. Grp., Inc., 639 F.3d 11, 18 (1st Cir. 2011) (citation omitted). Thus, district courts must ensure that "[t]he specific way an expert conducts such an analysis [is] reliable." Zoloft, 858 F.3d at 796. "In discussing the conclusions produced by such techniques in light of the Bradford Hill criteria, an expert must explain 1) how conclusions are drawn for each Bradford Hill criterion and 2) how the criteria are weighed relative to one another." Id.

III. Dr. Ness

Dr. Roberta Ness, M.D., M.P.H., has provided an expert report dated February 7, 2024.[27] Dr. Ness is an esteemed epidemiologist. She was the Rockwell Endowed Professor in

[27] Dr. Ness has not practiced medicine for over 25 years.

Public Health at the University of Texas at Houston, having retired in 2020. From 2008 to 2014, she was the Dean of the University of Texas School of Public Health. She holds an M.D. from Cornell University and an M.P.H. in epidemiology from Columbia University. She has received several honors throughout her career, including, in 2017, the Lilienfeld Award for extraordinary contributions to the field of epidemiology from the American College of Epidemiology. She served as the President of the American College of Epidemiology in 2008 and the President of the American Epidemiologic Society in 2012. She was also elected to the National Academy of Medicine in 2009.

Dr. Ness's areas of expertise are women's health and epidemiology; in particular, her research has focused on ovarian cancer, pelvic inflammatory disorder, and preeclampsia. She has published approximately 450 peer reviewed publications on topics such as risk factors for ovarian cancer, pregnancy complications, and gynecologic and sexually transmitted infections. Dr. Ness has served as an expert witness in several lawsuits in which plaintiffs alleged that their use of talcum powder caused them to develop ovarian cancer.

Dr. Ness has limited professional experience with psychiatry, toxicology, and neurology. She has not published

articles or conducted research in these areas. Her curriculum vitae does not list any publication related to the development of neurological disorders in utero. In the late 1990s and early 2000s, however, she served as a co-investigator in research on lead exposure, attention deficit disorder, and delinquency; in 2002, she co-authored an article examining associations between bone lead levels and behavioral issues in adjudicated delinquent youths.[28] Other than the bone lead article, she has not published articles on ADHD. She has not conducted research looking at in utero exposure to acetaminophen and neurodevelopmental disorders.

Dr. Ness's engagement with these issues began in August 2022, when she was retained by an attorney from one of the law firms serving as lead counsel in this litigation. At the attorney's request, Dr. Ness agreed to look at the literature on acetaminophen. She had not heard of a relationship between acetaminophen and ADHD prior to her work as a consultant in this case. After reviewing the literature presented to her by plaintiffs' counsel, she spoke to a news publication on the link between prenatal exposure to acetaminophen and both autism and

[28] Needleman et al., Bone Lead Levels in Adjudicated Delinquents: a Case-Control Study, 24 Neurotoxicol. Teratol. 711 (2002).

ADHD and reviewed the content of the Autism Justice website, a website used to "acquire" plaintiffs.

After the First Daubert Opinion was issued, Dr. Ness was asked by plaintiffs' counsel to assess "the degree to which the epidemiologic and other supporting literature supports a case for general causality between prenatal use of acetaminophen (APAP) and attention deficit hyperactivity disorder."[29] She offers the opinion that "within a reasonable degree of scientific certainty, prenatal use of APAP causes ADHD." Dr. Ness conducted "an analytical review and evaluation of the published literature," which, "along with [her] education, training and experience provide the basis for [her] opinion." Dr. Ness's report is silent as to how she identified the studies to which she applied her Bradford Hill analysis. She concludes that consistency, dose-response, temporality, analogy, biologic plausibility, and coherence are met. She concludes that strength of association is partially met and that specificity and experiment are not satisfied. Her report is strikingly similar to that of Dr. Andrea Baccarelli, whose testimony was ruled inadmissible in the First Daubert Opinion, 2023 WL

[29] In her capacity as a consulting expert, Dr. Ness initially assessed the literature provided to her by plaintiffs' counsel involving ASD as well as ADHD. After the First Daubert Opinion was issued, plaintiffs' counsel asked her to address only ADHD.

8711617, at *20, although it also contains passages responsive to that Opinion.

Defendants argue that Dr. Ness's opinions on strength, consistency, specificity, dose-response and analogy are unreliable for several reasons. Defendants further argue that Dr. Ness is not qualified to offer opinions about biological mechanism or temporality and that, in any case, her opinions on those two factors are speculative and unreliable. After her qualifications are addressed, her Bradford Hill analysis will be discussed.

A. Qualifications

Defendants argue that Dr. Ness is not qualified to opine on biological plausibility and temporality because she has no specific expertise in toxicology, teratology,[30] pharmacology, or psychiatry. This argument has force.

