UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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

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DENISE COTE, District Judge:

This Opinion addresses the Rule 702 motions filed by the parties in this multidistrict products liability litigation ("MDL"). The plaintiffs in this MDL assert that the defendants violated their state law duties to warn consumers of the risk that children may develop autism spectrum disorder ("ASD") and/or attention-deficit/hyperactivity disorder ("ADHD") as a result of in utero exposure to acetaminophen. The defendants include a manufacturer as well as several retailers of acetaminophen products. The parties have completed discovery on the issue of general causation -- that is, whether prenatal exposure to acetaminophen causes ASD and ADHD.

Plaintiffs have put forward five expert witnesses on general causation. Defendants have put forward six experts. Each of the parties' experts is eminently qualified.

For the following reasons, the defendants' motions to preclude the testimony of plaintiffs' general causation experts are granted. With these rulings, the plaintiffs do not have admissible evidence to demonstrate that prenatal exposure to acetaminophen causes either ASD or ADHD in offspring. The Court denies as moot plaintiffs' motions to preclude the testimony of defendants' experts.

Procedural Background

In 2022, plaintiffs -- children, parents, and guardians who allege 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. These lawsuits allege that defendants' labeling practices for acetaminophen were deficient under various state laws. Plaintiffs have sued the manufacturer of Tylenol (Johnson & Johnson Consumer Inc. ("JJCI")) and retailers of store-branded acetaminophen products ("Retailer Defendants"). Plaintiffs assert several state law causes of action: strict liability for failure to warn, strict liability for design defect due to inadequate warnings and precautions, negligence, negligent misrepresentation by omission, and breach of implied warranty.

On October 5, 2022, the Judicial Panel on Multidistrict Litigation ("JPML") consolidated eighteen of plaintiffs' cases (filed in seven districts) and transferred the cases to this Court under 28 U.S.C. § 1407. This MDL now includes around 600 member cases.

I. Prior Opinions in this Case

Two defendants (Wal-Mart Stores, Inc. ("Walmart") and JJCI) separately moved to dismiss a total of three actions on the

ground of preemption. Walmart's motion to dismiss two lawsuits filed in the Western District of Arkansas was denied on November 14, 2022. In re Acetaminophen – ASD-ADHD Prods. Liab. Litig., No 22md3043 (DLC), 2022 WL 17348351 (S.D.N.Y. Nov. 14, 2022). JJCI's motion to dismiss an action filed in the District of Nevada was denied on April 20, 2023. In re Acetaminophen – ASD-ADHD Pros. Liab. Litig., No 22md3043 (DLC), 2023 WL 3026412 (S.D.N.Y. Apr. 20, 2023). In April and May of 2023, motions to dismiss addressed to individual actions in this MDL were addressed.[1] The plaintiffs subsequently agreed to drop all strict liability misrepresentation claims, consumer protection claims, and standalone apparent manufacturer liability claims from all of the individual actions. 22md3043: ECF No. 772.

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 at issue in this litigation ("Plaintiffs' Proposed Warning"). The Plaintiffs' Proposed Warning is:

> **Autism/ADHD**: Some studies show that frequent use of this product during pregnancy may increase your

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

> child's risk of autism and attention deficit hyperactivity disorder. If you use this product during pregnancy to treat your pain and/or fever, use the lowest effective dose for the shortest possible time and at the lowest possible frequency.

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 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 complex products liability or 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. After additional conferences, an Order of February 1, 2023 set a schedule for fact and expert discovery and Rule 702 proceedings on the issue of general causation. All general causation fact discovery was to be completed on June 2.

Plaintiffs served their expert reports on June 16. Plaintiffs' experts are: Andrea Baccarelli, M.D., Ph.D. ("Dr. Baccarelli"), Brandon Pearson, Ph.D. ("Dr. Pearson"), Robert Cabrera, Ph.D. ("Dr. Cabrera"), Stan Louie, Pharm.D. ("Dr. Louie"), and Eric Hollander, M.D. ("Dr. Hollander"). Dr. Baccarelli is an epidemiologist, Dr. Pearson a toxicologist, Dr. Cabrera a teratologist and geneticist, Dr. Louie a pharmacologist, and Dr. Hollander a psychiatrist. One week later, plaintiffs emailed defendants with a link to amended reports for all five of plaintiffs' experts. Defendants' expert designation and report deadline was thus moved one week.

The defendants' experts are: Dr. Jennifer Pinto-Martin, Ph.D., M.P.H. ("Dr. Pinto-Martin"), Dr. Wendy Chung, M.D., Ph.D. ("Dr. Chung"), Dr. Craig Powell, M.D., Ph.D. ("Dr. Powell"), Dr. Mitchell McGill, M.D., Ph.D. ("Dr. McGill"), Dr. Stephen Faraone, Ph.D. ("Dr. Faraone"), and Dr. Alexander Kolevzon, M.D. ("Dr. Kolevzon"). Dr. Pinto-Martin is an epidemiologist, Dr. Chung a geneticist, Dr. Powell a neuroscientist, Dr. McGill a

toxicologist, Dr. Faraone a psychologist, and Dr. Kolevzon a psychiatrist. Plaintiffs' rebuttal expert reports were served on July 28, and all experts were deposed as of September 8.

The 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.[2]

Factual Background

Before addressing the individual Rule 702 motions, this Opinion sets out background information relevant to the motions. This background information describes 1) acetaminophen and its regulation; 2) ASD and ADHD and their characteristics; 3) the basics of epidemiological evidence; 4) the types of the scientific research and many of the studies on which the parties' experts have relied; and 4) the assessments, statements and conclusions of various medical and governmental bodies on the issue at stake in these motions.

IV. Acetaminophen and Regulation

Acetaminophen (sometimes referred to as "APAP" in the literature) is the active ingredient marketed for the relief of

[2] The Court advised the parties on November 7, 2023 that it 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").

fever and pain in Tylenol and 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[3] 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

[3] 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 (March 18, 2015) ("FDA 2015"); Mosholder, Neurodevelopmental Outcomes Following Prenatal Acetaminophen Exposure, U.S. Food and Drug Administration (October 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 July 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 (March 10, 2023) ("FDA 2023").

placental barrier and can thus enter fetal circulation. Ricci et al., In Utero Acetaminophen Exposure and Child Neurodevelopmental Outcomes: Systematic Review and Meta-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 In re Acetaminophen – ASD-ADHD Prods. Liab. Litig., 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).

V. ASD and ADHD

The essential features of ASD are persistent impairment in reciprocal social communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities. American Psychiatric Association, Diagnostic and

Statistical Manual of Mental Disorders (5th ed., Text Revision, 2022) ("DSM") at 60. These symptoms are present from early childhood and limit or impair everyday functioning. Id. Estimates of prevalence range from about 1% to 2% of children in the United States, and a little under 1% globally. Id. at 62-63. ASD is about three times as prevalent in males as in females, although there are concerns about under-recognition of ASD in women and girls. Id. at 63.

The precise cause of ASD is unknown. 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 80%. Id. at 64. About 15% of ASD cases appear to be associated with a known genetic mutation. Id. Even when a known genetic mutation is associated with ASD, not all individuals with that genetic mutation will have ASD. Id. Risk for the majority of cases appears to be polygenic (i.e., many genes each making relatively small contributions). Id. The DSM notes that "[a] variety of risk factors for neurodevelopmental disorders, such as advanced parental age, extreme prematurity, or in utero exposures to certain drugs or teratogens like valproic acid, may broadly contribute to risk of [ASD]." Id.

Like ASD, ADHD is a neurodevelopmental disorder ("NDD"). Its essential feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. Id. at 70. 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. 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-analysis 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. There is no single gene for ADHD. Heritability is estimated at approximately 74%. Id. at 71. As with ASD, 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.

ADHD is one of the most common comorbidities with ASD, along with depression and anxiety. Id. at 66. Both disorders include symptoms in the domains of social communication and abnormal attention; however, the DSM notes that "[t]he social dysfunction and peer rejection seen in individuals with ADHD must be distinguished from the social disengagement, isolation and indifference to facial and tonal communication cues" seen in individuals with ASD. Id. at 74. While children with ASD may display tantrums because of an inability to tolerate a change from their expected course of events, children with ADHD may misbehave or have tantrums during transitions because of impulsivity or poor self-control. Id. Further, "the developmental course and absence of restricted, repetitive

behaviors and unusual interests [in ADHD]" differentiate the two disorders. Id.

VI. 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"), 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 567-568.

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. For example, if a study found a risk ratio of 1.5 with a 95% CI of .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.

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.

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 ASD or ADHD. If, for example, fever during pregnancy is associated with development of ADHD or ASD, 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 ASD or 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 or ASD.

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 ASD or 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).[4]

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, 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

[4] 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).

factors, such as genetics or shared environmental factors, the risk should be similar for the two siblings. Id.

B. Animal Studies

In addition to observational studies, scientists use toxicology models based on live animal studies to determine toxicity in humans. RMSE at 563. The advantage of animal studies is that they can be conducted as true controlled experiments and thus can avoid the problem of confounding. On the other hand, a significant disadvantage of animal studies is that the results must be extrapolated to human beings, and differences in absorption, metabolism, and other factors may result in interspecies variation in responses -- that is, some agents cause birth defects or disease in rodents but not humans, and vice versa. Id. Another disadvantage is that the high doses customarily used in animal studies require consideration of the dose-response relationship and whether a threshold no-effect dose exists. Id. In this case, an additional concern is analogizing observed changes in animal behaviors to ASD and ADHD, neurodevelopmental disorders that consist of complex behavioral symptoms in humans.

C. 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, ASD, and ADHD.

VII. Types of Evidence at Issue Here

Since at least 1987,[5] 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 or ASD. Before reviewing the relevant literature from medical organizations and

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

regulatory bodies, a description of the types of studies that have been undertaken and of some of the individual studies will be helpful.

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. As Laue 2019[6] recognized, studies that rely on "parental report of behavior . . . may be inaccurate or biased."[7] Thus, before discussing individual studies, it is important to note that, 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 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

[6] Laue et al., Association Between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian Cohort Study, 167(1) Toxicol. Sci. 138, 142 (2019).

[7] Plaintiffs' expert Dr. Baccarelli was one of the authors of Laue 2019.

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. ASD

There are two studies examining the connection between prenatal acetaminophen exposure and an ASD diagnosis: Liew 2016a[8] and Saunders 2019.[9] Liew 2016a is a large cohort study analyzing 64,322 children from the DNBC that measured acetaminophen exposure using maternal self-report at 12 and 30 weeks gestation. It found that acetaminophen exposure was associated with ASD co-occuring with hyperkinetic disorder ("HKD")[10] (1.51; 95% CI 1.19-1.92) but not ASD without HKD (1.07; 95% CI 0.92-1.24). Saunders 2019, a small case-control study of 141 cases and 199 controls recruited by public campaign and medical records, found no association. Saunders 2019 measured exposure by maternal-self report at 0-10 years post-partum.

[8] Liew et al., Maternal Use of Acetaminophen During Pregnancy and Risk of Autism Spectrum Disorders in Childhood: A Danish National Birth Cohort Study, 9 Autism Research 951 (2016) ("Liew 2016a"). There are three Liew articles published in 2016. To distinguish among them, this Opinion uses the suffix "a" to describe the article addressed to ASD, "b" for the child IQ study, and "c" for the attention and executive function article.

[9] Saunders, A Comparison of Prenatal Exposures in Children with and without a Diagnosis of Autism Spectrum Disorder, 11(7) Cureus I (2019).

[10] 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.

Two studies, Ji 2018[11] and Ji 2020[12], 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. Ji 2018 measured acetaminophen metabolites in maternal blood plasma from 1,180 samples taken 1-3 days postpartum and found no association with a child's ASD diagnosis. 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. The authors found an association between those samples with the highest level of acetaminophen and a child's ASD diagnosis (3.65; 95% CI 1.62-8.60), and no association for comorbid ADHD and ASD. 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,

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

[12] 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).

rather than the entire prenatal period. The relevance of these studies to this litigation is disputed by the parties.

3. ADHD

There are several original studies, reflecting data from five cohorts, examining the connection between prenatal acetaminophen exposure and an ADHD diagnosis.

One study, Liew 2014,[13] drew data from the DNBC, which assessed exposure 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 HKD and first trimester use (1.35; 95% CI 1.07-1.72), use in both the first and third trimesters (1.41; 95% CI 1.07-1.84), 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 drug use, ADHD-related genetic factors, or co-exposures to other medications cannot be dismissed." Id. at 319.

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

Liew 2019[14] 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.[15] 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; 95% CI 1.07-1.71), but not with use four years before (1.12; 95% CI 0.91-1.38) or after (1.05; 95% CI 0.88-1.26). Id. at 773. In the subset of women who indicated they were pregnant at the time they completed the questionnaire, there was a statistically

[14] 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).

[15] 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.

insignificant association (1.39; 95% CI 0.99-1.95), although in the model with acetaminophen use in all exposure periods included together, the association was statistically significant (1.46; 95% CI 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,[16] 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; 95% CI 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; 95% CI 1.35-4.21). Id. The authors concluded that the association between prenatal acetaminophen and ADHD may be even stronger than previously estimated because prior studies may have been

[16] 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).

biased toward the null by inaccurate maternal recall, and that the FDA and SMFM should "consider re-evaluating the evidence regarding the safety of fetal acetaminophen exposure." Id. at 1080.

Ji 2020 and Ji 2018, discussed above, both reported associations between biomarkers and an ADHD diagnosis. As noted above, however, the biomarkers reflected at most peripartum (Ji 2020) and postpartum (Ji 2018) exposure.

Chen 2019,[17] a case-control study with 950 mother-and-child case pairs and 3800 control pairs, found an association between prenatal acetaminophen prescriptions in Taiwan and a child's ADHD diagnosis.

Finally, two studies -- Ystrom 2017[18] and Gustavson 2021 -- used data from the MoBa cohort. Ystrom 2017 found associations between two trimesters of use (1.22; 95% CI 1.07-1.38) and use for greater than 29 days (2.20; 95% CI 1.50-3.24) and an HKD diagnosis. The authors cautioned that they "d[id] not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD."

[17] 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).

[18] 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; 95% CI 1.17-3.25). Id. at 7. That association was attenuated to non-significance using the sibling-control analysis (1.06; 95% CI 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.

4. Studies Examining Possible Confounders: Fever and Genetics

A few studies have examined the associations between possible confounders and ASD or ADHD. One, Hornig 2018,[19] examined the association between maternal fever and ASD risk in children. The study used data from the MoBa cohort and had a sample size of 95,754. The authors found associations between second trimester fever and ASD (1.40; 95% CI 1.11-1.77), id. at 762, and three or more fevers after 12 weeks and ASD (3.12; 95% CI 1.28-7.63). Id. at 764. When the authors conducted a

[19] Hornig et al., Prenatal Fever and Autism Risk, 23 Molecular Psychiatry 759 (2018).

stratified analysis based on acetaminophen use, they found that acetaminophen use attenuated the risk. Id. at 762.

Another study, Brynge 2022,[20] had a sample size of 549,967 and initially found an association between prenatal maternal infection and autism (1.16; 95% CI 1.09-1.23), id. at 786, that was attenuated after a sibling analysis (0.94; 95% CI 0.82-1.08). Id. at 787.

Leppert 2019[21] examined associations between maternal polygenic risk scores (a measure of genetic variations associated with disease risk) for neurodevelopmental disorders and early-life exposures previously linked to the disorders. The study included 7,921 mothers with genotype data from the Avon Longitudinal Study of Parents and Children ("ALSPAC"). The authors found no associations between maternal risk scores for ASD and prenatal acetaminophen use or infection. Id. at 838. They found a slight association between maternal risk scores for ADHD and prenatal acetaminophen use in both the first (1.09; 95%

[20] Brynge et al., Maternal Infection During Pregnancy and Likelihood of Autism and Intellectual Disability in Children in Sweden: a Negative Control and Sibling Comparison Cohort Study, 9(10) Lancet Psychiatry 782 (2022).

