October 17, 2025

By Electronic Submission

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Comment to Docket No. FDA-2025-P-4153

We submit this comment on behalf of Kenvue Brands LLC ("Kenvue") in response to the citizen petition ("Citizen Petition") filed by the Informed Consent Action Network ("Petitioner") on September 22, 2025.[1] The Citizen Petition requests changes to the labeling of over-the-counter ("OTC") acetaminophen products for use during pregnancy that are unsupported by the scientific evidence and legally and procedurally improper—including requesting that the consumer-facing warning address a risk of acetaminophen use and neurodevelopmental disorders even though the overwhelming weight of the evidence contradicts the existence of any such risk.

Kenvue is an American-based global company committed to improving consumer and public health. We care deeply about the safety and efficacy of our products. For over a decade, we have continuously evaluated the science on acetaminophen use in pregnancy and neurodevelopmental disorders, including autism—also known as autism spectrum disorder ("ASD")—and attention-deficit/hyperactivity disorder ("ADHD"), and have found no causal association. The expansive scientific evidence developed over many years does not support a causal link, as confirmed in the Food and Drug Administration's ("FDA") own public statements and analyses.[2] Indeed, as detailed below, for over a decade—and as recently as August—FDA has fully evaluated the emerging scientific evidence and repeatedly concluded that the data do not

[1] *See* Citizen Petition from Siri & Glimstad LLP on behalf of Informed Consent Action Network, Dkt. No. FDA-2025-P-4153 (Sept. 22, 2025), https://www.regulations.gov/document/FDA-2025-P-4153-0001 ["Citizen Petition"]. FDA's acknowledgement letter reflects a receipt date of September 22, but the docket lists a "Received Date" of September 21, suggesting that the Citizen Petition actually was received by some component of the federal government a day earlier. *See* Citizen Petition from Siri & Glimstad LLP on behalf of Informed Consent Action Network, Dkt. No. FDA-2025-P-4153 (Sept. 25, 2025), https://www.regulations.gov/document/FDA-2025-P-4153-0001 (reflecting "Received Date" of "Sep 21, 2025"); Acknowledgement Letter from Karen Malvin, Branch Chief (Acting), Dockets Management Branch, to Elisabeth Brehm, Siri & Glimstad LLP, Dkt. No. FDA-2025-P-4153-0002 (Sept. 23, 2025), https://www.regulations.gov/document/FDA-2025-P-4153-0002 ("Your petition dated 09/22/2025 was received by this office on 09/22/2025 and is assigned to docket number FDA-2025-P-4153.").

[2] *See* FDA, *Acetaminophen: What You Should Know About Using Acetaminophen Safely* (Aug. 14, 2025), https://www.fda.gov/drugs/information-drug-class/acetaminophen. FDA's history of analyses and public statements addressing this question is further described in Section I.A., below.

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support a causal association between acetaminophen use in pregnancy and neurodevelopmental disorders such as autism. Moreover, FDA previously has evaluated—and rejected—updating the labeling to advise consumers to use the lowest dose for the shortest time. Instead, FDA has adhered to the current—and more conservative—approach of directing pregnant women to consult their health professionals, as provided in the warning prescribed by regulation: "**If pregnant or breast-feeding**, ask a health professional before use."

Consistent with the body of evidence, numerous leading professional organizations—including the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Psychiatric Association, and the Society for Maternal-Fetal Medicine—have independently reviewed the science and concluded that there is no causal association between acetaminophen use during pregnancy and neurodevelopmental disorders. Significant public health considerations, including the known risk of harm to unborn children of untreated high fevers during pregnancy and the lack of alternative safe treatment options available for use during pregnancy, weigh heavily against adding warning language that will discourage pregnant women from seeking medically appropriate treatment for pain and fevers during pregnancy in close consultation with health professionals, particularly in light of the existing scientific evidence.

FDA repeatedly has cautioned about the potential dangers of overwarning. There is significant value—as repeatedly recognized by FDA—in keeping OTC warnings concise, easily understandable, and calibrated. Because the science does not support a change to the warning language and the proposed labeling changes could be harmful to pregnant women and result in adverse pregnancy outcomes, Kenvue strongly opposes the changes and believes that the existing instruction to speak to a health professional before use in pregnancy is the most conservative and appropriate labeling.

In addition, because the Petitioner's proposed labeling changes are not supported by scientific evidence and would represent an unexplained departure from FDA's longstanding position regarding the use of acetaminophen during pregnancy, FDA should deny the proposed changes. Any other Agency action would be arbitrary and capricious in violation of the Administrative Procedure Act ("APA"). Furthermore, any labeling changes to acetaminophen products under the OTC monograph are subject to the administrative order process set forth in the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act"). FDA has consistently emphasized that OTC warnings must be clear, concise, and evidence-based. Overwarning confuses consumers and weakens key safety messages. The Petitioner's proposed acetaminophen warnings about autism and ADHD lack credible support and would mislead consumers. Finally, the proposed labeling changes are ultra vires in that they would intervene in the practice of medicine.

We therefore respectfully request that FDA deny the Citizen Petition. We ground this request in our commitment to ensuring that American consumers have access to the accurate, scientifically based safety information that they need to best manage their own health and the health of their children.

BACKGROUND

Kenvue is a global leader operating at the intersection of healthcare and consumer goods that is committed to the safety and quality of its products and the well-being of its consumers. Kenvue's portfolio of consumer brands includes some of the most recognizable household names in the consumer health industry, including Tylenol, Band-Aid, Listerine, Neutrogena, and Aveeno. Kenvue's products serve over 1.2 billion people in over 165 countries. For over 50 years, Tylenol has been available as an OTC medicine to treat pain and reduce fever, including during pregnancy. Tylenol's primary active ingredient is acetaminophen, which is one of the most common active drug ingredients found in multiple OTC and prescription medications.

Acetaminophen products are marketed as OTC products under the monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use ("OTC Monograph M013") as well as under approved new drug applications ("NDA") and abbreviated new drug applications ("ANDA"). Acetaminophen is marketed as both a stand-alone ingredient as well as an ingredient in combination products. Indeed, a search for acetaminophen in FDA's National Code Directory yields thousands of results. The labeling changes proposed by the Citizen Petition—if accepted—could impact hundreds, if not thousands, of products.[3]

Acetaminophen is one of the most studied medicines in history, and scientific evidence regarding acetaminophen use in pregnancy and neurodevelopmental outcomes has been continuously evaluated by FDA and industry for more than a decade. This scientific evidence does not support a causal association between acetaminophen use in pregnancy and neurodevelopmental disorders, including ASD and ADHD.

On September 1, 2025, Department of Health and Human Services ("HHS") Secretary Robert F. Kennedy, Jr., reached out to Kenvue to express his view about an association between acetaminophen and autism. On September 4, 2025, HHS Secretary Kennedy testified before the Senate Finance Committee that the White House's planned Make Our Children Healthy Again ("MAHA") Strategy would provide "the Trump Administration's solutions to address each cause" of childhood chronic diseases.[4] The White House's MAHA Assessment, released in May 2025, had previously focused on neurodevelopmental disorders such as ASD and ADHD, among other childhood chronic diseases.[5] Media reports suggested that Secretary Kennedy planned to publicly announce a potential association between acetaminophen use during pregnancy and ASD.[6]

On September 8, 2025, Kenvue met with Secretary Kennedy and other HHS personnel and communicated that the scientific evidence did not support a causal association between

[3] While acetaminophen may also be an ingredient in prescription products, this comment focuses only on OTC drugs just as the Citizen Petition does.

[4] *The President's 2026 Health Care Agenda*, Hearing before the Comm. on Finance, 119 Cong. 1 (2025), https://www.finance.senate.gov/hearings/the-presidents-2026-health-care-agenda (statement of Secretary Robert F. Kennedy, Jr.).

[5] The MAHA Report: Make Our Children Healthy Again Assessment at 12 (May 2025), https://www.whitehouse.gov/wp-content/uploads/2025/05/MAHA-Report-The-White-House.pdf.