The plaintiffs originally offered Dr. Robert Cabrera, an expert in teratology, to offer theories of biological plausibility. First Daubert Opinion, 2023 WL 8711617, at *37-40. He principally relied on a theory of oxidative stress. Id. at *38. The First Daubert Opinion struck Dr. Cabrera's opinion regarding oxidative stress for several reasons, including its

[30] Teratology is the study of abnormalities, malformations and developmental disabilities that occur during prenatal development.

failure to address two critical gaps in its analysis of the adverse outcome pathway and its cherry-picking of isolated findings. Id. at *39-40. The plaintiffs also relied on several experts with distinguished careers in the field of psychology and the treatment of NDDs. They included Dr. Andrea Baccarelli, who had co-authored studies on the impact of the use of acetaminophen during pregnancy on children's neurodevelopment, id. at *19, and Dr. Eric Hollander, a neuro-pharmacologist and psychiatrist who had published a book on ASD, id. at *40.

In contrast to the plaintiffs' five experts whose testimony was the subject of the First Daubert Opinion, Dr. Ness has little relevant expertise other than her substantial credentials as an epidemiologist. Dr. Ness's lack of expertise in the fields most pertinent to this litigation is concerning. Her lack of familiarity with ADHD was apparent at her deposition. Dr. Ness was frequently unable to answer even basic questions about ADHD -- such as examples of screening tools for ADHD -- without reading directly from her report. Nor could she answer questions of when ADHD develops in the fetal brain without reading from her report, or provide even a "high-level overview" of her proposed biological mechanism for its development.

Her lack of familiarity with the pertinent literature was also evident. For instance, her report states, regarding Baker

2020, that "[t]he use of MRI scanning validated the ADHD diagnosis." When questioned about the study, Dr. Ness was not able to answer without reading directly from her report or the study itself. As she ultimately conceded at her deposition, among the 48 children included in the study's MRI analysis, the authors did not measure ADHD directly. Baker 2020 at 1079. Importantly, MRI imaging is not a validation tool for ADHD. See DSM at 72 (noting that currently, "no form of neuroimaging can be used for diagnosis of ADHD"); see also Faraone 2021[31] at 792 (noting that although neuroimaging studies find small differences in the structure and functioning of the brain between people with and without ADHD, these differences cannot be used to diagnose ADHD).

Dr. Ness's lack of relevant pre-litigation expertise is particularly evident in the two areas identified by the defendants: the proposal of a biological mechanism by which prenatal exposure to acetaminophen may cause ADHD and the demonstration of temporality, that is, that cause precede effect. Her lack of expertise meant that she struggled to answer during her deposition even basic questions regarding these components of her report. Although Dr. Ness's proposed

[31] Faraone et al., The World Federation of ADHD International Consensus Statement: 208 Evidence-based Conclusions about the Disorder, 128 Neuro. Biobehavioral Rev. 789 (2021).

testimony will not be excluded on the basis that she is unqualified to offer it, the fact that her opinion was developed for litigation requires a court to undertake a particularly careful examination of the opinion to ensure its reliability.

B. Reliability

Defendants argue that Dr. Ness's analysis of causation is unreliable. They are correct. Before addressing the deficiencies in Dr. Ness's Bradford Hill analysis, however, her failure to treat the evidence of genetic confounding adequately will be described.

1. Genetic Confounding

Dr. Ness recognizes that genetic confounding is "very concerning" and requires her careful analysis. She acknowledges that genetics "could be a true confounder." She concludes, however, that genetic confounding "may partially inflate" the observed risk between maternal acetaminophen use and the risk of ADHD in offspring, but finds "no compelling" data to support the idea that genetics "could eliminate the association." In reaching this conclusion she identifies three studies that, in her view, are worth taking seriously: Ystrom 2017, Leppert 2019,[32] and Gustavson 2021. Then, based on the maternal negative

[32] Leppert et al., Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Expsoures, 76(8) JAMA Psychiatry 834 (2019).

control results from Ystrom 2017 and Liew 2019,[33] she concludes that confounding by genetics is not "the most likely" explanation for any apparent association between acetaminophen exposure and ADHD.

Dr. Ness's approach to this issue does not reflect the rigor required to render an admissible opinion on causation. The defendants point out not only the defects in her analysis of Ystrom 2017, Leppert 2019, and Gustavson 2021, but also the plaintiffs' failure to grapple with Ahlqvist 2024 and its impact on Dr. Ness's evaluation of genetic confounding. Because genetic confounding must be seriously considered when examining any association between prenatal exposure to acetaminophen and the diagnosis of ADHD in offspring, these deficiencies, by themselves, render the entire causation analysis advanced by Dr. Ness inadmissible.

As for the first study she highlights, Ystrom 2017, Dr. Ness does not seriously engage with its findings. Ystrom 2017 found that a father's preconceptual use of acetaminophen was as strongly associated with a child's diagnosis of ADHD as a mother's use in all three trimesters and in any two trimesters

[33] Ystrom 2017 used maternal prepregnancy use of acetaminophen as a maternal negative control, and found that it had no effect on offspring ADHD. Id. at 4. Liew 2019 found non-significant associations between maternal prepregnancy and post-pregnancy use and offspring ADHD. Id. at 773.

during the pregnancy. Id. at 5. Dr. Ness describes the finding as "unexpected" and "odd," and rejects it as irrelevant because it is not measuring the impact of the mother's contribution to her offspring's diagnosis. That misses the point. As the authors of Ystrom 2017 acknowledge, the association of paternal use with a diagnosis of ADHD in offspring is not definitive evidence of a causal relationship but it does raise a question of whether a causal relation between maternal use of acetaminophen and ADHD exists. At the very least, as the July 2022 Review by the FDA noted, the paternal result in Ystrom 2017 suggests unmeasured confounding. FDA 2022 at 26.