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

CI 1.02-1.17) and second (1.11; 95% CI 1.04-1.18) halves of pregnancy. Id.

5. Questionnaire Studies

Several other studies used the results of screening questionnaires as outcome measurements as opposed to diagnoses for specific disorders. 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"). The clinical relevance of these questionnaires is disputed. For example, the authors of Russell 2013[22] note that they "do not currently recommend using the SDQ as a screening tool for either disorder [ASD or ADHD] in clinical practice due to the high number of false positives." Id. at 7.

Most studies using screening data included several questionnaires, resulting in up to dozens of endpoints measured per study. Some studies used questionnaires administered by parents, others by teachers, and others by clinicians or

[22] Russell et al., The Strengths and Difficulties Questionnaire as a Predictor of Parent-Reported Diagnosis of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, 8(12) PLoS One e80247 (2013).

research professionals. A few studies used questionnaires completed by the child. Many studies used multiple informants (i.e., the individual completing or administering the questionnaire); the results of the study often differed by informant. The studies varied widely as to the child's age when the questionnaire was administered. In addition to heterogeneity of outcome measures, these studies reflect the same heterogeneity of exposure measures discussed supra.

6. Meta-Analyses

Finally, there have been at least five meta-analyses attempting to pool data from existing studies. 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 found that there "was an insufficient number of comparable studies due to heterogeneity and methodology to calculate pooled effect estimates for ASD." Id. at 482. The study did conduct an ADHD subgroup analysis using data from Baker 2020, Ji 2020, Liew 2019, and Ystrom 2017, which found an association (1.47; 95% CI 1.12-1.92); however, the authors were not able to adjust for confounding by indication or parental ADHD in this analysis.

The Ricci 2023 authors noted that their findings "should be interpreted in the context of the limitations of the included

studies[;] [o]ne-third of the studies included in the review were rated as having low or very low quality" based on concerns about caregiver self-report of exposures and outcomes, "incomplete control for confounding by indication and considerable variability across studies in terms of what indications were measured." Id. at 482. Further, "very few studies measured parental ADHD, which may also be an important covariate." Id. These limitations "increased the probability that findings could be explained by measurement error or confounding." Id. Finally, "[s]tudies were also fairly heterogenous with respect to their conceptualizations of child neuro-developmental outcomes and the ranges of tools used to assess these outcomes." Id.

The authors thus concluded that their findings "suggest 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.

7. Animal Studies

Animal studies, principally on mice and rats, have been conducted examining the effect of acetaminophen on a variety of

biological and behavioral outcomes. The outcomes measured in these studies will be discussed in more detail infra in relation to the reports of Drs. Cabrera and Pearson. Briefly, they tend to measure biomarkers of acetaminophen's proposed molecular and cellular impacts, as well as changes in behavioral characteristics proposed as analogues to hyperactivity, inattention, impulsiveness, and repetitive behaviors.

As in In re Mirena Ius Levonorgestrel-Related Products Liability Litigation (No. II), 341 F. Supp. 3d 213, 229 (S.D.N.Y. 2018), aff'd, 982 F.3d 113 (2d Cir. 2020) ("Mirena II"), the animal studies do not, and cannot, assess whether acetaminophen causes ADHD or ASD, although in this case some of the animal studies purport to measure ASD- or ADHD-like behaviors in animals. Instead, these studies "relate to discrete steps in longer biological chains of causation posited by individual experts who opine as to possible mechanisms by which" acetaminophen might cause ASD or ADHD. Id. Notably, "in order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans, just as the methodology of the studies must constitute good grounds to reach conclusions about the animals themselves." In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 743 (3d Cir. 1994). Where the animal studies on which experts

purport to rely are far-removed or too dissimilar from the facts of a case, they may not provide a proper foundation for the expert's opinion. See General Elec. Co. v. Joiner, 522 U.S. 136, 144 (1997).

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 is causal in nature remains uncertain." FDA 2015 at 3. 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 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 were in line with the conclusions reached by medical societies both in this country and in Europe. For example, the U.S.-based Society for Maternal-Fetal Medicine ("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." SMFM, SMFM Statement: Prenatal Acetaminophen Use and Outcomes in Children (Mar. 2017).[23] 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 two years ago. In 2021,

[23] https://www.smfm.org/publications/234-smfm-statement-prenatal-acetaminophen-and-outcomes-in-children.

a group of 13 authors (joined by 78 signees) -- consisting of scientists, clinicians, and epidemiologists -- published a "Consensus Statement" reviewing literature concerning prenatal acetaminophen use and fetal development. Bauer et al., Consensus Statement: Paracetamol Use During Pregnancy — A Call for Precautionary Action, 17 Nature Revs. Endocrinology 757, 758 (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.[24] 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, inter alia, the International Federation of Obstetrics and Gynaecology, 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

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

developmental issues." ACOG, ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy (Sept. 29, 2021).[25] 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.

Finally, 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

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

the evidence for causality for this claim is weak and has many fundamental flaws." SOGC, Statement on the Use of Acetaminophen for Analgesia and Fever in Pregnancy (Nov. 8, 2021).[26]

Discussion

As in all tort cases, plaintiffs in this MDL must prove by a preponderance of the evidence that defendants' breach of a duty it owed 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 population, while specific causation is whether a substance caused a particular individual's injury." Id.

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 and ASD. The epidemiological evidence is highly heterogenous, and major medical organizations and regulators have cautioned against drawing causal inferences from the

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

existing body of scientific literature. Nevertheless, three of plaintiffs' experts draw such an inference.

Plaintiffs proffer the testimony of five experts: Drs. Andrea Baccarelli, Robert Cabrera, Eric Hollander, Brandon Pearson, and Stan Louie. Drs. Baccarelli, Cabrera, and Hollander reviewed epidemiological, animal, and cell studies and undertook Bradford Hill analyses, each reaching the conclusion that acetaminophen causes ASD and ADHD. Dr. Louie offers the opinion that the children of pregnant women who take therapeutic doses of acetaminophen for at least 28 days have twice the risk of developing ASD or ADHD than the children of pregnant women who do not. Dr. Pearson conducted a "weight of the evidence" review of animal studies and opines that the literature shows that prenatal acetaminophen exposure can cause ASD and ADHD by disturbing normal neurodevelopmental processes through several mechanisms. Defendants argue that plaintiffs' experts' opinions regarding general causation, dose-response, and biological plausibility 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. For the following reasons, the Court agrees.

Before setting forth the legal standards that this Opinion applies in addressing the defendants' motions, a few

observations are appropriate. Each of the plaintiffs' experts is well qualified to render an opinion in the areas addressed by their reports. The defendants do not contend otherwise. None of the plaintiffs' experts, however, has published research that expresses the ultimate opinions they offer here. Indeed, the plaintiffs' lead expert on causation, Dr. Baccarelli, as recently as 2022, co-authored a study on the prenatal effects of acetaminophen that cautioned against any change in clinical practice.

To prepare their reports, the plaintiffs' experts have, appropriately, reviewed the body of scientific literature regarding in utero exposure to acetaminophen and its possible impact on neurodevelopment. As explained infra, however, they have not used that literature to render discrete opinions regarding that exposure and the risk of ASD and the risk of ADHD. Instead, they have applied a "transdiagnostic" analysis that sweeps into their analyses (and conclusions) ASD, ADHD and other neurodevelopmental disorders. They have failed to show that their methodology in doing so is generally accepted by the scientific community. In any event, here, their analyses have not served to enlighten but to obfuscate the weakness of the evidence on which they purport to rely and the contradictions in the research. As performed by the plaintiffs' experts, their

transdiagnostic analysis has obscured instead of informing the inquiry on causation.

The issues explored by this litigation have great public health significance. It matters to get this right. It matters to parents, their children, and their health care providers. ASD and ADHD are neurological disorders that can have profound consequences for families and communities.

Scientists have worked with great skill and dedication to explore many hypotheses that may lead us to better understand the etiology of these two disorders. This research has focused as well on acetaminophen -- a pharmaceutical that is critical to the treatment of an expecting mother's pain or fever and the protection of the health of her pregnancy. The FDA has been following this research closely for almost a decade. Internationally, medical associations have weighed in. As just described, there is no generally accepted scientific conclusion that in utero exposure to acetaminophen causes either ASD or ADHD. As explained below, the plaintiffs' experts have not reliably opined so either.

VIII. 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." Amorgianos v. Nat'l R.R. Passenger Corp., 303 F.3d 256, 265 (2d Cir. 2002) (citation omitted). Next, to determine whether 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.[27]

Further, 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

[27] 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.

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. 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.

IX. 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, such as those in this litigation, 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.

Courts have previously addressed some of the methodologies used by plaintiffs' experts here. One generally accepted methodology for determining causation among epidemiologists is a consideration of the "Bradford Hill" criteria. 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 "weight of the evidence analysis," also used by several of plaintiffs' experts, "involves a series of logical steps used to infer to the best explanation." Zoloft, 858 F.3d at 795 (citation omitted).

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.

No single Bradford Hill factor is required to infer causation; the criteria "are neither an exhaustive nor a necessary list." Zoloft, 858 F.3d at 796. Both the Bradford Hill analysis and weight of the evidence approach have been found to be "generally reliable" as methodologies. 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, such as the 'weight of the evidence,' 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.

Likewise, 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.

X. Dr. Baccarelli

Dr. Andrea Baccarelli has provided an amended expert report of June 23, 2023, and a rebuttal report of July 28. He was deposed on August 14.

Dr. Baccarelli is an epidemiologist, toxicologist, and physician whose research focuses on molecular mechanisms that

link environmental exposures to human disease. He is the Chair of the Department of Environmental Health Sciences and Epidemiology at the Columbia Mailman School of Public Health, and will become Dean of the Harvard T.H. Chan School of Public Health in 2024. He holds a Ph.D. in Toxicology and Occupational Health from the University of Milan, an M.S. in Epidemiology from the University of Turin, and an M.D. from the University of Perugia. He has published over 600 peer-reviewed papers, many of which investigate the effects of environmental toxins on neurodevelopment.

Of particular significance to this litigation, Dr. Baccarelli co-authored three studies that examined the impact of the use of acetaminophen during pregnancy on children's neurodevelopment by measuring levels of acetaminophen in fetal meconium. The studies, which used the same cohort, began with Laue 2019, which did not detect a statistically significant association between acetaminophen levels in meconium and intelligence scores of 118 children who were six to eight years old. The second study, Baker 2020 (discussed supra), which had a sample size of 345, found an association between acetaminophen levels in meconium and a child's ADHD diagnosis. Baker 2022[28]

[28] Baker et al., Association of Prenatal Acetaminophen Exposure Measured in Meconium with Adverse Birth Outcomes in a Canadian Birth Cohort, 10 Frontiers in Pediatrics 1 (2022).

examined the associations between meconium acetaminophen levels, with a sample size of 393, and a variety of outcomes including birthweight, gestational age, gestational diabetes, preeclampsia, and high blood pressure. The authors noted that "[w]hile this study may add evidence in support of questioning the safety of acetaminophen use during pregnancy, more work is needed to rule out confounding by indication and to assess generalizability before a change in clinical practice is recommended." Id. at 7.

Dr. Baccarelli was asked by plaintiffs' counsel to review the current state of the epidemiological scientific literature to determine whether the prenatal use of acetaminophen "causes NDDs, including ADHD, ASD, and/or symptoms consistent with those disorders in the child." Dr. Baccarelli began with a systematic search of the literature to identify original papers on the relationship between ADHD, ASD, and NDDs and prenatal exposure to acetaminophen. He located 6 original, non-duplicative studies in humans related to ASD, 14 related to ADHD, and 15 related to other neurodevelopmental deficits and disorders. He also examined meta-analyses and other studies and reviews.

Having identified relevant literature, Dr. Baccarelli offers the opinion that "there is a causal relationship between prenatal acetaminophen use and the NDDs of ADHD and ASD and the

related symptomology."[29] To reach this opinion, Dr. Baccarelli states that he used two methods, either of which would, in his view, be sufficient to determine a "causal association." The first, called the Navigation Guide, Dr. Baccarelli states was created to "assess causal relationships for toxic substances," and involves "a systematic rating and review of each identified study for bias, strength of evidence, and other indicia of study quality."[30] Using the Navigation Guide, Dr. Baccarelli concluded in three separate opinions that acetaminophen use during pregnancy is "known to be toxic" because of its ability to cause 1) ADHD, 2) ASD, and 3) other NDDs in children. Second, Dr.

[29] In his reports, Dr. Baccarelli uses various formulations in expressing his ultimate opinion. He opines that there "is likely a causal link between exposure to acetaminophen during pregnancy and offspring suffering from a NDD, including ASD and ADHD, and the related symptomology." Later, he opines that "prenatal use of acetaminophen exposure can cause the offspring to develop NDDs such as ADHD and ASD, as well as symptoms consistent with those diagnoses."

[30] Dr. Baccarelli explains that the Navigation Guide is recommended by the Committee to Review EPA's Toxic Substances Control Act as an approach the EPA should use in evaluating Toxic Substances Control Act risks. In fact, the document cited by Dr. Baccarelli explains that "there is no consensus on the best tool for risk-of-bias analysis," and lists the Navigation Guide as one of several tools; it recommends the Navigation Guide as a tool for assessing risk of bias and study quality, not for coming to a causal conclusion. Committee to Review EPA's TSCA Systematic Review Guidance Document, Board on Environmental Studies and Toxicology, The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations at 35 (2021).

Baccarelli "weigh[ed] and assess[ed] the Bradford Hill factors," with respect to NDDs as a group. He determined that each of the Bradford Hill factors except specificity was satisfied.

Defendants argue that Dr. Baccarelli's opinions are unreliable for several reasons. They contend that he improperly applied a "transdiagnostic" approach to neurodevelopmental disorders that elides meaningful differences between ADHD and ASD. They contend as well that he did not conduct a reliable Bradford Hill or Navigation Guide analysis for several reasons, including that he cherry-picked and misrepresented study results and refused to acknowledge the role of genetics in the etiology of either ASD or ADHD. They are correct. After addressing the reliability of his Bradford Hill analysis, his findings from his Navigation Guide analysis will be addressed.

A. Bradford Hill

1. Transdiagnostic Evaluation

"The Bradford Hill factors form the generally accepted set of criteria by which, when reliably applied, modern practicing epidemiologists assign causality to an association." Daniels-Feasel, 2021 WL 4037820, at *6 (emphasis added). It is not clear, therefore, that conducting a Bradford Hill analysis on multiple associations at once is informative or reliable. Moreover, his transdiagnostic approach raises a question of

relevance. After all, this litigation is brought to obtain recovery on behalf of those who have been diagnosed with ASD or ADHD, not on behalf of anyone with, for example, a deficit in communication or self-regulation.

Another consequence of his examination of a potpourri of evidence is that he has obscured limitations in the scientific literature. For example, there are only a limited number of studies associated with a population that is diagnosed as having either ASD or ADHD. If the studies for either ASD or ADHD were subjected to their own individual Bradford Hill analysis, it would be easier to discern whether there was actual support for a finding that prenatal exposure to acetaminophen causes either ASD or ADHD. And, as importantly, if the analysis were focused on a single disorder, the tensions among the studies and any contradictory conclusions would be more evident and more easily weighed by an epidemiologist. And, consequently, the reliability of any such expert analysis would be more easily assessed by other experts and ultimately by a court conducting a Rule 702 inquiry.

To make this concrete, Dr. Baccarelli reports that his survey of the scientific literature identified just six original, non-duplicative studies in humans of the relationship

between ASD and prenatal exposure to acetaminophen.[31] As discussed above, just two of these studies examined the connection between prenatal exposure and a diagnosis of ASD: Saunders 2019 and Liew 2016a. And, only one of them, Liew 2016a, found an association, although the association only existed for ASD with hyperkinetic disorder. The other studies include a peripartum exposure study (Ji 2020), and two studies examining possible confounding (Hornig 2018 finding an association with fever, and Leppert 2019, finding no association with a polygenic risk score). Finally, Avella-Garcia 2016[32] found an increase in CAST symptom scores for boys but not girls. Its authors identified several limitations of the study, including an inability to evaluate the dosage taken, confounding by genetics, and possible misclassification of exposure. Id. at 1994.