[6] *RFK, Jr., HHS to Link Autism to Tylenol Use in Pregnancy and Folate Deficiencies*, WALL ST. J. (Sept. 5, 2025), https://www.wsj.com/health/healthcare/rfk-jr-hhs-to-link-autism-to-tylenol-use-in-pregnancy-and-folate-deficiencies-e3acbb4c?st=Ra2t9A.

acetaminophen use during pregnancy and autism, and did not support an association between postnatal use of acetaminophen and autism. Kenvue highlighted that a failure to properly treat fever can result in adverse pregnancy outcomes, including miscarriage, preterm birth, preterm labor, fetal organ malformations, and fetal cardiovascular complications, and failure to treat pain can result in adverse pregnancy outcomes, including depression, anxiety, and high blood pressure in the mother.

On September 22, 2025, President Donald J. Trump, HHS Secretary Kennedy, Commissioner of Food and Drugs Dr. Martin A. Makary, and other HHS senior leaders appeared in a televised press conference (the "September 22 Announcement") during which they diverged from FDA's long-established approach to acetaminophen use during pregnancy. The September 22 Announcement included repeated incorrect statements about the well-established safety profile of acetaminophen, in general, and Tylenol, in particular, including statements implying a causal association between acetaminophen use during pregnancy and ASD.[7] Notwithstanding that failure to treat fever or pain during pregnancy can cause adverse pregnancy outcomes for both mother and child, listeners were advised that pregnant women should "tough it out" through fever or pain and that "[t]here's no downside in not taking [Tylenol]."[8] Pregnant women were told, simply: "Don't take Tylenol."[9]

On the same day, FDA issued two public communications regarding the state of the scientific evidence on acetaminophen use during pregnancy that contrasted sharply with the September 22 Announcement. In noting that it had "initiated the process for a label change"—a process that has not, to our knowledge, been further described by the Agency—FDA acknowledged that "while an association between acetaminophen and neurological conditions has been described in many studies, *a causal relationship has not been established* and there are contrary studies in the scientific literature."[10] A Notice to Physicians issued by Commissioner Makary on the same day used similar language, recognizing that "a causal relationship has not been established" and "[t]he association is an ongoing area of scientific debate."[11]

As detailed in footnote 1 above, the Citizen Petition was first "Received" by some component of the federal government on September 21, 2025, and was dated and received by FDA on September 22, 2025—the same day as the above-noted actions. The Citizen Petition was submitted by plaintiff-side lawyers.[12] According to a recent *New York Times* article, these lawyers

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[7] *Remarks: Donald Trump Makes an Autism Announcement at the White House – September 22, 2025*, ROLL CALL, at 00:13:29 (Sept. 22, 2025), https://rollcall.com/factbase/trump/transcript/donald-trump-remarks-health-autism-white-house-september-22-2025/ (at 00:13:29) ("We promise transparency as we uncover the potential causes and treatments. . . . First, HHS will act on acetaminophen.").

[8] *Id.* at 00:11:31, 00:42:46.

[9] *Id.* at 00:36:57.

[10] FDA, *FDA Responds to Evidence of Possible Association Between Autism and Acetaminophen Use During Pregnancy* (Sept. 22, 2025), https://www.fda.gov/news-events/press-announcements/fda-responds-evidence-possible-association-between-autism-and-acetaminophen-use-during-pregnancy (emphasis added).

[11] FDA, *Notice to Physicians on the Use of Acetaminophen During Pregnancy* (Sept. 22, 2025), https://www.fda.gov/media/188843/download?attachment (emphasis added).

[12] *Kennedy's Ties to Ally Leading Vaccine Lawsuits Raise Ethical Concerns*, N.Y. TIMES (Oct. 3, 2025), https://www.nytimes.com/2025/10/03/health/kennedy-aaron-siri-vaccines-lawsuits.html; *Kennedy's Lawyer Has Asked the F.D.A. to Revoke Approval of the Polio Vaccine*, N.Y. TIMES (Dec. 13, 2024), https://www.nytimes.com/2024/12/13/health/aaron-siri-rfk-jr-vaccines.html.

have encouraged people to file claims alleging an association between Tylenol and autism and may stand to benefit in this litigation, if FDA were to adopt a warning connecting the two.[13]

The Citizen Petition asks the Agency to mandate the addition of two warnings to all OTC acetaminophen products:

- The first, a consumer-facing warning, proposes an addition to the existing pregnancy/breast-feeding warning language, claims a causal connection between acetaminophen use during pregnancy and neurodevelopmental disorders, and directs that use be limited in terms of dose, duration and frequency.[14]

- The second, a proposed "revision to the . . . Professional Labeling" in the OTC monograph—which does not currently apply to acetaminophen products but addresses only aspirin—describes an association between the two.[15]

The Citizen Petition does not explain why the two proposed warnings describe significantly different degrees of scientific certainty or why a revision to professional labeling is proposed for acetaminophen products, which do not have professional labeling.[16] In addition, the Citizen Petition conflates two distinct neurological conditions, ASD and ADHD, treating them as one despite the clear differences between the two that would necessitate independent scientific evidence and analyses. Findings drawn for one neurological condition should not be automatically applied to the other condition without rigorous studies specific to each.

The first proposal addresses the pregnancy warning, codified at 21 C.F.R. § 201.63(a) ("general [pregnancy] warning"), which requires labels to include the following warning with the first four words in bold type: "**If pregnant or breast-feeding**, ask a health professional before use." The reach of this requirement is broad. It applies not only to OTC drugs that are generally recognized as safe and effective ("GRASE") or included in final OTC monographs, but also to "all" OTC drugs intended for systemic absorption, which includes acetaminophen products.[17] This long-standing warning takes the most conservative approach that pregnant women should consult with a health professional before taking any such medications during pregnancy.

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[13] *See Kennedy's Ties to Ally Leading Vaccine Lawsuits Raise Ethical Concerns*, *supra* note 12.

[14] *See* Citizen Petition, *supra* note 1, at 2 ("If you are pregnant or breastfeeding, ask a health professional before use. *Studies show that frequent use of this product during pregnancy may increase your child's risk of neurodevelopmental disorders*, including autism spectrum disorder 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.") (emphasis added).

[15] *See id.* ("Pregnant women should only take acetaminophen if, in consultation with her doctor, she determines it is strictly necessary. *Acetaminophen products used during pregnancy have been associated with risk of neurodevelopmental disorders*, including autism spectrum disorder and attention-deficit/hyperactivity disorder[.]") (emphasis added).

[16] FDA, OTC Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use at M013.95 (Oct. 14, 2022) (providing professional labeling for certain aspirin-containing products).

[17] 21 C.F.R. § 201.63(a); *see* 47 Fed. Reg. 54750, 54755 (Dec. 3, 1982) ("To ensure that when the general warning requirement becomes effective it will apply to all covered OTC drugs, the agency is placing the warning in Part 201 in new § 201.63 *Pregnancy-nursing warning*. A cross reference will be included in § 330.2 to clarify this location.").

The second warning is proposed to be added to Professional Labeling, which does not exist for acetaminophen. Incorporating this second warning into the current M013's Professional Labeling, which is for aspirin not acetaminophen, would not be appropriate. Accordingly, there is no basis to amend labeling that does not exist.

ARGUMENT

I. THE REQUESTED WARNINGS ARE NOT SUBSTANTIATED BY EXISTING SCIENCE

The safety and efficacy profile of acetaminophen is supported by more than 150 studies over the past 50 years. The safety of Tylenol at the currently recommended doses has also been established through over 50 years of use and scientific investigation. As described in greater detail below, there is no credible scientific evidence that shows acetaminophen use in pregnancy causes autism or ADHD. It would be inconsistent with and contrary to the understanding of the existing science, which has been affirmed by FDA, as well as courts and professional organizations, to adopt the two proposed warnings.