Dr. Ness's treatment of Leppert 2019 is also problematic. Leppert 2019 found an association between maternal polygenic risk score for ADHD and a mother's prenatal use of acetaminophen during both early and late pregnancy. Id. at 838. The results of the study indicated to the authors that "mothers with higher ADHD [polygenic risk scores] may also be more likely to use acetaminophen during pregnancy." Id. at 839. The authors observed that genetic confounding must be accounted for when studying any observed association between ADHD in offspring and the use of acetaminophen during the pregnancy. Id. at 840. Dr. Ness dismisses this study because the authors "did not show directly that genetic risk impacted the association between APAP

use and ADHD." Dr. Ness points to Stergiakouli 2016 and Ruisch 2018 as mitigating concerns over genetic confounding and elevates the results of those studies over Leppert 2019. Dr. Ness states that "Stergiakouli and Ruisch both actually applied the genetic risk score to the assessed link between APAP use and ADHD and found no substantial diminution of effect." This is not entirely correct. While Stergiakouli 2016 found that maternal polygenic risk score for ADHD was not associated with acetaminophen use during pregnancy (that is, did not find the link that Leppert 2019 found three years later), Ruisch 2018 controlled only for conduct disorder ("CD") polygenic risk scores, not ADHD polygenic risk scores.

But it is Dr. Ness's treatment of Gustavson 2021 that is most troubling. To recap, Gustavson 2021 used data from the MoBa cohort to conduct a sibling-control analysis with the goal of assessing the role of familial confounding. The study was based on over 21,000 children, comprised of over 10,000 sibling pairs,[34] and found that the association between HKD and use of acetaminophen for more than 29 days was attenuated to non-significance using a sibling control analysis (1.06; 0.51-2.05).

[34] Of the 21,448 children, over 19,000 belonged to a sibling pair, almost 2,000 belonged to a trio, and 80 children belonged to a quartet. Gustavson 2021 at 3.

Siblings were discordant on exposure to acetaminophen and an ADHD diagnosis in 306 families, and were discordant on long-term exposure (more than 29 days) and ADHD diagnosis in 34 families (comprising 72 children).

Dr. Ness acknowledges that the sibling control results in Gustavson 2021 are a "cause for concern" but dismisses the study as having serious limitations, most notably its small size. She prioritizes the results of Brandlistuen 2013[35] over Gustavson 2021. Brandlistuen 2013 studied 2,919 same-sex sibling pairs from the MoBa cohort who were three years old and concluded that children exposed to long-term use of acetaminophen during pregnancy had substantial adverse developmental outcomes, for instance externalizing problems, at that age. This comparison is inapt. Most strikingly, Brandlistuen 2013 studied three-year olds for whom there was no ADHD diagnosis while Gustavson 2021 relied on an ADHD diagnosis in older children from the very same cohort. Gustavson 2021 was specifically designed to better understand potential familial confounding of the association between prenatal acetaminophen exposure and ADHD.

[35] Brandlistuen et al., Prenatal Paracetamol Exposure and Child Neurodevelopment: A Sibling-Controlled Cohort Study, 42(6) Int'l J. Epidemiol. 1702 (2013).

In any event, Dr. Ness's report notes that if the results of Gustavson 2021 were replicated, "that would be a cause for greater concern about genetic confounding." As already described, the results of Gustavson 2021 were recently replicated with a much larger sample: Ahlqvist 2024 included over 31,000 sibling pairs discordant on both exposure and outcome. Its authors reported that an initially-observed association between prenatal acetaminophen use and ADHD (1.07; 1.05-1.10) was attenuated to non-significance (0.98; 0.94-1.02) among siblings. Id. at 1210. Although at her deposition Dr. Ness took issue with the low prevalence of both an ADHD diagnosis and acetaminophen use in the study population in Ahlqvist 2024 (5.90% and 7.49%, respectively), the authors noted that "even if acetaminophen use had been substantially underascertained, such measurement error would have been unlikely to result in the null associations observed with sibling control. Id.[36]

[36] Plaintiffs make much of the fact that in Ahlqvist 2024 only 7.49% of birthing parents reported acetaminophen use during pregnancy. Id. at 1213. They neglect, however, the authors' detailed analysis of that figure and its concordance with other studies measuring prenatal acetaminophen use in Sweden. Id. at eAppendix 1. Plaintiffs also neglect the authors' statement that "even large amounts of exposure measurement error could not explain the nullification of associations seen with sibling control." Id. at 1213.