[31] Dr. Baccarelli does not identify the six studies to which he is referring. They are not listed in either of his reports or in the tables accompanying his Navigation Guide. From context, he appears to be referring to the six identified supra. At oral argument, plaintiffs' counsel identified Alemany 2021 as one of the six and omitted Hornig 2018 for the list recited supra. Alemany 2021, however, is a metanalysis and not an original, non-duplicative study.

[32] Avella-Garcia et al., Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function and Autism Spectrum Symptoms, 45(6) Int. J. Epiemiol. 1987 (2016).

Dr. Baccarelli claims that a shared Bradford Hill analysis is "appropriate" because the symptoms associated with deficits in cognition, communication, motor skills, self-regulation or social-emotional function "transcend diagnostic boundaries" and because ASD and ADHD are both categorized as NDDs in the DSM. But the diagnostic criteria of the two disorders are undeniably distinct. A child may suffer from both disorders, from only one, or from neither, despite being described as having the neurological deficits that Dr. Baccarelli lists as relevant. The fact that ASD and ADHD are both categorized as NDDs does not suffice to explain the use of a transdiagnostic Bradford Hill analysis. After all, Dr. Baccarelli's analysis did not focus on the other NDDs categorized in the same section of the DSM, such as motor disorders, tic disorders, certain learning disorders, communication disorders, or intellectual disorders.

Equally troubling, Dr. Baccarelli's assessment of a study's use of a non-ADHD, non-ASD endpoint seems to depend on whether the study's result supports his ultimate opinion about a causal connection with prenatal exposure to acetaminophen. The following examples illustrate this point.

Dr. Baccarelli describes as a limitation on the reliability of Laue 2019, its use of "an outcome -- intelligence score -- that does not directly bear on ADHD or ASD." He makes that

assessment even though he lists cognition as a relevant deficit justifying his transdiagnostic analysis and even though intelligence scores "directly bear" on other neurodevelopmental disorders such as Intellectual Development Disorder. See DSM at 41. Notably, Laue 2019 found no statistically significant association between acetaminophen in meconium and a child's intelligence scores. Indeed, its conclusion was much broader. It stated, "we did not find evidence of neurodevelopmental harm from prenatal exposure to acetaminophen measured in meconium." Id. at 143. Dr. Baccarelli was one of the authors of Laue 2019.

Similarly, Dr. Baccarelli found Trønnes 2020[33] unpersuasive in part because it "did not have ADHD as an endpoint and was forced to rely on less clearly defined child outcomes." Trønnes 2020 found "a moderate increased risk of internalizing behaviors and a borderline [statistically insignificant] increased risk of externalizing behavior," but emphasized that "unmeasured confounding plays an important role and we cannot rule out chance or unmeasured confounding as possible explanations for our findings." Id. at 252.

[33] Trønnes et al., Prenatal Paracetamol Exposure and Neurodevelopmental Outcomes in Preschool-Aged Children, 34 (3) Peadtr. Perinat. Epidemiol. 247 (2020).

Trønnes 2020 used MoBa data to study the association between prenatal exposure to acetaminophen and a set of neurodevelopmental outcomes, such as language competence and dimensions of temperament, for children at age five. The outcomes were taken from responses to three questionnaires.[34] Yet the use of outcome measures from responses to the same questionnaires in Brandlistuen 2013,[35] which studied same-sex sibling pairs aged three in the MoBa cohort, did not trigger Dr. Baccarelli's concern. Brandlistuen 2013 concluded that children exposed to long-term use of acetaminophen during pregnancy had substantially adverse development outcomes at three years of age. Likewise, his summary of Liew 2016b,[36] which found an association between maternal acetaminophen use and lower IQ in 5-year-olds, does not list the non-ADHD, non-ASD outcome as a limitation. This list of the inconsistencies in Dr. Baccarelli's treatment of studies that did not use an ASD or ADHD endpoint could go on and on.

[34] The three questionnaires were the ASQ, the CBCL, and the EAS.

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

[36] Liew et al., Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study, 27(6) Epidemiology 912 (2016).

There is yet another reason to question Dr. Baccarelli's use of a transdiagnostic approach for his Bradford Hill analysis. Dr. Baccarelli does not explain why he did not apply the transdiagnostic approach to his Navigation Guide assessments. In conducting that assessment, he separated his evaluation of ASD, ADHD and other NDD studies. "[I]f 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." Zoloft, 858 F.3d at 797.

At oral argument, plaintiffs' counsel suggested that any failure by Dr. Baccarelli to conduct separate Bradford Hill analyses for ASD and ADHD could be excused by his having done separate literature reviews and separate analyses in connection with the Navigation Guide. Not so. The Navigation Guide is not designed to distinguish a causal connection from a mere association. At no point have plaintiffs suggested that their experts could have satisfied their burden to offer reliable testimony of general causation without performing a reliable Bradford Hill analysis.

To Dr. Baccarelli's cursory explanation for conducting a single Bradford Hill analysis, he adds that he has relied on Dr. Hollander in concluding that it is appropriate to consider not

only studies that assess ADHD and ASD specifically, but also those studies that "assess symptoms of NDDs that are consistent with ADHD and ASD". As explained below, Dr. Hollander's report does not fill this analytical gap. While a transdiagnostic Bradford Hill analysis may be appropriate if the basis for doing so is properly supported, that basis has not been supplied here.

At oral argument, plaintiffs' counsel referred to one meta-analysis, Alemany 2021,[37] as evidence that it was appropriate to conduct a transdiagnostic Bradford Hill analysis. This meta-analysis does not provide sufficient support for the admissibility of Dr. Baccarelli's own transdiagnostic Bradford Hill analysis. Alemany 2021 is a meta-analysis of questionnaire responses regarding use of acetaminophen during pregnancy and ASD and ADHD symptoms in six European birth/child cohorts with 70,000 children.[38] Alemany 2021 concluded from its meta-analysis that children prenatally exposed to acetaminophen were 19% and 21% more likely to subsequently have ASD and ADHD symptoms within the borderline/clinical range than non-exposed children. Id. at 999-1,000. It is true that Alemany 2021 briefly

[37] Alemany et al., Prenatal and Postnatal Exposure to Acetaminophen in Relation to Autism Spectrum and Attention-Deficit and Hyperactivity Symptoms in Childhood: Meta-Analysis in Six European Population-Based Cohorts, 36 Euro. J. Epidemiol. 993 (2021).

[38] Hospital diagnoses were available for one cohort, the DNBC.

mentioned Bradford Hill factors (biological plausibility, coherence, consistency, temporality, and dose response), but it did so by citing to other research. It did not conduct its own Bradford Hill analysis.

For each of these reasons, Dr. Baccarelli's use of a transdiagnostic Bradford Hill analysis fails to meet the requirements for admissibility on the issue of causation for either ASD or ADHD. But, even if it were appropriate to conduct a transdiagnostic Bradford Hill analysis, Dr. Baccarelli's analysis would nonetheless be excluded as unreliable.

2. Consistency/Replication

Beginning with a discussion of the Bradford Hill factor of consistency will place in context many of the deficiencies that appear in Dr. Baccarelli's application of the other Bradford Hill factors. The consistency factor arises from the insight that, to effectively demonstrate a causal relationship, it is important that a study be replicated 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. Baccarelli assigned the most weight in his Bradford Hill analysis to three factors: consistency, strength of

association, and dose-response. Dr. Baccarelli opines that the consistency element of the Bradford Hill test is "strongly" satisfied. He judges that there are at least ten studies showing an association between prenatal acetaminophen use and ADHD, three showing an association with ASD, and five showing an association with symptoms of NDDs. He acknowledges that there are studies that did not show such associations, but considers them to be in the "extreme minority." He adds that a set of studies can still be consistent even if some of their results are not statistically significant. He finds support for his finding of association in two meta-analyses: Gou 2019[39] and Alemany 2021.

Plaintiffs have failed to carry their burden to show that Dr. Baccarelli's analysis of this Bradford Hill factor is reliable. To begin with, it is cursory. It fails to engage meaningfully with the inconsistencies among the studies, inconsistencies which exist to a remarkable degree. He fails to address meta-analyses and scientific literature which do not find consistency among the study results. His failure to engage

[39] Gou et al., Association of Maternal Prenatal Acetaminophen Use with the Risk of Attention Deficit/Hyperactivity Disorder in Offspring: A Meta-Analysis, 53(3) Australian & New Zealand J. Psych. 195 (2019).

seriously with the complexity of the relevant studies' outcomes is well illustrated by his assertion regarding ASD.

It is difficult to understand where Dr. Baccarelli was looking when he found that the research regarding ASD was consistent and that there were three studies to support his conclusion. Of the six studies publishing risk ratios for prenatal, peripartum, or postpartum exposure and an ASD diagnosis, three found no association (Ji 2018, Leppert 2019, and Saunders 2019), one found an association only for ASD co-occurring with HKD (Liew 2016a), and one found a protective association among febrile women (Hornig 2018). While Ji 2020 did find an association, it has significant limitations.

Ji 2020 broke down the total level of acetaminophen detected in umbilical cord blood into thirds. It found a statistically significant increase in a diagnosis of ASD for mothers whose total level of acetaminophen (unchanged acetaminophen and its metabolites) was in the third tertile compared to the first. Among the study's limitations, however, the authors listed their inability to exclude genetic confounding and that they had only measured peripartum use of acetaminophen. Id. at 188. Since the half-life of acetaminophen is less than three hours, this study has limited relevance to use of acetaminophen during the pregnancy itself.

Although Dr. Baccarelli's report does not list which three studies he is counting as consistent with his thesis about ASD, Dr. Baccarelli's Navigation Guide chart suggests that he is counting the largely irrelevant Ji 2020 along with Liew 2016a and Avella-Garcia 2016. Consideration of these studies doesn't help him get to three or support a finding of consistency.

Avella-Garcia 2016 did not rest on a diagnosis of ASD. Instead, it examined a child's score on the CAST questionnaire, and found that there was an increase in CAST symptom scores among boys and decrease among girls. Independent of that difference, the authors "did not use cut-off points to evaluate the outcomes" and thus examined "symptoms in a manner that goes beyond examining only disorders, to include milder dysfunctions." Id. at 1993. In other words, the clinical significance of the results in Avella-Garcia 2016, and thus their consistency or lack thereof with other ASD studies is not clear.

And, as discussed supra, Liew 2016a found no association between in utero use of acetaminophen and a diagnosis of ASD unless the diagnosis was for ASD with HKD. The authors observed that, if those two disorders are considered to be different, then their results "can be interpreted as acetaminophen only having an impact of hyperkinetic disorder but not ASD." Id. at

954. Thus, considering the different outcome measurements and the authors' limitations, an expert assessing consistency between Avella-Garcia 2016 and Liew2016a should have explained the "analytical gap between the data and the opinion proffered." Joiner, 522 U.S. at 146. Dr. Baccarelli did not do so.

Further, while Liew 2016a found an association between acetaminophen and ASD with HKD, but not for ASD without hyperkinetic disorder, Ji 2020 found no significant association for ASD with ADHD, but did find a statistically significant association for ASD without ADHD.[40] Dr. Baccarelli does not mention, let alone address, the possibility that Liew 2016a is evidence only of ADHD. Nor does Dr. Baccarelli mention that the authors of Ricci 2023 -- the most recent meta-analysis and one that he has praised elsewhere in his report -- determined that

[40] Liew 2016a has another important complication that merits careful consideration when addressing consistency of results. The study measured exposure during each of a pregnancy's three trimesters. The associations between those exposures and the ASD diagnosis did not appear to be consistent with plaintiffs' other experts' opinions on when the critical window for acetaminophen exposure falls during a pregnancy. Dr. Louie opines that exposure for at least 28 days during pregnancy can cause ASD and ADHD no matter how those 28 days are spread out during the course of the pregnancy, Dr. Cabrera states that the second trimester is the critical window, and Dr. Hollander states that the second and third trimesters are the critical periods. But Liew 2016a found significant associations for use in all three trimesters, and the first and second trimester combined, but not the second and third trimester combined or the first and third trimester combined. Id. at 955.

studies examining ASD "were either too few or too heterogeneous in their measures to pool." Id. at 481.

In sum, Dr. Baccarelli's conclusory opinion about consistency does not adequately address the many conflicting study results. As the FDA's reviews of these studies have recorded time and again, the literature remains mixed. See, e.g., FDA 2022 at 33 ("[T]here are still study limitations and inconsistent study findings that prohibit causal interpretations of the association between [acetaminophen] exposure and functional neurobehavioral outcomes"); FDA 2023 at 17 ("[F]indings on the associations between [acetaminophen] use during pregnancy and neurobehavioral and urogenital outcomes remain mixed").

Another example of how Dr. Baccarelli's analysis of consistency fell far short can be found in his discussion of those studies that relied on questionnaires instead of diagnoses of either ASD or ADHD. Of course, the challenge in assessing consistency is particularly pronounced in studies that rely on questionnaires. If the multiple endpoints in these studies provide valuable evidence of a causal relationship, an assessment of consistency in a Bradford Hill analysis purporting to consider all NDDs should acknowledge and address inconsistent

questionnaire-based results within each study and also between such studies.

For example, in Trønnes 2020 (a study addressing non-diagnostic outcomes in the MoBa cohort), the authors found no statistically significant results at all for communication problems assessed by the ASQ or externalizing problems assessed by the CBCL and three trimesters of acetaminophen exposure. The authors did find a positive, statistically significant association between three trimesters of acetaminophen exposure and internalizing problems as measured by the CBCL (1.36; 95% CI 1.02-1.80). Id. at 252. Yet Brandlistuen 2013 found the inverse: a statistically significant, positive association between exposure for greater than 28 days and externalizing problems measured by the CBCL, and no significant association for internalizing problems. Id. at 1709.

Other inconsistencies for studies using questionnaires abound. Vlenterie 2016[41] found a significant association between acetaminophen use and motor milestone delay, but no associations between either short- or long-term use of acetaminophen and any other behavioral or temperamental problems as measured by the

[41] Vlenterie et al., Neurodevelopmental Problems at 18 Months Among Children Exposed to Paracetamol in Utero: A Propensity Score Matched Cohort Study, 45(6) Int. J. Epidemiol. 1998 (2016).

ASQ. Tovo-Rodrigues 2020[42] found no significant positive associations between acetaminophen use and CBCL or Battelle's Development Index scores, but did find a few statistically significant risk ratios below 1, which would suggest a protective effect. Liew 2016c[43] found just one statistically significant association (sustained attention; 2.80; 95% CI 1.5-5.5) among 36 reported outcomes; some of the reported outcomes in that study had risk ratios below 1, and all but one were statistically insignificant. Id. at 2012, 2014. Some studies found different results depending on who administered the questionnaire (Avella-Garcia 2016, Parker 2020[44], Thompson 2014[45]). Some studies found significant results for boys but not girls (Avella-Garcia 2016, Alemany 2021) and some found

[42] Tovo-Rodrigues et al., Low Neurodevelopment Performance and Behavioral/Emotional Problems at 24 and 48 Months in Brazilian Children Exposed to Acetaminophen During Foetal Development, 34 Pediatr. Perinat. Epidemiol. 27 (2020).

[43] Liew et al., Paracetamol Use During Pregnancy and Attention and Executive Function in Offspring at Age 5 Years, 45 Int. J. Epidemiol. 2009 (2016).

[44] Parker et al., Maternal Acetaminophen Use During Pregnancy and Childhood Behavioral Problems: Discrepancies Between Mother- and Teacher-Reported Outcomes, 34(3) Paediatr. Perinat. Epidemiol. 2999 (2020).