A. FDA Has Repeatedly Evaluated The Science On Acetaminophen Use In Pregnancy And Neurodevelopmental Disorders And Found No Causal Association

From the outset, it should be emphasized that FDA has reviewed the studies cited in the Citizen Petition, including as part of its ongoing epidemiological reviews. On the basis of this review, FDA repeatedly and consistently has concluded—across multiple prior years of analyses—that there is not sufficient scientific evidence to support a causal association between acetaminophen use during pregnancy and autism or other neurodevelopmental disorders, including ADHD. Accordingly, Petitioner's assertion that "FDA's internal assessments reflect an increasingly consistent pattern of concern" is irreconcilable with the record of FDA's careful consideration of this issue.[18]

First, the Citizen Petition entirely fails to discuss FDA's most recent May 2025 epidemiological review of the literature regarding neurobehavioral, pregnancy, and birth outcomes associated with prenatal acetaminophen exposure, which was completed by FDA's Division of Epidemiology I ("DEPI").[19] Regarding neurobehavioral and developmental outcomes, DEPI observed that "[t]he reported associations . . . were inconsistent overall" and noted "methodological limitations that p[re]clude our conclusions about the reported associations."[20] Similarly, regarding attention deficit disorder ("ADD") and ADHD, DEPI pointed to "residual confounding" as a potential explanation for the results in each of the two most methodologically rigorous studies.[21] Thus, FDA's DEPI analysis concluded:

[18] *See* Citizen Petition, *supra* note 1, at 4.
[19] *See* CDER, Epidemiology: Literature Review of Neurobehavioral, Pregnancy and Birth Outcomes Associated with Prenatal Acetaminophen Exposure (May 27, 2025) ["May 2025 DEPI Review"].
[20] *Id.* at 2.
[21] *Id.* at 2-3.

> Given the inconsistent findings and limitations identified in our current review of observational studies of prenatal [acetaminophen] use with pregnancy, birth, neurobehavioral, developmental and ADD outcomes, *the data covered in this review alone and in combination with previous DEPI literature reviews are insufficient to support a causal association at this time*.[22]

In its review, FDA focused on the Ahlqvist 2024 study, which FDA characterized as one of the "most methodologically rigorous studies," as it "utilized a sibling control model to address unmeasured familial confounding factors."[23] The Ahlqvist study was a collaborative research effort by Swedish and American investigators, funded by the National Institute of Neurological Disorders and Stroke ("NINDS") within the National Institutes of Health ("NIH"), that utilized data from a nationwide prospective cohort study including nearly 2.5 million children born in Sweden.[24] After sibling control analysis, the study "found *no evidence of increased risk of autism* (hazard ratio, 0.98), ADHD (hazard ratio, 0.98), or intellectual disability (hazard ratio, 1.01) associated with acetaminophen use" and noted that "associations observed in other models may have been attributable to familial confounding."[25] FDA concurred, concluding that "a null association was observed for [acetaminophen] use with ADHD, autism and intellectual disability."[26]

Again on August 14, 2025, FDA maintained this position on its website, explaining: "To date, *FDA has not found clear evidence that appropriate use of acetaminophen during pregnancy causes adverse pregnancy, birth, neurobehavioral, or developmental outcomes*."[27] As recently as September 22, 2025, FDA Commissioner Makary acknowledged: "To be clear, while an association between acetaminophen and autism has been described in many studies, *a causal relationship has not been established and there are contrary studies in the scientific literature*."[28]

Second, as FDA's DEPI observed in the conclusion of its May 2025 epidemiological review, the results of FDA's prior epidemiological reviews are consistent with the May 2025 review and FDA's August 2025 website statement. In 2014, 2015, 2016, 2017, 2018, 2020, 2022, and 2023, FDA undertook reviews examining neurodevelopmental outcomes associated with acetaminophen use during pregnancy, and each time has concluded that a causal association between acetaminophen and adverse outcomes had not been established.[29] In addition, when FDA considered the scientific evidence outside the context of epidemiological reviews during this time period, FDA similarly did not find causation and declined to make labeling changes that would signal that an increased risk had been established by the science.

- In its 2014 epidemiological review, FDA concluded that "[p]ositive associations observed between prenatal [acetaminophen] exposure and ADHD" in one study warranted additional

[22] *Id.* at 3 (emphasis added).
[23] *Id.* at 27.
[24] Viktor Ahlqvist et al., *Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability*, 331 JAMA 1205, 1205 (2024), https://jamanetwork.com/journals/jama/fullarticle/2817406.
[25] *Id*. at 1206 (emphasis added).
[26] May 2025 DEPI Review, supra note 19, at 33.
[27] *See* FDA, *supra* note 2 (emphasis added).
[28] *See* FDA, *supra* note 11 (emphasis added).
[29] FDA's 2019 epidemiological review is omitted from the discussion here because it focused on urogenital defects rather than neurodevelopmental disorders.

consideration, but that "the study's findings are difficult to interpret due to methodologic limitations and in the context of other existing evidence."[30] FDA thus recommended that "no regulatory action be taken at this time based on available data."[31]

- In its 2015 epidemiological review, FDA noted that "[w]hether the association is causal in nature remains uncertain" in light of new literature and recommended that additional long-term studies be conducted regarding prenatal exposure to acetaminophen.[32]

- In 2015, FDA also issued a Drug Safety Communication ("2015 DSC") explaining that it had "evaluated research studies published in the medical literature and determined they are too limited to make any recommendations based on these studies at this time."[33] Thus, FDA determined that its "recommendations on how pain medicines are used during pregnancy will remain the same at this time," and FDA recommended that pregnant women discuss any medication with a health professional before use, consistent with the labeled warning language for acetaminophen.[34]

- In its 2016 epidemiological review, FDA noted that while certain studies had found some association between prenatal acetaminophen use and neurodevelopmental outcomes, confounding factors precluded finding any causal relationship because "*conditions such as maternal fever and infection* that may prompt pregnant women to take [acetaminophen] . . . *may also be risk factors for neurocognitive problems*."[35] In addition, related to the potentially adverse effects of maternal fever, FDA observed that "data from two studies suggest that [acetaminophen] (or antipyretics in general) *might mitigate adverse neurodevelopmental effects of maternal fever*."[36]

- In February 2017, FDA's Division of Bone, Reproductive, and Urologic Products ("DBRUP") prepared a memorandum "regarding the clinical relevance of the published literature and the merit of updating public communication regarding prenatal acetaminophen (APAP) exposure and potential adverse neurodevelopmental outcomes in the offspring."[37] DBRUP observed that although studies "reported a small, positive

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[30] CDER, Epidemiology Review of Study on Acetaminophen Use in Pregnancy and Risks of ADHD in Offspring at 2-3 (May 15, 2014), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 427-4 (S.D.N.Y. Feb. 10, 2023) (citing Zeyan Liew et al., *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168 JAMA PEDIATRICS 313 (2014)).

[31] *Id.* at 3.

[32] CDER, Epidemiology: Review of Published Study at 8 (Mar. 18, 2015), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 427-5 (S.D.N.Y. Feb. 10, 2023).

[33] FDA, *FDA Drug Safety Communication: FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy* (Jan. 19, 2016), https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy.

[34] *Id.*

[35] CDER, Epidemiology: Review of Published Study at 15 (Oct. 14, 2016), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 427-6 (S.D.N.Y. Feb. 10, 2023) (emphasis added).

[36] *Id.* (emphasis added).