The implications from Ahlqvist 2024 for Dr. Ness's report are profound. It is undisputed that ADHD is highly heritable; indeed, Dr. Ness states that "[c]learly, genetics contributes to ADHD risk." Ahlqvist 2024, a sophisticated large-scale study funded by the NIH, finds that the apparent association between exposure to acetaminophen and ADHD disappears altogether when genetic confounding is accounted for through a sibling control study. These are complex issues to investigate and for over a decade scientists across the globe have been designing and running studies to gain insight. Ahlqvist 2024 must be taken seriously.

Plaintiffs argue -- without citation -- that the "Court is certainly not free to interpret a study result for itself, unconstrained by the actual record and adversarial process." The parties have submitted the studies, including Ahlqvist 2024, in connection with this Daubert motion and have relied upon the Court to examine all of the submitted evidence in light of their arguments. The parties have had an opportunity to be heard about Ahquvist 2024. The Court will not ignore this study.

Moreover, it is the plaintiffs' burden to demonstrate that Dr. Ness's proffered testimony is reliable. Her report and deposition testimony indicate that a study like Ahlqvist 2024 -- a larger scale study than that described in Gustavson 2021 --

might change her opinion. And, although she was presented with the study weeks before the parties' briefing deadlines, plaintiffs did not ask to supplement the record with expert testimony analyzing it. The Court declines to blinker its assessment of the reliability of Dr. Ness's testimony simply because plaintiffs prefer that the Court not consider the study. As Dr. Ness has acknowledged, the studies on which she relies reveal that any association between prenatal exposure to acetaminophen and ADHD in offspring is only "modest." If that evidence of a modest association is eliminated entirely by a sibling control study, that result should not be ignored. Where the expert is informed about a study, a court may consider an expert's failure to "explain . . . why [a] new study d[oes] not contradict his opinion," even if it "was not available to [the expert] when he prepared his report". See Zoloft, 858 F.3d at 790, 790 n.10. In any case, this Court would reach the same decision regarding Dr. Ness's reliability even if Ahlqvist 2024 had not been published.

Finally, plaintiffs insinuate some impropriety on behalf of defendants based on the fact that defendants "had prepared questions about the study in advance of the deposition" despite its publication that same day. There is no basis to find any impropriety. Many experts in the field would have had knowledge

well in advance of the publication date of both the existence of such an important study and then its submission for publication. It has 9 co-authors and was of course subject to peer review before publication. If the plaintiffs had learned of the study and its results before publication, no one would be surprised.

In sum, although Dr. Ness spends more time on the issue of genetic confounding than the plaintiffs' prior experts, her opinion on this important issue is ultimately unreliable. Because of the importance of this issue to the assessment of causation of ADHD, her failure to reliably assess genetic confounding renders her ultimate opinion on causation inadmissible under Rule 702.

2. Bradford Hill

Independent of Dr. Ness's failure to reliably assess the issue of confounding, her Bradford Hill analysis is deficient and inadmissible under Rule 702 standards. To begin with, she identifies three Bradford Hill factors as the most important factors in her causation opinion: consistency, temporality, and dose-response. Her discussion of each of these three factors, however, displays result-oriented reasoning, rendering her assessments unreliable. Since the remaining factors cannot support a finding of causation, her Bradford Hill analysis must be stricken.

i. Consistency

The consistency factor arises from the insight that, to effectively demonstrate a causal relationship, it is important that an association be observed in different populations and by different investigators. "Although inconsistent results do not necessarily rule out a causal nexus, any inconsistencies signal a need to explore whether different results can be reconciled with causality." RMSE at 604.

Dr. Ness places "great" weight on the consistency criterion and finds that it is met here. In support of her opinion that consistency is satisfied, she reports that the results of studies linking in utero exposure to acetaminophen and a diagnosis of ADHD "are almost uniformly positive and mostly statistically significant." Dr. Ness points repeatedly to meta-analyses by Ricci 2023 and Masarwa 2020, stating that those two studies showed "remarkable consistency" and "no significant heterogeneity." Dr. Ness acknowledges that the range of estimates within ADHD studies is broad but opines that when broken down by duration of use, the range is narrower. She also opines that the "great majority" of studies found dose-response relationships and identified a specific window of sensitivity, specifically the second and/or third trimesters. Finally, Dr. Ness also quotes FDA 2022 as stating that "neurobehavioral

outcome studies . . . suggest a consistent association between APAP or long durations of prenatal APAP exposure and ADHD."

As the defendants point out, each of these observations by Dr. Ness is faulty and is at odds with the data she cites. To begin with, Dr. Ness mischaracterizes Ricci 2023 and Masarwa 2020. The authors of Ricci 2023 actually state that "[e]ven in the ADHD meta-analyses, there was moderate heterogeneity." Id. at 482. Ricci 2023 added that the certainty of the evidence of even a small increased risk of ADHD "is low" in light of several factors, including the "limited number of sufficiently comparable studies available to meta-analyze." Id. at 483. The Masarwa 2020 authors state that "there was substantial heterogeneity in meta-analyses" and "insufficient data to explore the potential sources of this heterogeneity." Id. at 315. The authors of Ricci 2023 and Masarwa 2020 expressly caution that there was a need to conduct high-quality research and to explore the impact of confounding -- both by indication and parental ADHD -- on any perceived association. Ricci 2023 at 482, 483; Masarwa 2020 at 313-14, 316.