[45] Thompson et al., Association Between Acetaminophen Use During Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years, 9(9) PLoS One 1 (2014).

significant results for girls but not boys (Bornehag 2018,[46] Bertoldi 2020[47]) or stronger results for girls (Ji 2018).

Dr. Baccarelli's incomplete examination of the consistency factor cannot be excused by his reliance on meta-analyses. Dr. Baccarelli states that he finds confirmation for his conclusion on consistency from two meta-analyses (Gou 2019 and Alemany 2021) and from the Consensus Statement. But again, any examination of meta-analyses and the Consensus Statement required more care.

Gou 2019 did not study ASD. It searched for English-language publications relating to ADHD. Its authors stated that although they found a "moderate" association between acetaminophen use and ADHD development, "caution is advised when considering whether this association is causal, because potentially unidentified or inadequately controlled confounding factors in the observed studies may have unpredictable effects on the observed association". Id. at 205.

[46] Bornehag et al., Prenatal Exposure to Acetaminophen and Children's Language Development at 30 Months, 51 Euro. Psych. 91 (2018).

[47] Bertoldi et al., Associations of Acetaminophen Use During Pregnancy and the First Year of Life with Neurodevelopment in Early Childhood, 34(3) Paediatr. Perinat. Epidemiol. 267 (2020).

As explained above, Alemany 2021 is a meta-analysis of (mostly) questionnaire responses regarding use of acetaminophen during pregnancy and ASD and ADHD symptoms in six European birth/child cohorts with 70,000 children.[48] It concluded that children prenatally exposed to acetaminophen were 19% and 21% more likely to subsequently have ASD and ADHD symptoms within the borderline/clinical range than non-exposed children. A mother was classified as exposed to acetaminophen during her pregnancy if she reported when questioned that she had taken "any" dose. Id. at 994. This meta-analysis relied principally on reports of "borderline/clinical symptoms" instead of diagnoses of either ASD or ADHD. Thus, the proportion of children having symptoms associated with "Autism Spectrum Conditions" ("ASC") ranged between 0.9 and 12.9%, depending on the cohort. This compares, for example, to the incidence of diagnosed ASD in the United States of from 1 to 2%.

In a finding that is supportive of Dr. Baccarelli's analysis, the authors of Alemany 2021 did state that

> the consistent associations found across different sensitivity analysis including examining ASC and ADHD diagnosis in the largest cohort makes unlikely that the observed relationship between prenatal acetaminophen and ASC and ADHD symptoms is entirely explained by unmeasured confounding.

[48] Again, hospital diagnoses were available for one cohort.

Id. at 1001. Nonetheless, it cautioned that its findings need to be interpreted "with caution" given the various limitations the authors identified with its analysis. Id. at 1000.

What is remarkable, however, is that Dr. Baccarelli contends that meta-analyses support his finding of consistency but fails to mention Ricci 2013, of which he is well aware. As already discussed, Ricci 2023 concluded that there were too few studies to conduct a meta-analysis for ASD or indeed for anything other than ADHD. Id. at 482. This is true even though it had searched for all published, peer-reviewed studies written in English examining "the association between in utero acetaminophen exposure and child neurodevelopmental outcomes: ADHD, ASD, communication delays/disorder, motor delays/disorder, and other developmental delays/disorders." Id. at 475. It located twenty-two studies of twenty-three cohorts. While there were enough studies to conduct a meta-analysis of ADHD, one third of those were of low or very low quality. Id. at 482. Its meta-analysis suggested "a small increase in risk of child ADHD associated with in utero acetaminophen exposure" but noted that the certainty of the evidence was "low." It called for high-quality studies to be done. Id. at 483.

Dr. Baccarelli's reference to the Consensus Statement when discussing the issue of consistency is similarly troubling. As

described earlier, the Consensus Statement has experienced significant push-back from the scientific community and its authors responded in Bauer 2022 by stating "we avoided any inference of causality in our Consensus Statement." Id. at 192. In rendering his finding regarding the consistency of the evidence, Dr. Baccarelli does not address this debate or the more recent clarification by the authors of the Consensus Statement.

Of course, inconsistency of results in individual studies is best explored on cross-examination. Individual inconsistencies in the literature do not, by themselves, render Dr. Baccarelli's opinion unreliable. It is not the strength or lack thereof of the data on which a Rule 702 court must focus. And, as noted supra, not all Bradford Hill criteria need to be satisfied to make an inference of causation. But his wholesale failure to address the highly heterogenous nature of the studies or the inconsistencies between results that do address the same outcomes means that his consistency opinion "is connected to existing data only by the ipse dixit of the expert." Joiner, 522 U.S. at 146. And because Dr. Baccarelli placed great weight in his Bradford Hill analysis on his finding of consistency, this is a significant barrier to the admission of his opinion.

3. Strength of Association

The next Bradford Hill factor to be discussed is the strength of association. Dr. Baccarelli placed great weight on this factor as well. Underlying the factor is the understanding that, where the association is stronger, the support for a finding of causation is greater. "Although lower relative risks can reflect causality, the epidemiologist will scrutinize such associations more closely because there is a greater chance that they are the result of uncontrolled confounding or biases." RMSE at 602.

Dr. Baccarelli opines that there is a "moderate" degree of association between in utero exposure to acetaminophen and an increased risk of NDDs in children. He finds that the strength criterion is satisfied because so many of the findings in the studies on which he relies were statistically significant, because so many of the studies relied on maternal self-reporting, which he opines likely biased the exposure estimates toward the null, and because even a small magnitude of risk has public health importance given the prevalence in the use of acetaminophen.[49] Dr. Baccarelli does not separately address the strength of association for a diagnosis of either ASD or ADHD.

[49] Dr. Baccarelli's reference to the prevalence of acetaminophen use to support his finding of strength of association is highly questionable. Insofar as pregnant women are concerned, access

As Dr. Baccarelli acknowledges, most of the studies on which he has relied show risk ratios between 1.0 and 2.0. This is a far smaller magnitude of risk than that identified by the experts in Mirena II -- where the risk ratio was 7.69 for one group and 3.90 for another, see Mirena II, 341 F. Supp. 3d at 243 -- and is also smaller than that reported in Daniels-Feasel (2.2). See Daniels-Feasel, 2021 WL 4037820, at *8. The most recent meta-analysis reviewed by Dr. Baccarelli characterized the association between prenatal acetaminophen exposure and ADHD as "small to moderate." Ricci 2023 at 481. The FDA has likewise characterized the associations found in Ystrom 2017, Trønnes 2020, and Liew 2016c as "weak." FDA 2022 at 30-31.

Moreover, Dr. Baccarelli's reliance on the statistical significance of the study findings is questionable. As already

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to acetaminophen to treat fevers and pain is critical to their health and the wellbeing of their children. No one involved in this litigation disputes this. Therefore, it is particularly important to conduct a reliable analysis of whether use of acetaminophen causes ASD or ADHD without putting one's thumb on the scale. Dr. Baccarelli, as an author of Laue 2019, recognized this very point. Laue 2019 stated: "[b]ecause of the concerns regarding NSAIDs and high-dose aspirin, it is critically important that the risks and benefits of treating pain and fever during pregnancy with acetaminophen are thoroughly studied and understood before any recommendations are made to pregnant women." Id. at 142. Likewise, Baker 2022, which Dr. Baccarelli co-authored, concluded that "more work is needed to rule out confounding by indication and to assess generalizability before a change in clinical practice is recommended." Id. at 7.

discussed, it is misleading to characterize the highly heterogenous body of literature as reporting consistent statistically significant associations. Many of the studies found statistically insignificant or even negative associations. For example, Alemany 2021 found an overall association of 1.19 for ASD (95% CI 1.07-1.33). Id. at 998. But of the six underlying cohorts analyzed by this meta-analysis, only one (the DNBC) reported a statistically significant association with ASD. The DNBC was likewise the only study of the six with a significant association in the ADHD analysis, which found an overall association of 1.21 (95% CI 1.07-1.36). Id.

Additionally, the weakness of the evidence of association between in utero exposure to acetaminophen and ASD in particular has been masked by Dr. Baccarelli's decision to lump all NDD studies together. In the one study examining the association between prenatal use and an ASD diagnosis that found an association (Liew2016a), the association only existed for ASD with HKD (1.51; 95% CI 1.19-1.92), not ASD without HKD (1.07; 95% CI 0.92-1.24). Id. at 955.

Dr. Baccarelli opines that the magnitude of the risk in many studies has been dampened due to the inability to directly measure exposure to acetaminophen and the need to rely instead on maternal memory and reporting. He points to the measurement

of acetaminophen in umbilical cord plasma in Ji 2020 and in meconium in Baker 2020 as more reliable measures of the in-utero use of acetaminophen and as a consequence their association with statistically significant risks of ADHD and ASD. Ji 2020, as already discussed, however, only measured peripartum exposure to acetaminophen, so its relevance to prenatal exposure is highly questionable. Moreover, Ji 2020 has been sharply criticized on other grounds.[50] Baker 2020 on the other hand, is a well-regarded study, but it only measured the risk of ADHD, not ASD. Baker 2020 detected acetaminophen in the meconium of almost 58% of the cohort's infants and reported a risk ratio of 2.43 for ADHD. But, that finding was accompanied by a wide confidence interval (95% CI 1.41-4.21)), undercutting its reliability. Id.

[50] For example, the position statement by ENTIS, made in response to the Consensus Statement, addressed Ji 2020 in depth, stating that the study had

> severe issues with external and internal validity. APAP or metabolites were detected in every single of the 996 umbilical cord samples. This does not compare well to our knowledge on the use of APAP during pregnancy. Among the 996 children, an unprecedented large proportion were diagnosed with ADHD/ASD (37%) and only 33% had no 'developmental disability' diagnosis. Population prevalence estimates of ADHD is around 3-5%. The validity of the exposure construct 'burden of APAP exposure' is undocumented and actual levels are not presented. Analytical methods are insufficiently accounted for including stability from up to 20 years of sample storage.

European Network of Teratology Information Services, Position Statement on Acetaminophen (Paracetamol) in Pregnancy, at 2 (Oct. 3, 2021).

at 1077. Among the study's limitations, the authors noted that they had not controlled for confounding by either indication or genetics. Id. at 1079.

Because Dr. Baccarelli's discussion of this Bradford Hill factor does not separately address the ASD, ADHD, and the other NDD studies, he has not explained how the strength (or weakness) of association evidence for each of them has impacted his overarching assessment that the strength of the association should be judged as moderate for all NDDs. Moreover, given the complexity of this issue, it was particularly incumbent upon Dr. Baccarelli to consider with care the extent to which either confounding by indication and/or genetic confounding ameliorated any appearance of association. As discussed below, Dr. Baccarelli has failed to examine dispassionately and with care the evidence of genetic confounding.

In sum, the plaintiffs have not shown that Dr. Baccarelli has applied with sufficient rigor his profession's methodology for measuring the strength of association between in utero use of acetaminophen and NDDs. As a result, they have not shown that there is a reliable basis for finding a moderate degree of association between in utero use of acetaminophen and NDDs, much less either ASD or ADHD. For this reason as well, Dr. Baccarelli's opinion must be excluded.

4. Specificity

An association exhibits specificity "if the exposure is associated only with a single disease or type of disease." RMSE at 605. Where there is a good biological explanation for the absence of specificity, for example when the toxin consists of numerous harmful agents, a lack of specificity does not necessarily undermine a finding of causation. Id. at 606.

Dr. Baccarelli opines that the specificity criterion is not satisfied. He explains that not every child who develops NDDs will have been exposed to acetaminophen in utero and that the etiology of NDDs is multifactorial. He argues, however, that this factor is considered to be "all but irrelevant" by modern epidemiologists.

While it is important not to overestimate the importance of specificity, its absence highlights the complexity of the causation analysis. When the causal connection is complex, it is particularly important for the epidemiologist to consider whether the studies upon which she is relying adequately considered confounding effects, among other things. This Dr. Baccarelli did not do.

5. 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. Baccarelli's analysis of temporality is contained in a single paragraph. He finds that temporality is satisfied because prenatal use of acetaminophen has already occurred by the time a child is diagnosed with ADHD or ASD.

This factor requires a more rigorous analysis than that provided by Dr. Baccarelli. The question is not whether the exposure precedes the diagnosis but whether it precedes the development of the disorder. The studies Dr. Baccarelli reviewed collected data about acetaminophen use at a variety of points throughout pregnancy (and sometimes, as with Ji 2020, at delivery). A reliable assessment of the temporality factor would engage with the fact that it is not currently known when either ASD or ADHD develop in the fetal brain, and with the possibility that some studies measured acetaminophen use either before or after the development window.

6. Dose-Response

The factor of the dose-response relationship, which Dr. Baccarelli refers to as biologic gradient, 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 since some causal agents require that the exposure exceed a certain dose to have a causal effect. RMSE at 603.

Dr. Baccarelli placed great weight on this factor, along with consistency and strength of association. He opines that virtually every study that evaluated dose response found an association between the number of days of prenatal acetaminophen use and NDDs in children. He finds this compelling evidence of causation. Dr. Baccarelli identifies six studies for ADHD, two for ASD, and three for "general neurodevelopment." He emphasizes that Ji 2020 and Baker 2020[51] found a "clear" dose response. He finds further support for his opinion in the expert opinion of Dr. Louie. As discussed below, Dr. Louie's opinion is inadmissible. Dr. Louie opines that prenatal use of acetaminophen for 28 days or more during a pregnancy can cause ADHD and ASD -- a number that is neither reliably supported by the sources upon which he relies, nor tethered to any particular period during pregnancy.

Dr. Baccarelli is correct that Ji 2020 and Baker 2020 found results consistent with a dose-response, but his statement that

[51] It appears that Dr. Baccarelli's reference in his report to Baker 2022 is in fact a reference to Baker 2020. Thus, the change has been made in this Opinion.

"virtually every study that was powered to evaluate, and did in fact evaluate, dose response found an association" is misleading, as is his reliance on Alemany 2021. The authors of Alemany 2021 stated that "dose and frequency of use were not harmonized across cohorts and therefore, not analysed herein." Id. at 1001. As will be discussed below, many of the animal studies relied upon -- the only studies that could reliably record dosage during pregnancy -- do not show a dose response.

The plaintiffs have not carried their burden of showing that Dr. Baccarelli reliably applied epidemiological principles to this component of the Bradford Hill analysis. Dr. Baccarelli's dose-response opinion is more general than Dr. Louie's 28-days opinion. While that generality helps him avoid some of the pitfalls of Dr. Louie's approach, it does not grapple with a key issue in the underlying studies: none were able to record the actual dosages taken by pregnant women. The closest approximation to dose in the underlying studies is days of use.

Finally, Dr. Baccarelli's reliance on Ji 2020 and Baker 2020 required a more careful reading of those studies. Ji 2020 does not clearly map onto maternal dosing, because it only measured acetaminophen in umbilical cord blood at delivery. Baker 2020 did not adjust for indication or genetic confounding,

which is problematic because both factors can increase risk ratios. See Ricci 2023 at 482. Like his consistency opinion, Dr. Baccarelli's dose-response opinion skates over the complexities and limitations of the underlying literature, and is therefore not admissible under Rule 702.

7. Biological Plausibility

Biological plausibility depends upon existing knowledge about the mechanisms by which the disease at issue develops. Therefore, the weight assigned to this factor will depend upon the state of science. RMSE at 604-05.

Dr. Baccarelli opines that there are multiple plausible biological mechanisms that could explain the association between prenatal acetaminophen exposure and NDDs in offspring and mentions oxidative stress as a known pathway. He finds confirmation for his opinion in the opinions offered by Drs. Cabrera and Pearson. Dr. Baccarelli finds that the plausibility criterion is satisfied.