[37] Memorandum of Consultation from Christine P. Nguyen, Deputy Director for Safety & Audrey Gassman, Deputy Director, Division of Bone, Reproductive, and Urologic Products, to Janice Adams-King, Regulatory Project Manager, Division of Nonprescription Drug Products at 1 (Feb. 10, 2017), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 468-1 (S.D.N.Y. Mar. 2, 2023).

association between exposure and the outcomes of interest," "all of these studies had significant limitations that question the causal effect of [acetaminophen] on adverse neurodevelopmental outcomes."[38] For example, "it is unlikely that statistical adjustment alone could adequately correct for all confounders" related to maternal health, and "[m]aternal illnesses, smoking, and alcohol use could also adversely affect the pregnancy outcomes . . . which in turn, could put fetal neurodevelopment at risk."[39]

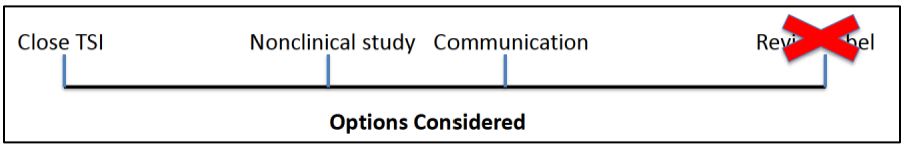
DBRUP's conclusion was consistent with FDA's prior reviews: "Although we have more studies, we do not have higher quality data to better inform drug causality and what these findings mean in clinical practice. . . . Thus, *we are unable to draw any conclusion about the causal association between prenatal APAP exposure and the different adverse neurodevelopmental outcomes, based on the available evidence*."[40] DBRUP thus recommended that FDA's conclusion in the 2015 DSC should not change.[41]

- In April 2017, FDA's Division of Pediatric and Maternal Health ("DPMH") prepared a memorandum to "address questions on clinical relevance and need for further Drug Safety Communication regarding use of acetaminophen [] during pregnancy and a potential association with attention deficit/hyperactivity disorder (ADHD)."[42] DPMH concluded that "[t]he findings of the clinical studies demonstrate some consistency of association among the outcomes related to attention problems and general behavioral problems; however, *the studies may only be demonstrating a common finding due to common use of the drug in the pregnant population*."[43] DPMH recommended that FDA communicate to the public that it was reviewing new information but explicitly did not recommend changing the conclusion in the 2015 DSC, explaining: "Because there are no alternative OTC medications to manage pain and/or fever during pregnancy, to raise concerns of a strengthened association with 'adverse neurodevelopmental outcomes', when important limitations exist for the data and *no causal relationship can be established*, would have a significant public health impact for the pregnant population and their healthcare providers."[44]

- In January 2018, FDA's Medical Policy and Program Review Council ("MPPRC") met to discuss the effects of acetaminophen use during pregnancy.[45] A slide deck accompanying FDA's meeting minutes shows that the objective of the 2018 MPPRC meeting was to "[s]eek advice on next steps," which could include, for example, additional communication or nonclinical study.[46] However, FDA explicitly *eliminated* from consideration the option

[38] *Id.* at 10.
[39] *Id.* at 10-11.
[40] *Id.* at 11-12 (emphasis added).
[41] *Id.* at 12.
[42] Maternal Health Memorandum from Tamara Johnson, Team Leader, Maternal Health, Division of Pediatric and Maternal Health, to Division of Non-Prescription Drug Products at 2 (Apr. 7, 2017), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 468-1 (S.D.N.Y. Mar. 2, 2023).
[43] *Id.* at 5 (emphasis added).
[44] *Id.* (emphasis added).
[45] Medical Policy and Program Review Council, Meeting to Discuss Tracked Safety Issue 1355 for Acetaminophen and Effects During Pregnancy at 1 (Jan. 24, 2018), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 468-1 (S.D.N.Y. Mar. 2, 2023).
[46] *Id.* at slide 7.

of revising the labeling.[47] That option was rejected by FDA with a red "X," as illustrated below:



- Likewise, FDA's MPPRC "agreed with the Division [of Nonprescription Drugs] and did not suggest making labeling changes."[48]

- In 2020, FDA's Division of Non-Prescription Drugs 1 ("DNPD 1") reiterated that in 2018, the "MPPRC did not suggest making any labeling changes. It agreed that given the uncertainty as to whether there is a causal association, issuing a communication at that time would not add substantively to the prior DSC."[49]

- FDA's DNPD 1 specifically noted that as of November 2018, the European Medicines Agency ("EMA") updated FDA that it had "requested that paracetamol [acetaminophen] sponsors revise the Summary of Product Characteristics (SPC) to state that epidemiologic studies have yielded conflicting results."[50] FDA's DNPD 1 at this time did not recommend similar changes to U.S. acetaminophen product labeling and instead recommended continuing to "evaluate this indeterminate risk."[51]

- In its 2022 epidemiological review, FDA concluded that "[o]verall, there are still study limitations and inconsistent study findings that prohibit causal interpretations."[52] FDA noted that while certain reviewed meta-analyses may suggest an association between prolonged prenatal exposure to acetaminophen and ADHD, the "most methodologically rigorous study" found only a "weak association."[53] In addition, FDA cautioned that "[s]tudies are still limited by crude operationalizations of [acetaminophen] exposure, unclear clinical meaning of findings, and the possibility of unmeasured confounding by factors such as indication, other medications, and genetic factors."[54] That same review, like

[47] *See id.*
[48] Medical Policy and Program Review Council, Follow Up Discussion of Tracked Safety Issue 1355 for Acetaminophen and Effects During Pregnancy at 1 (Oct. 3, 2018), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 468-1 (S.D.N.Y. Mar. 2, 2023).
[49] Division of Non-Prescription Drugs 1, Newly Identified Safety Signal (NISS) Integrated Review Memorandum at 2 (May 1, 2020), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 483-1 (S.D.N.Y. Mar. 7, 2023).
[50] *Id.* at 4. In addition, notwithstanding the Petitioner's characterization to the contrary, since the September 22 Announcement, the European Medicines Agency ("EMA") also issued a press release regarding the use of paracetamol during pregnancy, confirming that, after reviewing available evidence, its recommendations on the use of paracetamol in pregnancy remain unchanged. *Use of Paracetamol During Pregnancy Unchanged in the EU*, EUROPEAN MED. AGENCY (Sept. 23, 2025), https://www.ema.europa.eu/en/news/use-paracetamol-during-pregnancy-unchanged-eu.
[51] Division of Non-Prescription Drugs 1, *supra* note 49, at 4.
[52] CDER, Epidemiology: Review of Published Studies at 33 (July 15, 2022), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 427-7 (S.D.N.Y. Feb. 10, 2023) ["July 2022 Review"].
[53] *Id*.
[54] *Id* at 32.

the 2016 review, pointed to the potential protective effect of acetaminophen use during pregnancy when used to "attenuate the impact of fever on childhood outcomes."[55]

- In its 2023 epidemiological review, FDA again found no causal association between acetaminophen use during pregnancy and neurobehavioral outcomes, stating, "[o]verall, the three new studies reviewed are limited and do not change [DEPI's] conclusions from its most recent review—the limitations and inconsistent findings of current observational studies of [acetaminophen] and neurobehavioral . . . outcomes are unable to support a determination of causality."[56]

- In 2023, in response to an invitation by the United States District Court for the Southern District of New York to submit a Statement of Interest concerning the warning included in labeling for OTC acetaminophen products, the U.S. Department of Justice ("DOJ") and FDA provided FDA's 2023 epidemiology review and referred to the "multiple reviews of relevant epidemiological data" that FDA had conducted "[s]ince 2014."[57] DOJ and FDA's letter reiterated the conclusion in FDA's 2023 epidemiological review that "studies reviewed here are limited and do not change DEPI-I's conclusions from its most recent review—the limitations and inconsistent findings of current observational studies of [acetaminophen] and neurobehavioral . . . outcomes are unable to support a determination of causality."[58]

- Finally, as discussed above, in its 2025 epidemiological review, FDA again concluded that "the data covered in this review alone and in combination with previous DEPI literature reviews are insufficient to support a causal association at this time."[59]

Thus, FDA's position has remained remarkably consistent for over a decade. There is no basis to conclude, as the Citizen Petition suggests, that the scientific evidence now supports a different conclusion regarding causation than did FDA's multiple epidemiological reviews since 2014.