Next, the heterogeneity does not disappear, as Dr. Ness suggests it does, by looking at duration of use, dose-response, and trimester of use. As the defendants point out, although most of the studies found at least one statistically

significant, positive risk ratio, each study calculated risk estimates for a variety of exposure measurements and their results varied. It is not a scientifically sound practice to simply pick one or two risk estimates from each study without acknowledging the rest of that study's findings. Findings regarding trimester of use illustrate the problem with Dr. Ness's conclusion regarding consistency. For instance, Liew 2014 found a significant association between an HKD diagnosis and first trimester use, first and third trimester use, and use in all three trimesters, but not in second or third trimester use or use in both the second and third trimesters. The same study identified significant associations between ADHD medication use and third trimester exposure, first and third trimesters, second and third trimesters, and exposure in all trimesters, but not in first, second, or first and second trimesters. In contrast, Ystrom 2017 identified significant results only in the first and second trimester combined, but not in any individual trimester (despite having larger sample sizes than in Liew 2014) or in first and third, second and third, or all three trimesters. Next, Chen 2019 found no significant associations in any trimester or combination of trimesters in the general analysis, but did find a significant association in the second trimester and first and second trimester (but not

second and third or all three trimesters) in a sensitivity analysis excluding women with gestational infections and mental health disorders. The only way to find, as Dr. Ness did, that the "great majority" of studies identified the second and/or third trimester as most sensitive to APAP exposure is to ignore statistical significance, cherry-pick data, and ignore contrary findings. This is not a reliable application of scientific methodology.

Finally, Dr. Ness's quotation of FDA 2022 as stating that "in general, the functional neurobehavioral outcome studies examined in this review along with the reviewed meta-analyses suggest a consistent association between APAP or long durations of prenatal APAP exposure and ADHD" is misleading. FDA 2022 at 32. The following sentence, which she did not cite, reads, "However, findings for trimester-specific associations are not consistent." Id. Nor does she contend with the FDA's ultimate finding that "there are still study limitations and inconsistent study findings that prohibit causal interpretations of the association between APAP exposure and functional neurobehavioral outcomes." Id. at 33. Likewise, she does not mention FDA 2023's conclusion that "the limitations and inconsistent findings of current observational studies of APAP and

neurobehavioral and urogenital outcomes are unable to support a determination of causality." Id. at 17-18.[37]

The plaintiffs accuse the defendants of requiring an "impossible" standard for consistency that "requires all results and all sub-analyses to be statistically significant." Not so. Instead, what Rule 702 requires is an evenhanded application of methodologies. Here, instead of reliably describing and then grappling with the variability among -- and often within -- studies, Dr. Ness "cherry-pick[s] from the scientific landscape and present[s] the Court with what [s]he believes the final picture looks like." Daniels-Feasel, 2021 WL 4037820, at *4. She ignores the importance of statistical significance even in studies with large sample sizes like Ystrom 2017. Further, she misrepresents statements by the authors of the studies upon which she relies. Accordingly, her opinion on this factor does not pass muster under Rule 702.

[37] Indeed, Dr. Ness does not adequately address the FDA's repeated conclusion that the epidemiological evidence does not support her opinions. Despite including the "FDA productions in this litigation" in her list of materials considered, the entirety of her response to those materials is to complain that "the FDA nowhere explains why causation is still not the most likely explanation for the association, even if it is not the only possibility. Nor did FDA perform a Bradford Hill analysis, as I have here."

ii. Temporality

A temporal or chronological relationship must exist for causation to exist. RMSE at 601. If an exposure occurs after the disease develops, it "cannot have caused the disease." Id.

Dr. Ness puts "great weight" on the tenet of temporality and finds that it is met. Dr. Ness opines that the prefrontal cortex is the brain region most important to ADHD, and the greatest risk from exposure to acetaminophen is in the third and possibly from the middle of the second trimester of gestation, which is also when the prefrontal cortex is most sensitive to disruption. Dr. Ness points to Ystrom 2017, Chen 2019, Inoue 2021, and Stergiakouli 2016[38] to support her contention that acetaminophen use in the first trimester produced risk ratios of 1.09-1.31 and of 1.13-1.20 in the second semester. In support of her opinion that risk ratios for acetaminophen use during the third trimester ranged from 1.28-2.86, and were 1.88-2.86 in four of five studies, she relies on Liew 2014, Ji 2018, Gustavson 2019,[39] Baker 2020, and Ji 2020.[40]

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[38] It is assumed that Dr. Ness is referring to Stergiakouli 2016 when she cites Stergiakouli 2018.

[39] Gustavson et al., Maternal Fever During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder, 9 Scientific Reports 9519 (2019).