As will be explained in more detail during the discussion of Dr. Cabrera's report, the plaintiffs have not shown that any expert opinion purporting to identify the physiological processes that cause the development of either ASD or ADHD would survive scrutiny under Rule 702. At present, the precise physiological process or processes by which these conditions, or

NDDs more generally, develop are unknown. Scientists have at best developed hypotheses. Therefore, Dr. Baccarelli's conclusion that this factor is satisfied is stricken as failing to reflect a reliable application of scientific principles. The absence of an admissible opinion by Dr. Baccarelli on biological plausibility would not, however, preclude the admission of an otherwise admissible opinion by him on causation.

8. Coherence

Dr. Baccarelli next examines the coherence factor, which he describes as looking at whether a causal relationship conflicts with generally known facts about the history and biology of the disease. Dr. Baccarelli gives coherence only "minor" weight, but believes it is satisfied.

Dr. Baccarelli opines that the association between prenatal acetaminophen exposure and ADHD and ASD in children is coherent with existing knowledge and understanding of the diseases and their causes because environmental factors are known to affect neurodevelopment during pregnancy and the rates of ADHD and ASD have risen in tandem over the decades with use of acetaminophen. The plaintiffs have shown that Dr. Baccarelli's conclusion that the coherence factor is satisfied reflects a reliable application of scientific principles. While the defendants take issue with the accuracy of the data on which Dr. Baccarelli

relies to find an in tandem increase in the use of acetaminophen and a rise in either ADHD or ASD, those disagreements do not affect the admissibility of this opinion.

9. Analogy

The analogy factor examines whether similar drugs have been shown to cause the outcome of interest. "Substantiation of relationships similar to the putative causal relationship increases the likelihood of causation." Mirena II, 341 F. Supp. 3d at 243. Dr. Baccarelli placed "very little weight" on the analogy factor, but found it satisfied.

Dr. Baccarelli finds this factor satisfied because "[t]he FDA-approved label for Depakote, another drug previously used by pregnant women . . . states that 'the weight of the evidence supports a causal association between valproate exposure in utero and subsequent adverse effects on neurodevelopment, including increases in [ASD and ADHD]." Dr. Baccarelli states, without citation or discussion, that "[v]alproic acid, like acetaminophen, has been shown to increase oxidative stress and deplete glutathione levels." This bare assertion, unaccompanied by any discussion of the chemical structures of valproic acid and acetaminophen, does not reflect a reliable application of the analogy factor.

10. Experiment

Finally, epidemiologists consider a relationship of causation is more likely to exist if removing the exposure in a population results in a decrease in the occurrence of the disease or harm. Here, ethical considerations prevent the collection of direct experimental evidence.

Dr. Baccarelli assigns minimal weight to this factor, but nevertheless finds this factor satisfied because, using a "more modern approach", he has considered animal studies. As the parties acknowledge, the animal studies cannot bear the full weight of providing admissible evidence of causation in this case. They may, however, be supportive of other evidence of causation. The animal studies are addressed below, in connection with the discussion of the reports of Drs. Cabrera and Pearson.

11. Genetic Confounding

In addition to the disqualifying deficiencies just described, particularly with respect to the factors of consistency and the strength of association, Dr. Baccarelli's Bradford Hill analysis is unreliable due to his failure to assess with sufficient rigor the relevant evidence of confounding by genetics. By itself, this failure requires the exclusion of his opinion.

As described earlier, according to the DSM, a recent five-country cohort estimated ASD heritability at 80%. DSM at 64. Similarly, the heritability of ADHD is estimated to be approximately 74%. Id. at 71.

The parties agree that the existence of genetic confounding must be addressed when seeking to assess an association between prenatal use of acetaminophen and either ASD or ADHD. In its 2022 review of the literature, the FDA observed that studies are "still limited by . . . the possibility of unmeasured confounding by factors such as indication, other medications, and genetic factors." FDA 2022 at 32. The FDA observed in 2023 that high quality studies should adjust for confounders, including "genetic factors or . . . relevant familial factors such as parental neurobehavioral conditions (e.g., parental ADHD) or psychiatric conditions." FDA 2023 at 27.

Many of the studies that Dr. Baccarelli collected in his survey, including those upon which he relies most heavily, acknowledge the need for more work to account for the confounding effect of genetics. See, e.g., Liew 2014 at 319, Liew 2016a at 956, Ji 2020 at 188, Baker 2020 at 1079, Ricci 2023 at 482. And, a few studies have been specifically designed to try to measure that effect.

For example, Gustavson 2021 performed a sibling-control analysis on data from the MoBa cohort.[52] There were over 29,000 siblings in the study. The authors initially found a two-fold increase in the risk of an ADHD diagnosis for children born to a mother with a long-term use of acetaminophen (29 days or greater) during the pregnancy (2.02; 95% CI 1.17-3.25). Id. at 5. After performing the sibling-control analysis, however, that association was eliminated (1.06; 95% CI 0.51-2.05). Id. All children, whether exposed or not to acetaminophen in utero, who were born to a mother with long-term use of acetaminophen in one pregnancy had an increased risk of receiving an ADHD diagnosis compared to children of mothers who did not use acetaminophen in any pregnancy (2.77; 95% CI 1.48-5.05). Id. at 5, 7. From this nearly three-fold family effect, the authors concluded that familial confounding factors may explain at least part of the observed association between maternal long-term acetaminophen use and ADHD. In other words, a mother's long-term use of acetaminophen during pregnancy may indicate a preexisting risk of ADHD in the child, rather than causing the increased risk.

[52] The MoBa cohort is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Pregnant women from all over Norway were recruited between 1999 and 2008. Maternal questionnaires were answered at gestational weeks 17 and 30, as well as six months after birth. The study includes more than 114,000 children.

Another study, Leppert 2019, was designed to test whether maternal genetic risk scores were associated with early-life exposures of their offspring to a variety of experiences, from smoking to low birth weight. One of the measured exposures was in utero exposure to acetaminophen. Of the pregnant women recruited in Avon, United Kingdom in the years between 1990 and 1992, over 10,000 underwent genotyping for risk alleles associated with ADHD, ASD, and schizophrenia. The results from the study suggest that mothers with higher ADHD polygenic risk scores "may also be more likely to use acetaminophen in pregnancy." Id. at 839. It concluded that "to draw conclusions about causality, future studies need to account for potential genetic confounding." Id. at 840. In particular, it observed that "mothers with high genetic liability to ADHD may be at increased risk for many adverse pregnancy factors." Id.

Further, the authors of Masarwa 2020[53] -- who had previously conducted a meta-analysis, Masarwa 2018,[54] that found an

[53] Masarwa et al., Acetaminophen Use During Pregnancy and the Risk of Attention Deficit Hyperactivity Disorder: A Causal Association or Bias?, 34 Paediatric Perinatal Epidemiology 309 (2020).

[54] Masarwa et al., Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies, 187(8) Am. J. Epidemiology 1817 (2018).

association between prenatal acetaminophen use and ADHD symptoms -- updated their meta-analysis and conducted a bias analysis. They concluded that the "observed association between acetaminophen during pregnancy and the increased risk for ADHD in the offspring is likely the result of bias. This systematic error appears to be predominantly driven by unmeasured confounding and exposure misclassification." Id. at 316.

Despite the identified risk of genetic confounding, Dr. Baccarelli gives short shrift to the issue. The discussion in his reports is incomplete, unbalanced and at times misleading.[55]

In general, Dr. Baccarelli downplays those studies that undercut his causation thesis and emphasizes those that align with his thesis. A stark example of Dr. Baccarelli's result-driven analysis appears in his discussion of two sibling-control studies run from the same cohort -- the MoBa cohort -- eight years apart. Although the earlier study, Brandlistuen 2013, did not include any diagnosis of ADHD in offspring, its conclusion was a better fit for Dr. Baccarelli's thesis, and he praises it, stating that it offers "greater comfort that unmeasured, residual confounding is not driving the association between acetaminophen and ADHD." The more recent study, which due to

[55] During his deposition, Dr. Baccarelli repeatedly evaded defense counsel's inquiries on the issue.

the passage of time was able to incorporate actual diagnoses of ADHD, is Gustavson 2021. It has already been described and its results underscore the need to consider genetic confounding when analyzing whether in utero exposure to acetaminophen has caused ADHD. Dr. Baccarelli is dismissive of the study's results. At no point does he explain his disparate treatment of the two studies.

Dr. Baccarelli's dismissal of evidence that challenges his thesis is also illustrated by his discussion of Ystrom 2017, which also studied the MoBa cohort.[56] The authors of the study concluded, "given that paternal use of acetaminophen is also associated with ADHD, the causal role of acetaminophen in the etiology of ADHD can be questioned" and cautioned that "[w]e do not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD."[57] Id. at 7. In his report, Dr. Baccarelli speculates that paternal use might have been serving as an imperfect proxy for maternal use

[56] Ystrom 2017 found an association between maternal prenatal use of acetaminophen for 29 days or more and offspring diagnosed with ADHD (2.20, 95% CI 1.50-3.24). Id. at 6. But the study also found a two-fold association between paternal use of acetaminophen for 29 days or more before conception and ADHD in offspring (2.06; 95% CI 1.36-3.13). Id. at 7.

[57] The FDA, in its 2022 literature review, noted that the "NCE for paternal [use] suggests residual confounding." FDA 2022 at 54.

because, among other things, "fathers and mothers often share medications and medicine cabinets." This does not constitute a scientifically sound treatment of Ystrom 2017.

Dr. Baccarelli is also willing to press conclusions that study authors are not willing to make. This willingness creates an "analytical gap" between the conclusions reached by the authors and the conclusions he draws from their work. See Daniels-Feasel, 2021 WL 4037820, at *10. In doing so, Dr. Baccarelli repeatedly ignores authors' cautions that familial or genetic confounding may explain, at least in part, the observed association.

Overall, Dr. Baccarelli's testimony does not reflect a reliable application of scientific methods. Of the three Bradford Hill factors to which he accords the most weight, none have been analyzed in a reliable manner. Further, he "chooses not to consider evidence that undercuts his opinion" -- namely, evidence that genetic confounding may partially explain the observed associations. See Mirena II, 341 F. Supp. 3d at 252. Because "each of [Dr. Baccarelli's] departures from settled and rigorous methodology favors the same outcome," it "suggests motivated, result-driven, reasoning." Id. at 251. Dr. Baccarelli's proposed testimony regarding his Bradford Hill

analysis is inadmissible under the standards set forth by Daubert and Rule 702.

B. Navigation Guide

Dr. Baccarelli's applications of the Navigation Guide are similarly suspect. As Dr. Baccarelli acknowledges, it is the Bradford Hill methodology that epidemiologists have traditionally used to address questions of causation. In contrast, the Navigation Guide is a tool used to summarize evidence. Or, as Dr. Baccarelli explains in his rebuttal report, it is a "guide" that requires scientists to "objectively analyze each study and then transparently rate each study considered as part of the causal analysis."

The Navigation Guide methodology involves conducting a search of the relevant literature, extracting and evaluating data from the studies identified, rating the quality and strength of the evidence, and then coming to an overall conclusion about an agent's toxicity. See Woodruff & Sutton, The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes, 122(1) Environ. Health Perspect. 1007 (2014). It is intended to be used by teams to minimize bias in the evaluation of the evidence. Here, however, Dr. Baccarelli performed the analysis by himself.

As with the Bradford Hill criteria, there are many steps within the Navigation Guide framework that call for expert judgment. Several steps require the expert to use her subjective judgment to up- or down-grade an objective rating.[58] Thus, the Navigation Guide, like Bradford Hill, is a "flexible methodology" that "can be implemented in multiple ways." Zoloft, 858 F.3d at 795. Even assuming the Navigation Guide's utility in assessing causation for purposes of this litigation, "each application is distinct and should be analyzed for reliability." Id.

Dr. Baccarelli used the Navigation Guide methodology three times: once each for studies concerning ASD, studies concerning ADHD, and studies concerning other NDDs. In his analysis for ASD, Dr. Baccarelli reviewed six studies and included four of them in his overall evaluation of the strength of the evidence (the two he did not include, Leppert 2019 and Saunders 2019, would, if credited, detract from the evidence of causality). He states that these four "consistently reported a positive association between prenatal acetaminophen use and ASD, with an

[58] Dr. Baccarelli readily admits that the downgrading of each study is based on his judgment. Even in the case of summary scores, he used those scores "only as a guide reflecting the scores across the six factors. In other words, the summary scores informed my decision of the final expert opinion scores, but were not binding."

exposure-response relationship observed in two of the three studies." He rated two studies as "very strong" evidence: Ji 2020 and Liew 2016a. As noted above, Ji 2020 only measures peripartum exposure, the relevance of which Dr. Baccarelli does not sufficiently explain. Notably, he rated Alemany 2021 (a meta-analysis) as "strong" evidence, but did not include Ricci 2023 (a more recent meta-analysis), presumably because of its conclusion that there were too few ASD studies to reliably conduct a meta-analysis. Finally, his rating of Liew 2016a does not contend with that study's finding that acetaminophen was not associated with ASD without HKD.

Dr. Baccarelli devotes only one paragraph to the section titled "Final Determination Based on the Navigation Guide Analysis About the Toxicity of Prenatal Acetaminophen Use and Child's ASD." Dr. Baccarelli asserts that the studies consistently reported a positive association and that the studies controlled for confounding. Given the heterogeneity of the evidence, these cursory assertions do not sufficiently support his "final determination [] that there is strong evidence of a causal link between prenatal acetaminophen use and an increased risk of being diagnosed with ASD in children."

As for ADHD, Dr. Baccarelli based his Navigation Guide determination on "the evaluation of fifteen studies, including

four high-quality studies that provided very strong evidence of an association and five studies that provide strong evidence of an association." The rest of the paragraph describing the determination is a near-verbatim copy of the paragraph on ASD. His grading of the studies, examined closely, shows similar evidence of "result-driven analysis." Lipitor, 892 F.3d at 634.

Perhaps most tellingly, Baccarelli separated Gustavson 2021 into two studies: the initial data (which reported an association, and which Dr. Baccarelli rated as "strong evidence") and the sibling-control analysis (which attenuated the association, and which Dr. Baccarelli downgraded from "moderate" to "weak" evidence "due to concerns about small size and the bias toward the null likely introduced by the elimination of the effects of intermediate factors"). Yet he did not similarly downgrade Brandlistuen 2013, discussed supra, instead rating it as "strong evidence" that acetaminophen causes other NDDs. But Brandlistuen 2013's sibling-control analysis would similarly "eliminat[e] the effects of intermediate factors," and it included 134 sibling pairs discordant on exposure for greater than 28 days. Id. at 1704. Gustavson 2021, having the benefit of several more years of data on the same cohort, included 380 families with siblings discordant on exposure for 29 days or more. Id. at 5. This is a paradigmatic

example of interpreting results differently based on the outcome of the study, Zoloft II, 858 F.3d at 797, and it is illustrative of Dr. Baccarelli's approach to the Navigation Guide, in which he uses areas where an expert's subjective opinion comes into play to selectively downgrade studies not supporting his analysis and vice versa.

Finally, Dr. Baccarelli also disregards relevant reviews of epidemiological studies conducted by medical and governmental associations. He does not address the FDA's repeated conclusion that the epidemiological evidence does not support his opinions, other than to note his disagreement with that conclusion. Nor does he grapple with the contrary conclusions of the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, or the European Network of Teratology Information Services. This "rejection of a conclusion that could not be more relevant to his opinions is alarming." Daniels-Feasel, 2021 4037820, at *12.

In sum, Dr. Baccarelli failed to sufficiently explain the appropriateness of conducting a single Bradford Hill analysis for NDDs which included ASD and ADHD, selectively analyzed the consistency of the literature and the issue of genetic confounding, repeatedly pressed conclusions that study authors were not willing to make, and disregarded studies that do not

support his opinion due to limitations that he did not view as disqualifying in studies that did support his opinion. Together, these deficiencies demonstrate that his opinion does not "reflect[] a reliable application of the principles and methods to the facts of the case." Fed. R. Evid. 702. Thus, Dr. Baccarelli's causation opinions are not admissible.