B. The Most Recent Publication Relied Upon By The Citizen Petition Does Not Support The Requested Labeling Change

Since FDA's May 2025 DEPI review, one article reviewing pre-existing data has been published ("Prada 2025," sometimes referred to as the Harvard or Mt. Sinai study) in which the authors state that there is an association between prenatal acetaminophen exposure and increased risks of ASD/ADHD.[60] The Prada paper does not provide a basis to change FDA's position as set

[55] *Id.*
[56] CDER, Epidemiology: Literature Review at 3-4 (Mar. 10, 2023), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 1105-1 (S.D.N.Y. Sept. 8, 2023).
[57] Letter from Damian Williams, U.S. Attorney for the Southern District of New York, to The Honorable Denise Cote, U.S. District Judge at 1-2 (Sept. 8, 2023), *available at In Re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 1:22-md-03043, ECF No. 1105 (S.D.N.Y. Sept. 8, 2023).
[58] *Id.*
[59] May 2025 DEPI Review, *supra* note 19, at 19-20.
[60] Diddier Prada et al., *Evaluation of the Evidence on Acetaminophen Use and Neurodevelopmental Disorders Using the Navigation Guide Methodology*, 24 ENV'T HEALTH 1, 38 (2025),

forth in FDA's 2025 epidemiological review. The authors of the article *do not* conclude that there is a causal association between prenatal acetaminophen use and neurodevelopmental disorders.[61] Neither the press release announcing the study nor the study's authors claim that the article establishes causation.[62] And independent reviewers similarly agreed that the analysis in the article did not establish causation.[63]

Moreover, three of the four Prada 2025 authors—Drs. Beate Ritz, Ann Z. Bauer, and Andrea A. Baccarelli—are plaintiffs' experts in ongoing products liability litigation.[64] The review article itself borrows heavily from Dr. Baccarelli's purported expert opinions in that ongoing litigation—opinions that were ruled inadmissible by a federal court because they were scientifically unreliable.[65] As described further in Section I.C. below, the review suffers from the same flaws as his expert report.[66]

The Okubo 2025 study also was published after FDA's May 2025 review. This cohort study assessed 217,000 children in a Japanese database and, after a sibling control analysis,

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https://ehjournal.biomedcentral.com/articles/10.1186/s12940-025-01208-0 ("A causal relationship is plausible" but "observational limitations preclude definitive causation.").

[61] *Id*.

[62] *Press Release: Mount Sinai Study Supports Evidence That Prenatal Acetaminophen Use May Be Linked to Increased Risk of Autism and ADHD*, MT. SINAI (Aug. 13, 2025), https://www.mountsinai.org/about/newsroom/2025/mount-sinai-study-supports-evidence-that-prenatal-acetaminophen-use-may-be-linked-to-increased-risk-of-autism-and-adhd. ("While the study does not show that acetaminophen directly causes neurodevelopmental disorders, the research team's findings strengthen the evidence for a connection and raise concerns about current clinical practices," noted a Mount Sinai press release issued on August 13, 2025); *Using Acetaminophen During Pregnancy May Increase Children's Autism and ADHD Risk*, HARV. T.H. CHAN SCH. OF PUB. HEALTH (Aug. 20, 2025), https://hsph.harvard.edu/news/using-acetaminophen-during-pregnancy-may-increase-childrens-autism-and-adhd-risk/ ("Further research is needed to confirm the association and determine causality," stated Dr. Andrea Baccarelli, Dean of the Harvard T.H. Chan School of Public Health and co-author on the study); Azeen Ghorayshi, *Trump Issues Warning Based on Unproven Link Between Tylenol and Autism*, N.Y. TIMES (Sept. 22, 2025), https://www.nytimes.com/2025/09/22/health/kennedy-autism-tylenol-trump.html ("'We cannot answer the question about causation—that is very important to clarify,' Dr. Diddier Prada, an epidemiologist at Mt. Sinai and the first author on the study, told The New York Times this month."); Niha Masih & Ariana Eunjung Cha, *Trump Gave Medical Advice About Tylenol. Here's What Medical Experts Say*, WASH. POST (Sept. 23, 2025), https://www.washingtonpost.com/health/2025/09/22/tylenol-pregnancy-autism-risk-rfk-jr/ ("'We show that acetaminophen is associated with a higher risk, but not causing it. Those are very different things,' [Prada] said in an interview with the Washington Post earlier this month.").

[63] After receiving a reviewer comment suggesting the article "temper language to 'association' unless a causal inference is strongly justified," the abstract was revised to only reference an "association." *See* Andrea Baccarelli, Response to Reviewers at 11 (July 3, 2025), https://ehjournal.biomedcentral.com/articles/10.1186/s12940-025-01208-0/peer-review).

[64] Drs. Baccarelli and Ann Z. Bauer are plaintiffs' experts/consultants in the acetaminophen litigation. Dr. Beate Ritz is a plaintiffs' expert in baby food litigation. Drs. Bauer and Ritz did not disclose this potential conflict in Prada 2025.

[65] *In re: Acetaminophen – ASD-ADHD Products Liability Litigation*, 707 F. Supp. 3d 309, 342, 348 (S.D.N.Y. 2023) (concluding that Dr. Baccarelli's opinions were "unreliable" and lacking "sufficient rigor").

[66] For example, he performs two separate analyses for Gustavson 2021's "initial" and "sibling-control" results where the "sibling-control" results show no association, but he conducts one analysis for Brandlistuen 2013, a sibling control analysis that is more favorable to his opinions; discounts Tronnes 2020 for its reliance on a diagnostic questionnaire but does not do the same to Brandlistuen 2013, the sibling control study that uses the same questionnaire; excludes two studies (Leppert 2019 and Saunders 2019) from his analysis even though they are publicly available—these are two studies that undermine his opinions; and rates Ji 2020 (cord blood study with 100% detection of acetaminophen—a data point later proven to be invalid in Li 2024) and Liew 2016 (a study with internally inconsistent results) as strong evidence of association despite the obvious study flaws.

reported that there was no association between maternal use of acetaminophen and neurodevelopmental disorders, including ASD and ADHD.[67] In light of these findings, the authors concluded that unmeasured confounding, misclassification, and other biases may partially explain associations that have been reported in some prior studies (none of which used the sibling control model).[68]

An additional study released since FDA's May 2025 review, the Bérard 2025 study, also assessed acetaminophen exposure during pregnancy.[69] The meta-analysis performed a pooled analysis for ASD when considering physician-based diagnoses involving 222,096 children. The authors found no significant evidence of a clinically meaningful increased risk for ASD among the children of mothers who were treated with acetaminophen during pregnancy when considering physician-based diagnoses.

C. Courts That Have Evaluated The Science Agree That It Does Not Show Acetaminophen Use In Pregnancy Causes Neurodevelopmental Disorders, And Have Excluded Opinions By Authors On Which the Petition Relies

The Citizen Petition relies extensively on plaintiff-side expert reports from products liability suits involving acetaminophen that were not peer reviewed and that were excluded as lacking scientific reliability. In an exhaustive and independent review of evidence in product liability lawsuits, a federal court judge who reviewed the scientific evidence and undisputed facts, including the expert opinions on which the Citizen's Petition relies, dismissed more than 500 product liability cases finding that the scientific evidence did not support causation. In 2023 and 2024, the Honorable Denise Cote, United States District Court Judge for the United States District Court for the Southern District of New York, explained that "[p]laintiffs in this MDL presented six experts to opine that prenatal exposure to acetaminophen can cause ADHD and/or ASD," and, after she "carefully considered each expert's proffered testimony," held that "none of these experts presented reliable testimony on general causation."[70] Judge Cote concluded that "there is no generally accepted scientific conclusion that in utero exposure to acetaminophen causes either ASD or ADHD."[71]

Similarly, in May 2025, a state court case in California was dismissed on summary judgment. The California judge ruled that "[b]ecause any potential risk of autism spectrum disorder (ASD) from prenatal ingestion of acetaminophen (APAP) was neither known nor