[40] As previously discussed, the two Ji studies do not reflect third trimester exposure; Ji 2020 reflects at most peripartum

The defendants challenge Dr. Ness's qualifications to opine on the trimester that is most sensitive for the development of the prefrontal cortex and take issue with the sources on which she relies to support her opinion. But assuming that she could support that opinion, the defendants contend that the studies on exposure to acetaminophen by trimester found no statistically significant association between exposure in the third trimester and an ADHD diagnosis, with the majority of studies reporting lower effect estimates for the third trimester compared to the first or second trimester.

The defendants are correct to emphasize the importance of locating statistically significant results in those ADHD diagnosis studies that compare exposure by trimester. As discussed below, only one sub-analysis in the studies cited by Dr. Ness showed a statistically significant positive risk ratio for acetaminophen exposure in the third trimester alone. Dr. Ness insists that, because "[s]tatistical significance depends on sample size and any particular cut-off is arbitrary," it need not be "used as a measure of impact or import"; instead, "[e]ffects found in some studies can contribute to the case for

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exposure. Gustavson 2019, which primarily studied fever, found that children of mothers with fevers during pregnancy had similar odds of receiving an ADHD diagnosis whether or not the mother had taken acetaminophen for her fever. Id. at 4.

causality even if they are not, alone, statistically significant." But Dr. Ness's reframing of the importance of statistical significance goes beyond merely considering insignificant results along with those that are significant, or reading less into significance where sample sizes are small. Instead, in her analysis of temporality, Dr. Ness often disregards statistically significant results, or results from studies with large sample sizes, and highlights insignificant results in their stead. This is not a reliable application of scientific methodology.

Moreover, as the defendants rightly point out, Dr. Ness engages in flagrant cherry-picking. The defendants emphasize three of the studies listed by Dr. Ness to make their point. (The plaintiffs in their opposition brief do not suggest that this choice omits a study of significance to Dr. Ness's analysis.)

For instance, in Chen 2019's general analysis, the authors found risk ratios of 1.09 (0.92-1.28) in the first trimester, 1.19 (1.00-1.40) in the second, and 0.97 (0.83-1.13) in the third -- that is, no statistically significant result for any trimester. There were also no statistically significant results among combined trimesters. In the sensitivity analysis omitting women with infections and mental health disorders, Chen 2019

found a risk ratio of 1.27 (1.00-1.61) in the first trimester, 1.33 (1.04-1.69) in the second trimester, and only 1.05 (0.85-1.29) in the third trimester. For the first and second trimester combined, the Chen 2019 sensitivity analysis resulted in a risk ratio of 1.68 (1.18-2.40) for an ADHD diagnosis, and there were no statistically significant results for the first and third trimester, second and third trimester, or all three trimesters. Thus, the only statistically significant results from the sensitivity analysis in Chen 2019 were for the second trimester and first and second trimester combined. Of this data, Dr. Ness picked only the lower, non-significant first trimester risk ratio from the general analysis, ignoring the significant second trimester risk ratio in the sensitivity analysis and the fact that in both analyses the risk ratio was lower in the third trimester than the first, contrary to her opinion that the third trimester presents the greatest risk.

The next study is similarly problematic for Dr. Ness's conclusion. Ystrom 2017 -- which had large samples for each trimester of exposure -- found risk ratios of 1.12 (0.94-1.32) for the first trimester, 1.04 (0.92-1.18) for the second, and 1.12 (0.75-1.67) for the third. Thus, the risk ratios were the same for the first and third trimester, and none of the ratios were statistically significant. But Ystrom 2017 found a

statistically significant risk ratio of 1.21 (1.06-1.39) for the first and second trimester combined -- again, contrary to Dr. Ness's opinion that the third trimester presents the greatest risk.

Finally, Liew 2014 found the following associations between exposure and an HKD diagnosis: 1.35 (1.07-1.72) for the first trimester, 1.26 (0.91-1.73) for the second, and 1.22 (0.97-1.53) for the third -- again showing a smaller (non-significant) risk for the third trimester than the (significant) first. The same study, when assessing ADHD medication rather than an HKD diagnosis, found risk ratios of 1.09 (0.89-1.33) for the first trimester, 1.20 (0.91-1.55) for the second, and 1.28 (1.07-1.52) for the third. Of all the Liew 2014 data, Dr. Ness picks only the third trimester risk ratios for ADHD medication use, ignoring the diagnostic data altogether, including the fact that again, the risk ratio for first trimester exposure and an HKD diagnosis was higher than for third trimester exposure.

Plaintiffs do not seriously engage with the above issues in their brief in opposition to this motion. Instead, they devote most of their argument on temporality to the assertion that temporality should be considered satisfied because the exposures precede the development of ADHD symptoms. But, as explained in the First Daubert Opinion, the relevant question is not whether

exposure precedes diagnosis but whether it precedes the development of the disorder. 2023 WL 8711617, at *31.