At oral argument, the plaintiffs asked the Court to focus on the fact that Dr. Baccarelli is a preeminent epidemiologist, which he is. They ask that the Court ignore his published statements acknowledging the weakness in the literature, arguing that he has been correct to change his mind when rendering his opinion here. They stress the direction of the association evidence, ignoring those studies finding no association or a negative association. They argue that it is unnecessary to insist that a finding of association be statistically significant, arguing that a more flexible standard should be adopted. They contend that the limitations expressed by authors in their studies should be ignored as simply an overly conservative requirement that scientists impose on each other to get peer reviewed studies published. They suggest that the FDA's surveillance of this issue since 2014 means little since the FDA was not vigilant in reviewing the risks associated with certain other drugs and that it has not performed a Bradford

Hill analysis. These and more arguments like them do not relieve the Court of the obligation to scrutinize the methodology applied by Dr. Baccarelli to ensure that it is sufficiently rigorous to pass muster by the standards established by his discipline, Rule 702 and Daubert.

XI. Dr. Cabrera

Dr. Robert Cabrera has provided an amended expert report of June 22, 2023, a supplemental expert report dated July 17, and a rebuttal expert report dated July 28. He was deposed on August 2.

Dr. Cabrera's expertise is in teratology, the study of abnormalities, malformations, and developmental disorders that occur during prenatal development. He is an Associate Professor of Molecular and Cellular Biology at Baylor College of Medicine and an Adjunct Professor of Biology at San Jacinto College. He obtained his Ph.D. in Medical Sciences from Texas A&M University Health Science Center. His research focuses on the interrelationships between maternal immunity and birth defect risks, and he is currently leading research efforts to test developmental toxicity of anti-retroviral therapies. Dr. Cabrera does not specialize in ASD or ADHD.

Dr. Cabrera was asked by plaintiffs' counsel to examine the developmental and reproductive toxicity of acetaminophen. Dr.

Cabrera states that he reviewed the chemical profile of acetaminophen; a published regulatory adverse outcome pathway ("AOP") linking mercury exposure to deficits in learning and memory; and the preclinical, in vitro, ex vivo, and in vivo studies of potential reproductive, developmental, and neurodevelopmental effects of therapeutic doses of acetaminophen.

Dr. Cabrera combined several methodologies in his report. He relied in part on the AOP construct, which "consider[s] data describing the adverse consequences of exposure to a toxin at the molecular, cellular, tissue, organ, whole body, and population levels in assessing questions of association and causality." Dr. Cabrera applied parts of the published AOP 20, and otherwise used the AOP construct to organize his weight of the evidence analysis of whether acetaminophen exposure during pregnancy can cause functional deficits in offspring, specifically, ASD and ADHD. He adds a brief Bradford Hill analysis at the end of his report.

Dr. Cabrera offers both general causation and biological mechanism opinions. He opines that therapeutic dosages of acetaminophen taken by pregnant women are sufficient to cause neurotoxicity, neurodevelopmental disorders, ASD, and ADHD in their children. He primarily relies on two biological

mechanisms, the first involving oxidative stress and the second involving endocannabinoid disruption.[59]

Dr. Cabrera's application of each of the above methodologies is unreliable. His Bradford Hill analysis is "unweighted and unmoored." Mirena II, 341 F. Supp. 3d. at 247. His weight of the evidence analysis repeatedly cherry picks isolated findings in studies measuring multiple outcomes, ignores inconsistent results, and dismisses the express limitations of study authors. He fails to adhere to principles he claims are important guidelines for analyzing animal studies, uncritically presents unreplicated and at times irrelevant findings, and obfuscates critical gaps in his biological mechanism analysis. His testimony is inadmissible under Rule 702.

A. Bradford Hill

Dr. Cabrera devotes only a few pages to his Bradford Hill analysis. There is an overarching methodological flaw in Dr. Cabrera's Bradford Hill analysis: he "does not explain the weight that he attaches to any of the Bradford Hill criteria or address the relationship among them." Mirena II, 341 F. Supp. 3d. at 248. By "leaving obscure the weight that he attaches to

[59] The plaintiffs originally identified a half dozen biological mechanisms, but in their defense of these motions rely on two.

each of the nine Bradford Hill factors and the relationship among them, Dr. [Cabrera's] approach effectively disables a finder of fact from critically evaluating his work." Id. Because, as explained supra, "[f]lexible methodologies . . . can be implemented in multiple ways," it is critical that an expert "explain 1) how conclusions are drawn for each Bradford Hill criterion and 2) how the criteria are weighed relative to one another." Zoloft, 858 F.3d at 796. "Otherwise, such methodologies are virtually standardless and their applications to a particular problem can prove unacceptably manipulable." Mirena II, 341 F. Supp. 3d at 247. Dr. Cabrera's failure to explain how he weighted the Bradford Hill factors renders his analysis an unreliable application of a theoretically valid methodology and is in itself a sufficient reason to exclude his Bradford Hill opinion. Further, like Dr. Baccarelli, he conducts a transdiagnostic analysis, addressed to "neurodevelopmental toxicity." He combines studies on ASD, ADHD, and a variety of symptom outcomes without adequately explaining his basis for doing so or confronting the complexities created by this conflation.

In addition, Dr. Cabrera's assessment of the individual Bradford Hill factors is cursory and unreliable. It amounts to little more than his ipse dixit. He acknowledges, for example,

that "[i]n general, an odds ratio between 1 and 2 is deemed low, a ratio from 2 to 6 is deemed moderate, and a ratio above 6 deemed high." Despite the fact that the majority of studies show at most (by his definition) a low odds ratio, he states that the strength of association criterion is met. To get to that conclusion, he states that "the totality of the data is consistent with 'clear evidence of developmental toxicity'" because there are "data that indicate a dose-related effect" on functional deficits. This conflation of the dose-response and strength criteria is per se not reliable. In any event, the weakness in the evidence of any association cannot be overcome by evidence of dose-response, which is similarly weak at best.

Dr. Cabrera also opines that the consistency factor is met. His section on consistency spans all of five paragraphs and is unreliable for the same reasons explained in detail supra with regards to Dr. Baccarelli's analysis. Considering the heterogenous nature of the epidemiological evidence -- particularly the variety in exposure and outcome assessments -- a much more thorough analysis would be necessary to reliably opine on the literature's consistency.

His temporality analysis is flawed for the same reason as Dr. Baccarelli's. He finds the dose-response criterion satisfied even though meta-analyses, which he places at the top

of the hierarchy of evidence, were unable to analyze a dose response due to the heterogeny of exposure assessments in the literature.

He states that the experiment criterion is met because "[t]he available experimental evidence from animal models consistently demonstrates dose-responsive reproductive, developmental, and neurodevelopmental toxicity with pre-, peri- and post-natal [acetaminophen] exposures." As will be explained in detail infra, this is a highly inaccurate representation of the animal study literature. Briefly, the animal studies, like the epidemiology studies, measure many different behavioral and biological outcomes; and, as with the epidemiology studies, the devil is in the details. Dr. Cabrera presents many studies as "clear evidence" of acetaminophen's purported impact on rodent behavior and biology when in reality those studies reported conflicting or unreplicated individual outcomes with varying relevance to either ADHD or ASD.

As will be discussed infra, Dr. Cabrera's analysis of the biological mechanism contains key gaps in the causal chain; given those gaps, his analysis of biological plausibility cannot outweigh the weaknesses in the rest of his Bradford Hill analysis. To his credit, Dr. Cabrera does acknowledge that the specificity factor "is not fully met"; however, without

specificity or a reliable analysis of strength, consistency, temporality, dose-response, biological mechanism, or experiment, Dr. Cabrera is left with coherence and analogy. Without any explanation of his weighting of the factors, the last two factors alone cannot reliably be used to opine on general causation.

Thus, Dr. Cabrera's proposed testimony that a Bradford Hill analysis supports his general causation opinion is inadmissible under Rule 702. It must be excluded.

B. Adverse Outcome Pathway

Dr. Cabrera purports to offer several theories of biological plausibility linking the use of acetaminophen to NDDs, including ASD and ADHD. But he does not identify a mechanism by which either ASD or ADHD is created in utero. For this and the other reasons described below, his opinions of biological plausibility are excluded.

In offering opinions of biological plausibility Dr. Cabrera relies heavily on the OECD's AOP 20.[60] According to the OECD, "[a]n AOP is an analytical construct that describes a sequential

[60] Tschudi-Monnet et al, Binding of electrophilic chemicals to SH(thiol)-group of proteins and/or seleno-proteins involved in protection against oxidative stress during brain development leading to impairment of learning an memory, OECD Series on Adverse Outcome Pathways, No. 20, OECD Publishing, Paris, at https://doi.org/10.1787/4df0e9e4-en.

chain of causally linked events at different levels of biological organization that lead to an adverse health or ecotoxicological effect."[61] Thus, an AOP is a useful construct to consider plausible biological mechanisms by which chemicals may impact health. AOPs progress from data on molecular interactions with the chemical, to cellular responses, to organ responses, to responses at the organism (and sometimes population) level. Dr. Cabrera uses this analytical construct to structure his weight of the evidence analysis.

To the extent that Dr. Cabrera opines that his application of acetaminophen studies to AOP 20 provides independent support for his causation opinion regarding ADHD and ASD, his testimony is inadmissible for the following reasons. The authors of AOP 20 state that

> [t]he weight-of-evidence supporting the relationship between the described key events is based mainly on developmental effects observed after an exposure to the heavy metal, mercury, known for its strong affinity to many SH-/seleno-containing proteins, but in particular to those having anti-oxidant properties, such as glutathione (GSH).

Id. at 4. The AOP posits that chemicals binding to, e.g., GSH depletes those protective proteins, resulting in decreased protection against oxidative stress, which in turn results in

[61] Organisation for Economic Co-operation and Development, Adverse Outcome Pathways, at https://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm.

increased oxidative stress. Oxidative stress then causes a cascade of events leading to cell injury and/or death, which then leads to decreased network formulation and function, and then to impairment in learning and memory. Id.

Because this litigation involves acetaminophen, not mercury, and ADHD and ASD, which may or may not involve deficits in learning and memory, Dr. Cabrera must independently fill the gaps at the beginning and end of the pathway. That is, a reliable application of the AOP/weight of the evidence methodology he purports to perform must show that maternal prenatal acetaminophen use can cause depletion of GSH in the fetal brain, and that "decreased network formulation and function" can lead to ASD and ADHD. Otherwise, his causation and oxidative stress biological mechanism opinions would be connected to existing data "by the ipse dixit of the expert." Mirena II, 341 F. Supp. 3d at 271 (citation omitted). His attempt to fill these gaps does not reflect a reliable application of scientific principles.

Briefly, Dr. Cabrera posits that a minor but toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone imine ("NAPQI"), which accounts for about 5-15% of metabolized acetaminophen, binds to GSH, initiating the pathway described above. Although GSH depletion is generally accepted as a

biologically plausible mechanism for liver toxicity resulting from acetaminophen overdose, there is no replicated data showing that prenatal exposure to clinically relevant doses of acetaminophen causes GSH depletion in the fetal brain. Most studies that Dr. Cabrera cites in support of this link in the chain examined either adult rodents (thus having limited relevance to prenatal exposure), doses too high to be clinically relevant, and/or reduction of GSH in the liver, not the brain.

The studies that did measure GSH in the brain after prenatal exposure do not support his oxidative stress theory. For example, he relies on Klein 2020[62] and Rigobello 2021[63] as providing evidence that acetaminophen reduces GSH. But Klein 2020 found that exposure to acetaminophen during gestation did not affect "GSH levels in the prefrontal cortex or hippocampus . . . indicating that the exposure regimen did not cause long-term alterations in oxidative balance in these two brain regions." Id. at 6. Rigobello 2021 found decreased GSH in the hippocampus in males only at the lower tested dose, and no difference from

[62] Klein et al., Gestational Exposure to Paracetamol in Rats Induces Neurofunctional Alterations in the Progeny, 77 Neurotoxicology and Teratology (2020) ("Klein 2020").

[63] Rigobello et al., Perinatal Exposure to Paracetamol: Dose and Sex-Dependent Effects in Behavior and Brain's Oxidative Stress Markers in Progeny, 408 Behavioral Brain Research e113294 (2021) ("Rigobello 2021").

controls in females, at the higher tested dose, or in the other brain regions studied (prefrontal cortex, striatum, and cerebellum). Id. at 6. Thus, out of sixteen measurements of GSH in the brain, only one supports Dr. Cabrera's theory; the other fifteen do not. Yet he includes Rigobello 2021 in a chart as evidence of decreased GSH with no mention of the fifteen findings of no effect.

Further, in his weight of the evidence analysis, he states that "[t]he effects described above by exposing acetaminophen were dose and duration dependent. Exposure to greater doses and for longer durations increased the effects on brain tissues and behavior." But he does not mention that Rigobello 2021's one significant GSH finding only occurred at the lower dose -- the opposite of a dose-response. That study's authors note that the "non-monotonic relationship observed . . . may be a consequence of an adaptive response[, however,] this is a speculative hypothesis that warrants future studies." Id. at 5.

Similar issues arise in Dr. Cabrera's analysis of the final gap in the AOP's causal chain -- that is, whether this causal pathway can lead to ADHD and ASD. Dr. Cabrera cites many studies of animal behavior in support of this causal link. The behavioral outcomes measured by these studies are highly variable and of contested translational validity, i.e.,

scientists disagree over whether the outcomes measured are indicative of clinically relevant traits in humans.[64] For example, scientists place rodents in compartments containing marbles atop bedding and measure how many marbles the rodent buries; theoretically, an increase in the number of marbles buried is indicative of repetitive and restrictive behaviors associated with ASD in humans. Another test places a rodent in a central chamber connected to two other chambers: one with an object and one with another rodent. Scientists then measure the amount of time spent exploring the cage with the 'social peer' compared to the time in the cage with the object. Another outcome measured is pup ultrasonic vocalizations, where a young rodent is separated from its mother, and the quantity and quality of its calls are recorded.

As with the oxidative stress marker studies, Dr. Cabrera presents isolated findings from behavioral studies in his weight of the evidence analysis without reconciling inconsistent findings. For example, he states that Baker 2023 provides "clear evidence" of impaired social behavior. In fact, the findings of Baker 2023, which measured dozens of outcomes, are much more mixed. For example, pup ultrasonic vocalizations were

[64] See, e.g., Silverman et al., Reconsidering Animal Models Used to Study Autism Spectrum Disorder: Current State and Optimizing Future, 21(5) Genes Brain Behav. e12803 (2022).

measured on four days. The authors found one significant change (an increase in vocalizations rather than the expected decrease) in males on postnatal day 8. Id. at 4. But there were no significant changes in vocalizations among males on the other three days or among females on any day. Id.

Another study, Harshaw 2022,[65] is presented as "clear evidence of impaired social-emotional and repetitive behaviors." But the authors of that study, which also found a variety of potentially inconsistent results, stated that "[a] key implication of our findings is that no simple conclusion regarding the relative safety vs. danger of [acetaminophen] early in life is yet possible." Id. at 13.

Further, some animal behavior studies relied upon by Dr. Cabrera measure the acute effects of acetaminophen administered to adult rodents and are thus only peripherally relevant. See, e.g., Ishida 2007,[66] Gould 2012.[67] Notably, Dr. Cabrera takes

[65] Harshaw & Warner, Interleukin-1B-induced Inflammation and Acetaminophen During Infancy: Distinct and Interactive Effects on Social-Emtional and Reptetitive Behavior in C57BL/6J Mice, 220 Pharmacology, Biochemistry and Behavior e173463 (2022).

[66] Ishida et al., Effect of Acetaminophen, a Cyclooxygenase Inhibitor, on Morris Water Maze Task Performance in Mice, 21(7) J. Psychopharmacology 757 (2007).