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[67] Yosuke Okubo et al., *Maternal Acetaminophen Use and Offspring's Neurodevelopmental Outcome: A Nationwide Birth Cohort Study*, PAEDIATRIC & PERINATAL EPIDEMIOLOGY, Sept. 2025, at 1, 1. https://pubmed.ncbi.nlm.nih.gov/40898607/.
[68] *Id.* at 6-7.
[69] *See generally* Anick Bérard et al., *Systematic Review and Meta-Analysis: Acetaminophen Use During Pregnancy and the Risk of Neurodevelopmental Disorders in Childhood*, J. AM. ACAD. CHILD & ADOLESCENT PSYCHIATRY, Oct. 5, 2025, https://www.jaacap.org/article/S0890-8567(25)02106-9/fulltext.
[70] *In re: Acetaminophen – ASD-ADHD Products Liability Litigation*, No. 1:22-mc-03043, at 6 (S.D.N.Y. 2024) (final judgment) (Cote, J.), *appeal pending*, Nos. 24-916, 24-1121, 24-2360 (2d Cir.).
[71] *Id*. at 49.

knowable during the relevant time period (2018-2019) as a matter of law, and indeed remains a matter of considerable uncertainty to this day, Defendants are entitled to summary judgment."[72]

Yet Petitioner relies on these same plaintiff-side expert reports. For example, Dr. Haotian Wu's report failed to support causation in the May 2025 suit that was dismissed in California. In addition, Dr. Baccarelli's, Dr. Robert Cabrera's, and Dr. Brandon Pearson's opinions were held to be inadmissible in federal court litigation because they were scientifically unreliable.[73] Judge Cote roundly criticized Dr. Baccarelli and the plaintiffs' experts for using unreliable and biased scientific methods. The court ruled that Dr. Baccarelli, "downplay[ed] those studies that undercut his causation thesis and emphasize[d] those that align with his thesis,"[74] and that "Dr. Baccarelli, as recently as 2022, co-authored a study on the prenatal effects of acetaminophen that cautioned against any change in clinical practice,"[75] and noted that "Dr. Baccarelli's testimony does not reflect a reliable application of scientific methods."[76] The court concluded that Dr. Baccarelli's "failure to engage seriously with the complexity of the relevant studies' outcomes is well illustrated."[77]

The Southern District of New York court further held that the excluded plaintiffs' experts:

> 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.[78]

Finally, the court held that "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."[79] Given the court's explanation that these paid expert opinions—not subjected to peer review—are unreliable, it would be anomalous for FDA to accept them as scientifically credible.

D. The Body Of Scientific Evidence Does Not Support Petitioner's Requested Labeling Changes

The scientific evidence does not support the labeling changes that Petitioner seeks. There are eight studies that analyze the association between maternal use of acetaminophen and diagnosed ASD. The three most methodologically robust studies (Janecka et al. 2018, Ahlqvist et

[72] *Ashley Davey et al. v. Safeway Inc. et al.*, No. 24CV064095 (Cal. Super. Ct. Alameda Cnty. May 5, 2025) (Schwartz, J.), *appeal pending*, No. A173412 (Cal. 1st App. Dist., Div. 2).
[73] *In re Acetaminophen*, 707 F. Supp. 3d at 309.
[74] *Id*. at 353.
[75] *Id.* at 333-44.
[76] *Id*. at 354.
[77] *Id.* at 343.
[78] *Id.* at 334.
[79] *Id*. at 364.

al. 2024, and Okubo et al. 2025) reported no association.[80] Three additional studies (Ji et al. 2018, Saunders et al. 2019, and Mkhitaryan et al. 2024) reported no significant association.[81] The only two studies reporting a positive association (Liew et al. 2016 and Ji et al. 2020) have significant methodological limitations, including a lack of sufficient data to properly adjust for known confounders, including genetics/familial factors and indication for use.[82]

As to ADHD, there are twelve studies that assess the relationship between maternal use of acetaminophen and diagnosed ADHD. The studies reporting a positive association, however, have significant limitations (e.g., internally inconsistent data (Liew et al. 2014, Ystrom et al. 2017, Ji et al. 2018, Chen et al. 2019, Ji et al. 2020, Anand et al. 2021, Baker et al. 2025), insufficient adjustment for key confounders such as indication of use and genetics/familial factors (Liew et al. 2014, Ystrom et al. 2017, Ji et al. 2018, Chen et al. 2019, Liew et al. 2019, Baker et al. 2020, Ji et al. 2020, Anand et al. 2021, Baker et al. 2025), exposure assessment derived from data of uncertain relevance to maternal acetaminophen use (Ji et al. 2018, Liew et al. 2019, Baker et al. 2020, Ji et al. 2020, Anand et al. 2021, and Baker et al. 2025), and small samples sizes (Baker et al. 2020, Baker et al. 2025)).[83] Similar to the literature assessing ASD, the most methodologically robust studies demonstrate the reported associations were due to confounding (Gustavson et al. 2021, Ahlqvist et al. 2024, and Okubo et al. 2025).[84]

There also are some studies that use screening tools to assess a relationship between in utero exposure and symptoms of ASD and/or ADHD. These tools, however, have significant limitations compared to clinical diagnosis. As to the studies using screening tools and

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[80] *See generally* Magdalena Janecka et al., *Association of Autism Spectrum Disorder With Prenatal Exposure to Medication Affecting Neurotransmitter Systems*, 75 JAMA PSYCHIATRY 1217 (2018), https://pubmed.ncbi.nlm.nih.gov/30383108/; Ahlqvist et al., *supra* note 24; Okubo et al., *supra* note 67.

[81] *See generally* Yuelong Ji et al., *Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder*, 8 BRAIN SCI. 127 (2018); Alexandra Saunders et al., *Comparison of Prenatal Exposures in Children with and without a Diagnosis of Autism Spectrum Disorder*, 11 CUREUS e5223 (2019); Meri Mkhitaryan et al., *A Case–Control Study on Pre-, Peri-, and Neonatal Risk Factors Associated with Autism Spectrum Disorder Among Armenian Children*, 14 SCI. REPS. 12308 (2024), https://pmc.ncbi.nlm.nih.gov/articles/PMC11137108/.

[82] *See generally* Zeyan Liew et al., *Paracetamol Use During Pregnancy and Attention and Executive Function in Offspring at Age 5 Years*, 45 INT'L J. EPIDEMIOLOGY 2009 (2016); Yuelong Ji et al., *Association of Cord Plasma Biomarkers of ln Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood*, 77 JAMA PSYCHIATRY 180 (2020); *see also* FDA's July 2022 Review, *supra* note 52, at 23; FDA's May 2025 DEPI Review, *supra* note 19, at 25-26.

[83] *See generally* Zeyan Liew et al., *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168 JAMA PEDIATRICS 313 (2014); Eivind Ystrom et al., *Prenatal Exposure to Acetaminophen and Risk of ADHD*, PEDIATRICS, Nov. 2017; Ji et al., *supra* note 81; Ji et al., *supra* note 82; Mu-Hong Chen et al., *Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan*, J. CLINICAL PSYCHIATRY, Sept. 2019; Zeyan 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 AM. J. EPIDEMIOLOGY 768 (2019); Brennan H. Baker et al., *Association of Prenatal Acetaminophen Exposure Measured in Meconium with Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity*, 174 JAMA PEDIATRICS 1 (2020); Neha S. Anand et al., *Perinatal Acetaminophen Exposure and Childhood Attention-Deficit/Hyperactivity Disorder (ADHD): Exploring the Role of Umbilical Cord Plasma Metabolites in Oxidative Stress Pathways*, 11 BRAIN SCIS. 1302 (2021); Brennan H. Baker et al., *Associations of Maternal Blood Biomarkers of Prenatal Exposure with Placental Gene Expression and Childhood Attention Deficit Hyperactivity Disorder*, NATURE MENTAL HEALTH, Feb. 2025.

[84] *See generally* Kristin Gustavson et al., *Acetaminophen Use During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder – A Longitudinal Sibling Control Study*, JCPP ADVANCES, Apr. 2021; Ahlqvist et al., *supra* note 24; Okubo et al., *supra* note 67; FDA May 2025 DEPI Review, *supra* note 19, at 27-28.

questionnaires to assess neurodevelopmental outcomes, these instruments are designed to be highly inclusive and do not map onto any precise disorder, including ASD and ADHD. Accordingly, and as noted by the authors in Brandlistuen et al. 2013, the clinical significance of any such results cannot be determined.[85] In addition, Damkier et al. (2022), pointed out methodologic issues and challenged the interpretation of some of the studies.[86] For example, the publication notes that many of the outcome measurements are unvalidated and were not developed for the purpose for which they are being used, such as the Strengths and Difficulties Questionnaire (SDQ), which was originally designed as a screening tool.[87] The results based on screening instruments were inconsistent and reported associations were generally small in magnitude. Accordingly, there is no support in the literature of a causal association between maternal use of acetaminophen and childhood ASD or ADHD. The table in Appendix A hereto further addresses the Citizen Petition's "evidence supporting [its] position," providing paragraph-by-paragraph responses.