Because Dr. Ness's analysis of temporality repeatedly cherry picks isolated findings in studies, ignores those that are unsupportive of her ultimate opinion, and highlights statistically insignificant results while ignoring statistically significant results, her opinion on temporality is a "result-driven analysis" that "undermines principles of the scientific method." Daniels-Feasel, 2021 WL 4037820, at *5. It is not sufficiently reliable under Rule 702 standards to be admissible.

iii. Dose-Response

The factor of the dose-response relationship means that the greater the exposure, the greater the risk of disease. If this relationship exists, it is strong but not essential evidence of causation because some causal agents require that the exposure exceed a certain dose to have a causal effect. RMSE at 603.

Dr. Ness weighed dose-response "heavily" in her determination of causality and found that it is met. Dr. Ness states that longer durations of use, greater frequency of use, and higher concentration (in meconium, cord blood and maternal blood) demonstrate a dose-response relationship between exposure

to acetaminophen and an ADHD diagnosis.[41] Dr. Ness considers Baker 2020 to be "most informative regarding this criterion." Dr. Ness also claims that the authors of Liew 2014 "found exposure response trends with increasing frequency of use during gestation."

Defendants argue that Dr. Ness does not effectively engage with the difficulty of measuring dosage, is over-reliant on Baker 2020, misreads Liew 2014, and fails to acknowledge those studies that did not show dose-response. Their arguments are well taken.

It is challenging, as everyone recognizes, to formulate a reliable dose-response study for acetaminophen exposure during a pregnancy. Because with rare exceptions acetaminophen is not a prescription medication, it is difficult to measure the actual amount consumed by pregnant women. First Daubert Opinion, 2023 WL 8711617, at *7-8. Dr. Ness justifies her reliance on crude exposure measurements by a comparison to the government studies of contaminated drinking water at Camp Lejeune. But anyone who lived or worked at Camp Lejeune would most likely have been exposed daily to the drinking water, so duration of exposure was

[41] Dr. Ness does not opine that exposure to acetaminophen for at least 28 days in utero increases the risk of developing ADHD twofold. This is the opinion proffered by Dr. Louie, on whom the plaintiffs first relied. See First Daubert Opinion, 2023 WL 8711617, at *47.

a reasonable proxy for dosage there. In contrast, in the acetaminophen studies, one week of exposure (as reported or remembered by mothers), could be one tablet (of unknown dose) or over seven. Similarly, one trimester could be exposure to one tablet or over 90 or indeed many more. Even if it were possible to overlook this vulnerability in Dr. Ness's analysis, her treatment of the studies on which she relies and her failure to discuss other clearly relevant studies are a different matter.

Dr. Ness relies most heavily on Baker 2020. To recap, Baker 2020 measured acetaminophen levels in meconium samples and found that a low acetaminophen level did not significantly modify the risk of ADHD compared with no acetaminophen (1.44; 0.79-2.63), but high levels increased the odds of ADHD more than four-fold (4.10; 2.41-6.95). The authors of Baker 2020 cautioned, however, that they did not correlate maternal acetaminophen use with the acetaminophen concentrations in meconium. Id. at 1078-79.

Moreover, Baker 2020 did not adjust for confounding. First Daubert Opinion, 2023 WL 8711617, at *30. And, studies like Ystrom 2017 have shown that longer-term use may indicate longer-term indication for use, particularly to treat pain.[42] Out of

[42] Headache is the most common indication for use during pregnancy and is rarely accounted for in the studies on which Dr. Ness relies. Vlenterie 2016 found that, of women in the

1034 mothers in that study reporting 29 or more days of use, 609 indicated use for pain, while 200 did not specify an indication. Id. at 6. Thus, an over-reliance on Baker 2020 compared to studies that were able to adjust for confounding, including by indication, presents a serious problem for Dr. Ness's dose-response analysis.

Significantly, Gustavson 2021, which used more recent data from the same cohort used by Ystrom 2017, found, like Ystrom 2017, a doubling of the risk (2.02; 1.17-3.25) for 29 or more days of use. But equally if not more important, Gustavson 2021 addressed the issue of genetic confounding. The increased risk of an ADHD diagnosis associated with long term exposure to acetaminophen was attenuated to 1.06 (0.51-2.05) and not statistically significant when adjusted for family effect. Id.

MoBa cohort who used APAP for 28 or more days during pregnancy, the most common indications for use were headache or migraine (80.2%), back pain (66%), and pelvic girdle pain (49.9%). Vlenterie et al., Neurodevelopmental Problems at 18 Months Among Children Exposed to Paracetamol in utero: A Propensity Score Matched Cohort Study, 45 Int. J. Epidemiol. 1998, 2002 (2016). Gustavson 2021 found that pain conditions constituted 82% of the conditions for which acetaminophen was used for 29 days or more. Id. at 5. In support of her assertion that pain is not a confounder, Dr. Ness lists studies which, with one exception, did not include ADHD as an endpoint. The study that did use ADHD as an endpoint found that adjusting for maternal migraine decreased the association between prenatal acetaminophen exposure and an ADHD diagnosis. Masarwa 2020 at 314.

at 7. Dr. Ness does not discuss this in her analysis of dose-response.