[67] Gould et al., Acetaminophen Differentially Enhances Social Behavior and Cortical Cannabinoid Levels in Inbred Mice, 38 Prog. Neuropsychopharmacology Biol. Psych. 260 (2012).

issue with Zhao 2017's[68] use of adult rats but not with Ishida 2007's or Gould 2012's, perhaps because unlike those two studies, Zhao 2017 found that acetaminophen may in fact "alleviate cognitive impairment" due to its "antioxidant and anti-inflammatory properties." Id. at 13. Dr. Cabrera's dismissal of Zhao 2017 as an "[i]nadequate study of developmental toxicity" and simultaneous branding of Ishida 2007 and Gould 2012 as "clear evidence" of learning deficits and repetitive behavior, respectively, is an example of "cherry-pick[ing] those findings that support his conclusions while failing to note that they also suffer from the same weaknesses as the studies he disregards." Daniels-Feasel, 2021 WL 4037820, at *9.

Thus, Dr. Cabrera does not reliably fill two critical gaps in his application of the adverse outcome pathway construct. These gaps are therefore fatal to his general causation opinion to the extent it relies on the adverse outcome pathway analysis, because there is "too great an analytical gap between the data and the opinion proffered." Joiner, 522 U.S. at 146. But the above issues are also emblematic of several overarching methodological flaws in Dr. Cabrera's weight of the evidence

[68] Zhao et al., Acetaminophen Attenuates Lipopolysaccharide-Induced Cognitive Impairment Through Antioxidant Activity, 14 J. Neuroinflammation 17 (2017).

analysis: cherry-picking isolated findings, ignoring inconsistent findings, and disregarding limitations expressed by a study's authors as well as generally accepted statistical principles.

Cherry-picking of isolated findings is of particular concern here given that most of the studies measured many markers of oxidative stress and behavioral outcomes at once and many did not correct for multiple comparisons. "Repeated testing complicates the interpretation of significance levels" because "[i]f enough comparisons are made, random error almost guarantees that some will yield [significant] findings, even when there is no real effect." RMSE at 256. When studies did correct for multiple comparisons and as a result found no significant effects, for example in Saad 2016,[69] Dr. Cabrera argues that the authors should not have corrected for multiple comparisons. Dr. Cabrera cites an article from the American Statistical Association on the strengths and weaknesses of overreliance on statistical significance,[70] but that article does

[69] Saad et al., Is There a Causal Relation Between Materanl Acetaminophen Administration and ADHD?, 11(6) PLoS One e0157380 (2016). Saad 2016 concluded that "[o]ur results do not support a causal relationship" and thus "[r]esults of epidemiological studies may be due to confounding factors that were not accounted for." Id. at 9.

[70] Wasserstein & Lazar, The ASA Statement on p-Values: Context, Process, and Purpose, 70 The American Statistician 129 (2016).

not take issue with multiple comparison corrections at all. More importantly, it is the role of the district court to "function as a gatekeeper; it is not for the courts to be the pioneers, forging new trails in scientific thinking, especially when that means departing from well-established research principles, such as the principle of statistical significance." In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation, 26 F. Supp. 3d 449, 456 (E.D. Pa. 2014).

Thus, Dr. Cabrera's general causation opinion is inadmissible under Rule 702, as his biological mechanism opinion based on oxidative stress. His proposed testimony regarding endocannabinoid disruption is far less developed than his oxidative stress opinion.

XII. Dr. Hollander

Dr. Eric Hollander has provided an amended expert report of June 22, 2023, and a rebuttal report dated July 28. He was deposed on August 9.

Dr. Hollander is a psychiatrist who specializes in neuropharmacology and neuropsychiatry. He received his M.D. from SUNY Downstate Medical College, Brooklyn, New York in 1982. He is a Professor of Psychiatry and Behavioral Sciences and the Director of the Autism and Obsessive Compulsive Spectrum Program at the Psychiatry Research Institute of Montefiore-Einstein at

Albert Einstein College of Medicine and Montefiore Medicine in the Bronx. He is Chair of the Board of Directors of the International College of Obsessive Compulsive Spectrum Disorders. He currently serves as the Director of the Spectrum Neuroscience and Treatment Institute. He has published more than 500 peer-reviewed papers and served as an editor for 20 books, including the textbook Autism Spectrum Disorders.

Dr. Hollander was asked by plaintiffs' counsel to opine about "the interconnectedness of various neurodevelopmental disorders, including [ASD and ADHD]"; whether the scientific evidence regarding the association between prenatal exposure to acetaminophen and NDDs "informs the question of whether prenatal exposure" to acetaminophen can "cause" ASD and ADHD; and whether there are "plausible biological mechanisms" to explain how acetaminophen "can cause" ASD and ADHD.

As reflected in his initial report, Dr. Hollander was not asked to and does not (initially) opine that acetaminophen causes ASD or ADHD, that it is appropriate to conduct a transdiagnostic Bradford Hill analysis to answer that question, or that Drs. Baccarelli and Cabrera properly structured their transdiagnostic analyses. Instead, in response to the questions posed to him, he opines that ASD and ADHD are "highly heterogenous" both in terms of etiology and presentation and do

not have a single cause or risk factor. He explains that they do, however, overlap with each other and other NDDs. He adds that, because of this overlap, transdiagnostic processes can provide valuable insight. Speaking from his extensive experience as a treating psychiatrist, he opines that clinicians must take a transdiagnostic approach in their assessments of patients, because without such an approach "similarities in behavioral profiles between [ASD and ADHD] disorders could lead to challenges in both the diagnosis and intervention efforts."

Dr. Hollander defines a transdiagnostic process as a "mechanism that underlies and connects a group of disorders that transcends traditional diagnostic boundaries." He opines that based on the interconnectedness of NDDs, including ADHD and ASD, "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." Dr. Hollander opines as well that there are "multiple, plausible mechanisms of action to explain how [acetaminophen] can impact fetal brain development and lead to neurodevelopmental disorders in offspring."

Dr. Hollander's rebuttal report, unlike his initial report, includes a Bradford Hill analysis and a general causation opinion. During his deposition, Dr. Hollander confirmed that the first time he conducted a Bradford Hill analysis was in his rebuttal report. Holl. Dep. at 29:12; 71:15-21. A rebuttal report generally provides an expert the opportunity to respond to criticisms of the original report by the other experts or provide an update should new science have emerged in the interim. A rebuttal report is not the proper avenue to introduce entirely new analyses or opinions.[71] Nevertheless, the Court will assess the reliability of the opinion offered in the rebuttal report after assessing the reliability of the initial report.

The defendants argue that Dr. Hollander's proposed testimony is inadmissible insofar as he seeks to transform a simple observation that ASD and ADHD can have overlapping features "into a blank check to treat studies of these conditions (indeed, virtually all neurodevelopmental disorders) interchangeably" and because it fails to address critical evidence or account for the limitations of studies on which he relies heavily. They add that his untimely Bradford Hill

[71] The plaintiffs relied at oral argument on the Bradford Hill analyses conducted by Drs. Baccarelli and Cabrera.

analysis should be stricken because, inter alia, he misstates basic epidemiological principles and was insufficiently familiar with "the building blocks of his own opinions." The defendants are correct.

As for Dr. Hollander's opinion regarding evidence of a biologically plausible mechanism, it is relatively cursory and suffers from the same critical gaps as Dr. Cabrera's analysis. For instance, Dr. Hollander misleadingly references Ghanem 2016's[72] "finding that NAPQI is generated in the brain." That publication is not a study but rather a comprehensive literature review that concluded that, while toxic doses of acetaminophen "promote oxidative stress and produces damage to different cell types in the brain . . . this should be the subject of further investigations to clearly discriminate between liver-driven versus true in situ adverse effects of APAP in brain." Id. at 130. The authors stated it was "very important to point out that additional investigations on this subject are needed to define the pathways mediating APAP toxicity in the brain." Id. Most strikingly, they also "want[ed] to re-emphasize that there is sufficient and convincing evidence that APAP at low doses has a protective effect in the brain." Id.

[72] Ghanem et al., Acetaminophen; From Liver to Brain: New Insights Into Drug Pharmacological Action and Toxicity, 109 Pharmacol. Res. 119 (2016).

A. Transdiagnostic Approach

It bears emphasizing that the transdiagnostic Bradford Hill analysis undertaken by Drs. Baccarelli and Cabrera is not a methodology that has been subjected to peer review and publication either generally or as applied to ASD and ADHD.[73] It is not a methodology that has been tested; it has no established error rate or published standards. Accordingly, Dr. Hollander plays a critical role for the plaintiffs. They rely on Dr. Hollander to give his imprimatur to the transdiagnostic Bradford Hill analysis of causation applied by their other experts. His reports do not do so.

As already described in connection with the discussion of Drs. Baccarelli and Cabrera, their analyses do not separately address the complexity of the universe of ASD studies and that of ADHD studies and then examine whether a combined analysis can and should be done. Nor do their Bradford Hill analyses confine themselves to studies that relate to diagnoses of ASD and ADHD. Instead, their single transdiagnostic analysis relied as well on studies of symptoms that reflect many endpoints relevant to NDDs

[73] One meta-analysis, Alemany 2021, did reference several Bradford Hill factors in passing. That publication's cursory reference to Bradford Hill factors is not a sufficient basis for the plaintiffs' contention that a transdiagnostic Bradford Hill can reliably support a general causation opinion for ASD and ADHD.

generally, including to ASD and ADHD. But, again, there was no separate analysis of, for instance, the consistency among the findings in those symptom studies, the strengths of any association, or any other relevant Bradford Hill factor, before the results of those studies were combined with the conclusions they drew from studies of ASD and ADHD. Instead, the unstructured approach adopted by the plaintiffs' experts permitted cherry-picking, allowed a results-driven analysis, and obscured the complexities, inconsistencies, and weaknesses in the underlying data.

No expert presented by the plaintiffs -- not Dr. Baccarelli, Dr. Cabrera, or Dr. Hollander -- describes how to structure a reliable transdiagnostic Bradford Hill analysis, either generally or specifically to assess whether in utero exposure to acetaminophen causes ASD and/or ADHD. Dr. Hollander in particular has not suggested whether a structure akin to that just outlined or some other structure altogether should be used to create a reliable transdiagnostic analysis of causation. Dr. Hollander's opinions are rendered on a far more abstract plane.

Dr. Hollander opines in his initial report that "there is significant overlap and co-morbidity between the symptoms of ASD and ADHD, and there may be overlap in the underlying biology that accounts for common features that supersede traditional

diagnostic categories." That opinion -- that there may be overlap in the underlying biology of some of the symptoms of the disorders, which may be relevant to a causal analysis -- appears to be a reliable assessment of the literature cited by Dr. Hollander. What it is not, however, is the linchpin that allows the plaintiffs' Bradford Hill analyses to be admitted.

Dr. Hollander observes, unremarkably, that traditional diagnostic categories do not always reflect the constellation of symptoms that he sees in his patients. Dr. Hollander then cites Barch 2020[74] for the proposition that biological factors behind symptoms "cut across traditional diagnostic boundaries, as demonstrated by recent transdiagnostic research that shows shared neural, genetic physiological, structural, and psychological traits." Barch 2020 is a short editorial by a Washington University faculty member that discusses the promise and potential pitfalls of transdiagnostic research. As described by Barch, the focus on transdiagnostic research is whether neural alterations in the human brain may be associated with broad risk factors for psychopathology, cutting across individual diagnostic categories. Although the editorial focuses on schizophrenia, bipolar disorder, major depression,

[74] Barch, What Does it Mean to be Transdiagnostic and How Would We Know?, 177(5) Am. J. Psychiatry 370 (2020).

anxiety disorders, and substance disorders -- not NDDs -- it does note that "some dimensions of disordered behavior cut across traditional diagnostic boundaries, and thus the biological factors that align with these dimensions also likely cut across traditional diagnostic boundaries." Id. at 370.

Of particular relevance to the Rule 702 motions at issue here, Barch is careful to "raise[] the question of what we mean by transdiagnostic and how we should define and determine what neural or psychological impairments are transdiagnostic." Id. As regards "examining whether a particular symptom or behavior dimension relates to a particular neurobiological factor 'transdiagnostically,'" Barch states that "strong claims about transdiagnostic relationships would seem to require demonstrating that such dimensional relationships hold within diagnostic categories as well as across diagnostic categories, or at least that the dimensional relationships do not differ across diagnostic groups." Id. at 371. Barch, therefore, provides no support for finding that the transdiagnostic Bradford Hill analysis undertaken by the plaintiffs' experts is accepted by the scientific community.

As further support for his contention that a transdiagnostic approach will become more common and is helpful to understanding the biology behind overlapping disorders, such

as ASD and ADHD, Dr. Hollander cites Vandewouw 2023.[75] Vandewouw 2023 is a case-control study that used neuroimaging data to explore whether certain functional brain characteristics could be linked to behaviors implicated in neurodevelopmental conditions. Vandewouw 2023 found that "homogeneity in the neurobiology of neurodevelopmental conditions corresponded to behavior, not diagnostic category." Id. at 1. The participants included children who had been diagnosed with ASD, ADHD, and obsessive-compulsive disorder between the ages of 5 and 19, and others who were developing "typically." The authors found subgroups with similar biology that differed significantly in intelligence and hyperactivity and impulsivity problems but did not show consistent alignment with the diagnostic categories. Id. at 10. Further, the children without neurodevelopmental disorders "were also spread across all identified brain-based subgroups, emphasizing that an overlap in neurobiology exists not only across conditions, but also across typical development." Id. at 11. The authors suggest that their findings should "promot[e] a shift in the research community away from classic case-control designs that rely on diagnostic

[75] Vandewouw et al., Identifying Replicable Subgroups in Neurodevelopmental Conditions Using Resting-State Functional Magnetic Resonance Imaging Data, 6(3) JAMA Network Open: e232066 (2023).

categories, which have increasingly been shown not to reflect distinct biological and phenotypic constructs." Id. at 12. Vandewouw 2023 also indicates, as Dr. Hollander opines, that "a holistic and transdiagnostic approach that uses continuous measures of behavior is necessary to fully understand the highly heterogenous conditions of ASD and ADHD."[76] And finally, as Vandewouw 2023 observes, transdiagnostic research may be "promoting a shift in the research community" towards new types of study design that help "target treatments and interventions." Id.

The findings of Vandewouw 2023 are surely relevant to the research community's prioritization of topics and choice of study designs, today and in the future. It may be that as more transdiagnostic research is done, scientists will be able to connect specific neurobiology with specific symptoms, with resulting implications for both treatment and causal analyses. What Vandewouw 2023 does not do, though, is transform the observation that ASD and ADHD share some symptoms and are sometimes co-morbidities into carte blanche for conducting a single causal analysis for these two disorders. Nowhere in his

[76] Dr. Hollander misstates the findings of Vandewouw 2023, stating that the study found differences not only in hyperactivity and impulsivity but also "externalizing behaviors, conduct problems, [and] emotion regulation difficulties."

initial report does Dr. Hollander state that proof of a causal relationship between exposure to acetaminophen and development of ADHD suffices as proof of a causal relationship between exposure to acetaminophen and development of ASD, or vice versa.[77] And, as Dr. Hollander noted in his deposition, he does not opine that "if acetaminophen is associated with hyperactivity, then it must also cause ASD and ADHD." Holl. Dep. at 339:24-340:3.

Thus, Dr. Hollander's opinion regarding a transdiagnostic analysis is largely irrelevant. It is insufficiently tethered to the transdiagnostic Bradford Hill analyses presented by the plaintiffs' experts to support their admissibility, and it is too undeveloped to be otherwise admissible.

B. Bradford Hill Analysis

In his rebuttal report, Dr. Hollander presents a Bradford Hill analysis. That analysis is inadmissible. The plaintiffs have not shown that it reflects Dr. Hollander's own work. Moreover, it suffers from the same deficiencies that appear in Dr. Baccarelli's Bradford Hill analysis, which it largely

[77] In his rebuttal report, Dr. Hollander states that "[i]f acetaminophen exposure during pregnancy causes hyperactivity in ASD and ADHD individuals, and if hyperactivity is a common feature of ADHD and ASD, then acetaminophen causes ADHD and ASD." At his deposition, however, he walked back this statement. Holl. Dep. at 336:3-340:3.

mimics. Finally, because Dr. Hollander rushed to assemble a Bradford Hill analysis, it contains so many errors in its description of the relevant research that it is inherently unreliable.