E. Leading Professional Health Organizations And Authorities Have Independently Found No Causal Association

In contrast to litigation experts who have a vested interest in this issue, professional medical organizations comprised of health professionals who care for pregnant women and children have repeatedly reviewed the science and continue to recommend prenatal use of acetaminophen. In 2017, the Society for Maternal-Fetal Medicine ("SMFM") published an article in the American Journal of Obstetrics and Gynecology expressing support for continued prenatal acetaminophen use:

> Based on our evaluation of these studies, we believe that *the weight of evidence is inconclusive regarding a possible causal relationship* between acetaminophen use and neurobehavioral disorders in the offspring. As with all medication use during pregnancy, communication regarding the risks versus the benefits of prescription and over-the-counter medications use should occur between patient and provider. The SMFM Publications Committee continues to advise that acetaminophen be considered a reasonable and appropriate medication choice for the treatment of pain and/or fever during pregnancy.[88]

Similarly, in 2021, the American College of Obstetricians and Gynecologists ("ACOG"), in response to a 2021 "consensus statement" calling for action to limit the use of acetaminophen in pregnancy,[89] issued a public statement reiterating support for its clinical guidance:

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[85] *See generally* Ragnhild Eek Brandlistuen et al., *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Sibling-Controlled Cohort Study*, 42 INT'L J. EPIDEMIOLOGY 1702 (2013).

[86] *See generally* Damkier et al., *Shelter From The Storm: Acetaminophen (Paracetamol) In Pregnancy, Urogenital Malformations, And Childhood Neurodevelopment*, 22 OBSTET MED. 77 (2022), https://pmc.ncbi.nlm.nih.gov/articles/PMC9277736/.

[87] *See id.* at 77.

[88] Society for Maternal-Fetal Medicine Publications Committee, *Prenatal Acetaminophen Use and Outcomes in Children*, 216 AM. J. OBSTETRICS & GYNECOLOGY B14, B15 (2017), https://www.ajog.org/article/S0002-9378(17)30128-X/fulltext (emphasis added).

[89] *See generally* Ann Z. Bauer et al., *Paracetamol Use During Pregnancy — A Call for Precautionary Action*, 17 NATURE REVS. ENDOCRINOLOGY 757 (2021), https://pubmed.ncbi.nlm.nih.gov/34556849/.

> ACOG and obstetrician-gynecologists across the country have always identified acetaminophen as one of the only safe pain relievers for pregnant individuals during pregnancy. This consensus statement, and studies that have been conducted in the past, show no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any trimester and fetal developmental issues.[90]

Since the September 22 Announcement, multiple medical organizations have come forward and challenged the statements and actions by FDA, HHS, and the White House. The American Academy of Pediatrics concluded that:

> Studies do not point to a causal link between the use of acetaminophen and autism in children or in pregnancy, and extensive research indicates there is no single root cause of autism.[91]

The American Psychiatric Association issued a statement explaining:

> A strong base of evidence shows that acetaminophen, when taken as directed, is safe for use during pregnancy. Any decisions around a course of treatment should be determined by a patient and their doctor.[92]

ACOG issued a similar statement the same day, underscoring:

> Suggestions that acetaminophen use in pregnancy causes autism are not only highly concerning to clinicians but also irresponsible when considering the harmful and confusing message they send to pregnant patients, including those who may need to rely on this beneficial medicine during pregnancy. Today's announcement by HHS is not backed by the full body of scientific evidence and dangerously simplifies the many and complex causes of neurologic challenges in children.[93]

SMFM issued its own statement, in which it:

> reiterates its recommendation advising both physicians and patients that acetaminophen is an appropriate medication to treat pain and fever during pregnancy. Despite assertions to the contrary, a thorough review of existing research suggesting a potential link between acetaminophen use during pregnancy and an increased risk of autism and attention deficit and hyperactivity disorder

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[90] *See ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy*, AM. COLL. OF OBSTETRICIANS & GYNECOLOGISTS (Sept. 29, 2021) https://www.acog.org/news/news-articles/2021/09/response-to-consensus-statement-on-paracetamol-use-during-pregnancy.

[91] American Academy of Pediatrics, *Acetaminophen is Safe for Children When Taken as Directed, No Link to Autism* (Sept. 30, 2025), https://www.aap.org/en/news-room/fact-checked/acetaminophen-is-safe-for-children-when-taken-as-directed-no-link-to-autism/?srsltid=AfmBOopDWr9LlwN9xuIOOdmgX_CoRJaITtGReNQE6aR_jDjcfq8w-q0v&utm_source=chatgpt.com.

[92] American Psychiatric Association, *APA Statement on White House Announcement on Autism* (Sept. 22, 2025), https://www.psychiatry.org/news-room/news-releases/apa-statement-on-white-house-announcement-on-autis#:~:text=Autism%20is%20a%20complex%20disorder,treatment%20for%20individuals%20with%20autism.

[93] *See ACOG Affirms Safety and Benefits of Acetaminophen During Pregnancy*, AM. COLL. OF OBSTETRICIANS & GYNECOLOGISTS (Sept. 22, 2025), https://www.acog.org/news/news-releases/2025/09/acog-affirms-safety-benefits-acetaminophen-pregnancy.

> (ADHD) in children has not established a causal relationship. To be clear, SMFM stands behind our recommendation that acetaminophen use during pregnancy has not been shown to cause or increase the risk of autism or other neurobehavioral problems in children.[94]

Likewise, the World Health Organization released a statement on September 24, 2025, "emphasiz[ing] that there is currently no conclusive scientific evidence confirming a possible link between autism and use of acetaminophen (also known as paracetamol) during pregnancy."[95]

On September 29, 2025, an editor of *JAMA* (the *Journal of the American Medical Association*) and obstetrician-gynecologist Dr. Linda Brubaker interviewed a senior author of Ahlqvist 2024, Dr. Brian Lee, a professor of epidemiology at Drexel University Dornsife School of Public Health. As discussed in Section I.A., Ahlqvist 2024, studied 2.5 million pregnancies in Sweden and found no causal association between acetaminophen use during pregnancy and autism, ADHD, or other neurodevelopmental disorders after controlling for genetics and confounders. Drs. Brubaker and Lee emphasized that "the studies that have better control of potential confounders, especially those that do sibling analyses, tend to find no evidence to support a causal association" and that acetaminophen remains safe when used appropriately during pregnancy.[96]

More recently, on October 7, 2025, six former U.S. Surgeons General—appointed by every president since George H.W. Bush—published an opinion piece in the *Washington Post*, criticizing the September 22 Announcement as "ignor[ing] science" and "causing confusion, fear and harm," rather than "helping pregnant women make informed decisions during a critical period in their lives."[97]

II. COMPELLING PUBLIC HEALTH CONSIDERATIONS COUNSEL AGAINST THE PETITION'S PROPOSED LABELING REVISIONS

Compelling public health considerations also warrant rejecting Petitioner's requested labeling. As noted above, the first proposed addition to acetaminophen labeling by the Citizen Petition claims a causal connection that is neither supported by existing science, nor consistent with FDA's own September 22 Announcement and Notice to Physicians.[98] Including such unsubstantiated and excessive warning on the labeling may discourage appropriate use of

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[94] *SMFM Response to Administration Announcement on Acetaminophen Use During Pregnancy and Autism,* SOC'Y FOR MATERNAL-FETAL MEDICINE (Sept. 22, 2025), https://www.smfm.org/news/smfm-response-to-administration-announcement-on-acetaminophen-use-during-pregnancy-and-autism.