The defendants argue as well that it is significant that Dr. Ness dismissed Chen 2019 as an "outlier." Chen 2019 found a lower, non-significant risk ratio for acetaminophen use in all three trimesters (1.12; 0.97-1.29) compared to use in any trimester (1.40; 1.14-1.73). Id. at e5. She states that "this is to be expected given small sample sizes and wide confidence intervals." But Chen 2019 had larger sample sizes and narrower confidence intervals than Baker 2020.

Overall, Dr. Ness's assessment of dose-response is undercut by the limited data on which it is based and her failure to consider the impact of confounding by indication and genetics on the studies on which she relies most heavily for this factor. As a result, her assessment of this factor is not sufficiently reliable to support her heavy reliance on it in her overall causation analysis.

iv. Strength, Biological Plausibility, Analogy, Coherence, Specificity, Experiment

Dr. Ness's assessment of the remainder of the Bradford Hill factors does not support a finding of causality. She admits that neither specificity nor experiment are met. Dr. Ness opines that the strength of association is "modest" and finds that factor only "partially met." Dr. Ness puts "little weight"

on the criterion of analogy, which examines whether exposures with similar mechanisms have been shown to cause the outcome of interest. That leaves two other factors.

Dr. Ness agrees with the observation that biologic plausibility "is neither necessary nor sufficient for causation -- it merely bolsters the case for causation that is evident from the human epidemiology." Nonetheless, she gives this factor moderate weight and finds it is met. Her opinion on a potential biological mechanism, which is largely derived from her reading of animal studies, is flawed for the same reasons as those of plaintiffs' prior experts: it fails to reliably fill critical gaps in the purported mechanistic pathway. See First Daubert Opinion, 2023 WL 8711617, at *38-41.

Finally, Dr. Ness describes the coherence criterion as addressing the overarching question of whether the hypothesized causal relation conflicts with current biological and epidemiological understandings of the disease process. Dr. Ness places low weight on coherence, but believes it is satisfied. She draws her opinion on coherence entirely from her opinions on strength, consistency, dose-response, temporality, analogy, and biological plausibility. Because Dr. Ness's treatment of coherence explicitly relies on opinions that this Opinion finds

unreliable, it cannot fill the gap and support a finding of causation.

In sum, Dr. Ness's analyses of the factors upon which she placed the most weight -- consistency, temporality, and dose-response -- are unreliable. Accordingly, her Bradford Hill assessment of causation fails the requirements of Rule 702. Even if it were possible to rely solely on the additional Bradford Hill factors (and it is not), they also fail to support a finding of causation.

To be sure, given the state of the science Dr. Ness confronted long odds in offering her opinion on causation. ADHD can be a serious disorder, and scientists have sought to understand its origins. It is now estimated to be approximately 74% heritable. Many potential linkages to ADHD have been studied, among them the potential association between ADHD and prenatal exposure to acetaminophen. Dr. Ness acknowledges that the evidence of any association between prenatal exposure to acetaminophen and an ADHD diagnosis in offspring is only "modest." Sibling control studies, which Dr. Ness rates as among the most reliable of studies, have found that any apparent association between acetaminophen exposure and ADHD disappears altogether when genetic confounding is accounted for. Medical associations and government bodies have weighed in on this issue

and none has opined that there is a causal link through prenatal exposure to acetaminophen. Even the authors of the Consensus Statement clarified that they had avoided any inference of causality. Against this backdrop, Dr. Ness offers her opinion that "within a reasonable degree of scientific certainty, prenatal use of APAP causes ADHD."

Admittedly, in giving this opinion, Dr. Ness avoids some of the difficulties posed by the analyses of the plaintiffs' first set of experts. She does not attempt to provide a transdiagnostic analysis of the literature and does not opine that exposure to acetaminophen causes ASD. She instead limits her Bradford Hill analysis to ADHD and largely focuses on studies with an ADHD diagnosis as the measured endpoint. She also more seriously considers the issue of confounding. Nevertheless, the weaknesses in her report, confirmed by her deposition testimony, render her opinion on causation unreliable and inadmissible. Simply stated, her Bradford Hill analysis is not an objective or rigorous application of scientific methodology. It was result driven. Independently, her failure to confront carefully and fairly the profoundly important issue of confounding by genetics renders her opinion on causation inadmissible.

The plaintiffs argue that a jury and not a court must determine whether Dr. Ness's opinion on causation is correct because this is an issue on which reasonable scientists can disagree. Had Dr. Ness's opinion passed muster under Rule 702, it would be the jury's duty to assess it. But as the Supreme Court determined in Daubert, Rule 702 requires that "an expert's testimony pertain to 'scientific knowledge,'" thereby establishing a standard of evidentiary reliability. 509 U.S. at 590. Under the Rules of Evidence, it is the task of the trial judge to "ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." Id. at 589. The plaintiffs have failed to make the requisite showing of reliability required by Rule 702.

Conclusion

The defendants' motion of March 29, 2024 to exclude Dr. Ness's general causation opinion is granted.

Dated: New York, New York
July 10, 2024

DENISE COTE
United States District Judge