Dr. Hollander's Bradford Hill analysis was created in the small window of time permitted him to file a rebuttal report. He did not therefore have months to prepare his own, independent analysis. It does not appear that he independently reviewed the body of relevant literature or that he created a written analysis of the studies he mentions. He readily acknowledged in his deposition that he relied upon the assessment of the epidemiology presented in Dr. Baccarelli's' expert report. At the deposition, Dr. Hollander looked at a summary chart created by Dr. Baccarelli nearly every time defense counsel asked him about a study referenced in his report.

Dr. Hollander's unfamiliarity with the underlying epidemiological studies upon which he claims to have relied was stark. For example, his rebuttal report states that several high-quality "meta-analyses" show a positive association between prenatal exposure to acetaminophen and ASD and ADHD, and then lists studies that are not meta-analyses.[78] Later, when he does

[78] Dr. Hollander lists Liew 2014, Avella-Garcia 2016, and Ystrom 2017.

cite five actual meta-analyses, in his section on the strength of association factor, he states that the association between acetaminophen exposure and "ASD and ADHD has been found consistently in meta-analyses and systematic reviews." He cites Masarwa 2018, Ricci 2023, Gou 2019, Kim 2020,[79] and Alemany 2021. But Gou 2019 and Kim 2020 only addressed ADHD. Ricci 2023 found the literature on ASD too sparse and heterogenous to perform a meta-analysis -- implicitly critiquing Alemany 2021's approach. And the authors of Masarwa 2018 published another study in 2020, Masarwa 2020, determining their 2018 results were due to unmeasured confounding and exposure misclassification, a development Dr. Hollander failed to mention in his report.

The deficiencies in Dr. Hollander's Bradford Hill analysis no doubt reflect the limited time he had to prepare his opinion. That excuse, however, does not render his Bradford Hill analysis admissible. His analysis fails to pass muster under Rule 702 and Daubert.

XIII. Dr. Pearson

Dr. Brandon Pearson submitted an expert report of June 21, 2023. He supplemented the report on July 14. His rebuttal report is dated July 28. He was deposed on August 11.

[79] Kim et al., Environmental Risk Factors, Protective Factors, and Peripheral Biomarkers for ADHD: An Umbrella Review, 7(11) Lancet Psych. 955 (2020).

Dr. Pearson is an Assistant Professor of Environmental Health Sciences at Columbia University. He received his Ph.D. in Behavioral Neuroscience at the University of Hawaii and in 2015 completed a postdoctoral fellowship at the University of North Carolina at Chapel Hill. During the fellowship he shadowed clinicians assessing ASD.

In 2017, he established an independent research laboratory at Columbia focused on neurotoxicology. Neurotoxicology focuses on understanding how chemicals, drugs, and environmental factors can impact the structure and function of the nervous system. Dr. Pearson's laboratory conducts studies using cell cultures, fish and mice, human observational cohorts, and human biospecimens. He has experience extrapolating data from animal studies to human populations. He is a co-investigator and laboratory director of the Columbia Center for Children's Environment Health. He has published 40 peer-reviewed articles.

Dr. Pearson has studied acetaminophen toxicity for approximately ten years, largely through research with mice. He has performed inter-disciplinary work with Dr. Baccarelli and Canadian researchers on a birth cohort analysis of meconium acetaminophen levels and ADHD outcomes.

Dr. Pearson was asked to address the following issues: is the hypothesis that there is a causal association between in

utero exposure to acetaminophen and NDDs, including ASD and ADHD, "consistent with existing biological knowledge and preclinical literature;" and "[i]s there sufficient preclinical evidence to conclude that in utero exposure to acetaminophen can cause NDDs, including ASD and/or ADHD?" Dr. Pearson's report "does not give an opinion on epidemiological methods, confounding, clinical dose, or human cases" except as relates directly to the preclinical findings he discusses.

Scientists have designed studies of animals in order to test hypotheses and to test drug interventions. Examples of the endpoints studied in animal models are discussed supra in relation to Dr. Cabrera's report. Dr. Pearson explains that the animal models of ADHD are less developed than animal models of ASD because the relevant ADHD animal studies have been used principally to test ADHD treatments. Through genetic manipulation and selective breeding, rodent species have been created as "genetic models of ADHD-like phenotypes." They display behaviors characterized as hyperactive (such as increased locomotion), impulsive (e.g., choosing a smaller but immediate reward instead of a larger, delayed award) and inattentive (e.g., after learning a display-reward task, failing at the task when the duration of the display decreases).

The core of Dr. Pearson's initial report describes studies of mice and rats. From that review, Dr. Pearson opines that preclinical studies show that acetaminophen (1) causes neurodevelopmental disruption; (2) is capable of causing cascading changes in central nervous system structures, molecular pathways, and neurotransmission in offspring exposed in utero; and (3) disrupts neurodevelopment via multiple mechanisms, including oxidative stress, DNA damage, and endocannabinoid system disruption. He also opines that the weight of the preclinical studies supports the biological plausibility of an association between in utero exposure to acetaminophen and NDDs including ASD and ADHD because these preclinical studies account for confounding factors that may be present in epidemiological studies.

The defendants argue that Dr. Pearson's reports must be stricken as fundamentally unreliable. Because animal studies require us to assume that the chemical of interest behaves similarly in a different species, expert opinions relying on animal studies "may only be admitted where the gap between what [they] reasonably imply and more definitive scientific proof of causality is not too great." Daniels-Feasel, 2021 WL 4037820, at *14 (citation omitted). Beyond that impediment, the defendants argue that Dr. Pearson's methodology is flawed. They

point to the difference between the essential features of ASD and ADHD described in the DSM and the modeled animal behaviors and his admission that the studies point in contradictory directions, arguing that his opinions rely on cherry-picking those that support his thesis.

Dr. Pearson states early in his report that data is reliable when "there is a sufficient amount of quality data that are internally consistent." He notes that it is an objective of integrating lines of evidence, "[i]n case of inconsistencies, to try to understand and explain the reasons for them, possibly deciding if more than one answer to the formulated problem is plausible."

As described above, the preclinical data on acetaminophen's effects on animal biology and behavior contain many inconsistencies. Dr. Pearson does acknowledge that the studies he has surveyed point in a variety of directions and are often at odds with each other. Indeed, throughout his report, Dr. Pearson describes many of the limitations and inconsistencies in the data.

Critically, however, in drawing his conclusion, Dr. Pearson takes the position that the "heterogeneity of the results," with even individual studies showing "mixed or bidirectional results," is "not a reason to dismiss the effects" of

acetaminophen shown in the studies. He opines, without citation, that "neurodevelopmental perturbation of prenatal APAP can manifest in various ways in terms of directionality" -- that is, that any change in behavior provides evidence of causation regardless of the direction of the change. Dr. Pearson insists that the "heterogeneity of ultimate endpoints seen in the preclinical studies . . . makes sense given the context of the extremely delicate cascading cellular processes disturbed by APAP use."

"[N]othing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data by only the ipse dixit of the expert." Joiner, 522 U.S. at 146. Dr. Pearson's decision to confine his late-in-the-game, ipse dixit assertion that heterogeneity and outright inconsistency of results don't ultimately matter to a single paragraph in the conclusion section is concerning. It also presents a deviation from the principles of scientific reliability Dr. Pearson promotes earlier in his report -- a telltale indication that his ultimate opinion does not "reflect[] a reliable application of the principles and methods to the facts of the case." Rule 702.

The result is that "there is simply too great an analytical gap between the data and the opinion proffered." Joiner, 522

U.S. at 146. Dr. Pearson's expert testimony is thus inadmissible under Rule 702.

XIV. Dr. Louie

Dr. Stan Louie filed an amended expert report on June 21, 2023, and a reply report on July 28. He was deposed on August 7.

Dr. Louie is a Professor of Clinical Pharmacy at the University of Southern California, Alfred Mann School of Pharmacy and Pharmaceutical Sciences. He received his Doctor of Pharmacy degree from the University of California, San Francisco, School of Pharmacy. His research currently includes drug development for inflammatory and immune-mediated diseases.

Dr. Louie has also focused on developing new drugs or new chemical entities. He is the founder and President of StimuFact, Inc., a consulting company that advises clients on drug development. He is a co-founder of start-up companies in the pharmaceutical industry.

Dr. Louie was asked to determine the "dose/duration" at which prenatal exposure to acetaminophen increases the risk of developing ASD and ADHD. Dr. Louie opines that acetaminophen taken for at least 28 days over the course of a pregnancy, for a total of between 18.2 grams and 112 grams, increases the risk of developing ASD and ADHD in offspring two-fold. He explains that

the reason for this increased risk is that acetaminophen can deplete glutathione ("GSH"), thereby causing oxidative stress systemically and in the brain and that one its metabolites, NAPQI, and its adducts can induce oxidative stress, immune reactivity, and inflammation.

To reach these opinions, Dr. Louie did not conduct any research of his own; he relied on his review of others' studies. He did not perform either a Bradford Hill or a weight of the evidence analysis. Instead, he reviewed first the literature provided him by plaintiffs' counsel, and then the literature resulting from his own "comprehensive" literature search. He located seven studies with findings about the duration of exposure and elevations in risk. Of these, he assigned the greatest weight to Brandlistuen 2013. He concluded that a wider body of literature also supported his conclusion.

The defendants contend that Dr. Louie's opinions are unreliable. For one thing, as he admitted at his deposition, his epidemiological analysis of causation depends entirely on Dr. Baccarelli's analysis, and therefore must be excluded if Dr. Baccarelli's analysis fails to survive. Moreover, they contend, his opinions are not supported by the studies on which he reports he relied.

The plaintiffs have not shown that Dr. Louie's expert reports are admissible pursuant to Rule 702. His opinion of causation must be stricken since it relies on Dr. Baccarelli's expert reports. The plaintiffs acknowledge that Dr. Louie was not asked and did not seek to perform a Bradford Hill or other general causation analysis.

But, even if another expert had admissible evidence on the issue of general causation, the plaintiffs have failed to show that Dr. Louie has presented any admissible opinion about dose/duration. His opinions are inadmissible due to their omissions and their misstatement of the evidence on which he purports to rely.

Dr. Louie's reports fail to address several obvious issues. He does not explain when in the course of a pregnancy the 28-day use of acetaminophen creates a risk for the offspring, for instance, whether it arises in a particular trimester or each trimester. Nor does he distinguish between use for consecutive days or sporadic use over the duration of the entire pregnancy. He simply opines that the cumulative use of acetaminophen for 28 days over the course of nine months creates a two-fold risk of both ASD and ADHD. He does not provide any basis for finding that such an unbounded use of acetaminophen poses any risk.

The plaintiffs argue that there is nothing unscientific about lumping together all pregnant women who use acetaminophen for more than 28 days at any point during the nine months of their pregnancies. But, Dr. Louie provides no scientific basis for doing so, and it was his burden to explain why such aggregations of behavior are scientifically sound. Instead, it appears that he selected this metric because the few studies that have included data on duration of use chose to divide their study participants into two categories reflecting use of fewer or more than 28 days. This does not suffice to provide a scientifically sound basis for a causation opinion or a dose/response opinion.

As significantly, Dr. Louie's opinion is not supported by the seven studies on which he purports to have relied. The seven studies he identifies are: Brandlistuen 2013, Liew 2014, Liew 2016, Vlenterie 2016,[80], Ystrom 2017, Gervin 2017,[81] and Gustavson 2021. During the briefing on these motions, the plaintiffs appear to have abandoned any reliance on two of these studies: Vlenterie 2016 and Gervin 2017.

[80] Vlenterie et al., Neurodevelopmental Problems at 18 Months Among Children Exposed to Paracetamol in Utero: A Propensity Score Matched Cohort Study, 5(6) Int. J. Epidemiol. 1998 (2016).

[81] Gervin et al., Long Term Prenatal Exposure to Paracetamol is Associated with DNA Methylation Differences in Children Diagnosed with ADHD, 9 Clin. Epigenetics 77 (2017).

Dr. Louie represents that Brandlistuen 2013, Ystrom 2017 and Gustavson 2021 found that acetaminophen exposure beyond 28 days showed a two-fold increased risk for childhood "ADHD and ASD diagnosis." Not so. None of these studies involved an ASD diagnosis. Moreover, while he placed the "greatest weight" on Brandlistuen 2013, a sibling control study, it did not involve even an ADHD diagnosis.

Brandlistuen 2013 evaluated psychomotor, behavior, and temperament problems using the ASQ, CBCL, and EAS questionnaires for evaluating children who were, at the time of the study, three years of age. Id. at 1708. The authors of Brandlistuen 2013 noted that future studies should seek to include clinical diagnoses. Id. at 1711. Nor is Brandlistuen 2013 a reliable source for measuring risk as of 28 days of exposure. As described earlier in this Opinion, the article reports on a study of the MoBa cohort, which collected data from mothers at weeks 17 and 30 of their pregnancies, and 6 months after the child's birth. Id. at 1703. The mothers indicated whether they had used acetaminophen and other medications to treat various ailments, such as fever and back pain. The women reported the number of days they had used the drug during each four-week period within the pregnancy. Id. at 1704. The study then divided all mothers with two or more children into two groups:

those who used acetaminophen for 27 days or less and those who used it for 28 days or more. Thus, mothers with widely varying exposures were grouped together in the latter category. The authors note that they could not take dose into consideration "because it was not reported, and we could not distinguish between continuous use for 28 days or more and long-term sporadic use across pregnancy because the number of mothers reporting continuous use was too small." Id. at 1712.

Also, as already described in this Opinion, the other two studies come with significant caveats. In Ystrom 2017, because the paternal use of acetaminophen was found to be associated with ADHD, the authors warned that "the causal role of acetaminophen in the etiology of ADHD can be questioned." Id. at 7. While Gustavson 2021 found that there was a two-fold increased risk of receiving an ADHD diagnosis if the child was born to a mother who used acetaminophen 28 days or more during the pregnancy, that increased risk "was no longer present" after adjusting for the sibling mean. Id. at 10. The authors suggested that maternal long-term use of acetaminophen may be a marker for increased familial risk of ADHD. Id.

Dr. Louie attempted to salvage his reliance on Gustavson 2021's pre-sibling-control result at his deposition, by explaining that he gave virtually no weight to the sibling-

control results because, as he stated, "I don't know where I read it, but it was the number of patients that were evaluated were relatively low." Louie Dep. at 119. He admitted he did not read the supplemental materials of Gustavson 2021. Id. at 116-118. The authors of Gustavson 2021 do note that because only discordant siblings contribute to detecting associations in sibling control models, even with the large MoBa cohort, "reduced power is reflected in wide confidence intervals." Id. at 5. But the authors stated they were "not aware of any other data that could be used to perform a more powered sibling control study of prenatal acetaminophen exposure and ADHD," id., and concluded that their sibling control results suggest that the association "may at least partly be due to familial confounding." Id. at 8. As the plaintiffs acknowledge, an expert's opinion may not exceed the limitations that authors place on their own studies. Thus, neither Ystrom 2017 nor Gustavson 2021 supports Dr. Louie's opinion that taking a certain dose of acetaminophen or taking it more than 28 days creates a two-fold risk for either ASD or ADHD.

A discussion of the remaining two studies would not resurrect a reliable or admissible basis for Dr. Louie's opinion. His biological mechanism opinion is inadmissible for the same reasons discussed supra with respect to Dr. Cabrera's

AOP analysis. Accordingly, the defendants' motion to exclude his reports is granted.

Conclusion

The defendants' motions of September 19, 2023 to exclude plaintiffs' general causation experts' opinions regarding Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, and biological plausibility are granted.

Dated: New York, New York
December 18, 2023

DENISE COTE
United States District Judge