[95] *WHO Statement on Autism-Related Issues*, WORLD HEALTH ORG. (Sept. 24, 2025), https://www.who.int/news/item/24-09-2025-who-statement-on-autism-related-issues.

[96] Kate Schweitzer, *Acetaminophen Use in Pregnancy—Study Author Explains the Data*, JAMA (Sept. 29, 2025), https://jamanetwork.com/journals/jama/fullarticle/2839562.

[97] Jerome Adams, Richard Carmona, Joycelyn Elders, Vivek Murthy, Antonia Novello & David Satcher, Opinion, *Six Surgeons General: It's Our Duty to Warn the Nation about RFK Jr.*, WASH. POST (Oct. 7, 2025), https://www.washingtonpost.com/opinions/2025/10/07/surgeons-general-rfk-jr-robert-kennedy/.

[98] *See* FDA, *supra* note 10 ("[W]hile an association between acetaminophen and neurological conditions has been described in many studies, a causal relationship has not been established and there are contrary studies in the scientific literature."); FDA, *supra* note 11 (providing that "a causal relationship has not been established" and "[t]he association is an ongoing area of scientific debate").

acetaminophen, lead to other unintended harmful outcomes for the mother and/or developing baby, and risk "overwarning" and confusing consumers.

A. Deterring Acetaminophen Use May Result In Significant Negative Health Outcomes For Pregnant Women And Their Babies

Pregnant women and their developing babies face a number of significant negative health outcomes if acetaminophen use is inappropriately deterred. Untreated fever in pregnant women has been associated with a range of adverse pregnancy outcomes beyond neurodevelopmental disorders, including miscarriage, preterm birth, preterm labor, and birth defects.[99] The Centers for Disease Control and Prevention ("CDC") has recognized that "[i]n some cases, increased internal temperature and fever during pregnancy have been linked to birth defects and other pregnancy complications."[100] CDC also notes that "[a] common flu symptom is fever, which has been associated in some studies with neural tube defects and other adverse outcomes for a developing baby."[101] Moreover, as FDA has recognized, "[s]evere and persistent pain that is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure in the mother."[102] ACOG has explained that:

> Untreated maternal conditions for which acetaminophen is indicated—such as fever, migraines and other headaches, and pain—can lead to significant maternal and fetal morbidity and mortality. Fever during pregnancy, for example, has been associated with increased risk of neural tube defects and other birth defects such as oral clefts and cardiac defects. Inadequate treatment of pain can destabilize maternal physiology, with potential downstream effects on fetal well-being.[103]

Access to a safe and effective treatment for fever during pregnancy is essential to the public health because a fever itself—rather than acetaminophen use—may increase the risk of a range of serious adverse outcomes for mothers and babies.[104] Thus, as FDA recognized in two of its reviews of the literature, "[acetaminophen] (or antipyretics in general) might mitigate adverse developmental outcomes of maternal fever" and "prenatal [acetaminophen] use may attenuate the impact of fever on childhood outcomes."[105] As FDA has explained, "studies . . . suggest that prenatal [acetaminophen] use may attenuate the impact of fever on childhood outcomes," and "[u]ntreated fevers during pregnancy are associated with poor pregnancy outcomes; there is some evidence that treatment of fever during pregnancy may attenuate these risks or be protective."[106]

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[99] *See SMFM Response to Administration Announcement on Acetaminophen Use During Pregnancy and Autism*, *supra* note 94.
[100] CDC, *Heat and Pregnancy*, https://www.cdc.gov/heat-health/risk-factors/heat-and-pregnancy.html (last visited Oct. 16, 2025).
[101] CDC, *Flu and Pregnancy*, https://www.cdc.gov/flu/highrisk/pregnant.htm (last visited Oct. 16, 2025).
[102] *See* FDA, *supra* note 33.
[103] ACOG, *Acetaminophen Use in Pregnancy and Neurodevelopmental Outcomes* (Sept. 2025), https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2025/09/acetaminophen-use-in-pregnancy-and-neurodevelopmental-outcomes.
[104] *Can Having a Fever While Pregnant Hurt My Baby?*, MARCH OF DIMES (Mar. 30, 2021), https://www.marchofdimes.org/find-support/blog/can-having-fever-while-pregnant-hurt-my-baby.
[105] *See supra* notes 36 & 55 and accompanying text.
[106] *See, e.g.*, CDER, *supra* note 52.

Indeed, FDA has suggested that use of acetaminophen during pregnancy "might mitigate adverse neurodevelopmental effects of maternal fever."[107]

Acetaminophen plays a unique and crucial role in treatment of pain and fever for pregnant women because there is no known, safe alternative to acetaminophen for pregnant women throughout a woman's entire pregnancy.[108] Indeed, other therapeutic options routinely used for similar indications as acetaminophen in non-pregnant individuals have well-documented risks associated with them. For instance, non-steroidal anti-inflammatory drugs ("NSAIDs"), such as aspirin and ibuprofen, have been linked to fetal renal dysfunction and other adverse pregnancy outcomes, and FDA has specifically warned against their use after 20 weeks.[109] Other typical treatment options for pain and migraines such as carbamazepine are also contraindicated in pregnancy due to known risks of congenital malformations.[110] In addition, the use of opioids poses significant potential risks in pregnancy, including dependence, opioid use disorders, and overdose. This lack of viable alternatives was acknowledged by the Administration during the September 22 Announcement.[111]

The proposed labeling change, however, could cause confusion and cause pregnant women to turn to more dangerous alternatives. According to a recent survey of more than 500 American acetaminophen consumers from households expecting the birth of a child—which was conducted following the September 22 Announcement discouraging acetaminophen use during pregnancy—more than one-third of expecting households (34%) said that they would choose a different type of OTC pain reliever (e.g., NSAIDS such as ibuprofen and naproxen) the next time they needed pain relief, notwithstanding the heightened risks of such choices.[112] Moreover, STAT News detailed a notable uptick in interest in "natural," "organic," and "clean alternative[]" remedies for fevers, headaches, and pain in children since the September 22 Announcement, despite these products being "neither well-regulated nor well-researched."[113] These findings underscore the harmful potential consequences of unsubstantiated public health messages.

In short, the dangers of untreated pain or fever during pregnancy for the mother as well as the developing baby are well established. The proposed labeling changes in the Citizen Petition

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[107] *See* CDER, *supra* note 35.

[108] *See, e.g.*, *Acetaminophen in Pregnancy, Frequently Asked Questions*, AM. COLL. OF OBSTETRICIANS & GYNECOLOGISTS, https://www.acog.org/clinical-information/physician-faqs/acetaminophen-in-pregnancy (last visited Oct. 16, 2025) ("Acetaminophen is well studied and proven to be safe for use in pregnancy, and is one of the only medicines available to pregnant women for pain relief and treatment of headaches and fevers. . . . There are a small number of alternatives to acetaminophen for pain relief and treatment of fevers or headaches during pregnancy, but many of those come with usage restrictions or contraindications. . . .").

[109] FDA, *FDA Recommends Avoiding Use of NSAIDs in Pregnancy at 20 Weeks or Later Because They Can Result in Low Amniotic Fluid* (Oct. 15, 2020), https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-avoiding-use-nsaids-pregnancy-20-weeks-or-later-because-they-can-result-low-amniotic.

[110] *See* Carbamazepine Extended-Release Capsules Prescribing Information, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020712s030lbl.pdf (last visited Oct. 16, 2025).

[111] *See Remarks: Donald Trump Makes an Autism Announcement at the White House – September 22, 2025*, *supra* note 7, at 00:10:28.

[112] *See 93% of Acetaminophen Buyers Plan to Continue Purchasing; Tylenol Brand Trust Remains High, Numerator Reports*, FOX 8 NEWS (Oct. 2, 2025), https://fox8.com/business/press-releases/globenewswire/9538950/93-of-acetaminophen-buyers-plan-to-continue-purchasing-tylenol-brand-trust-remains-high-numerator-reports/.

[113] Sarah Todd, *Parents Are Flocking to Natural and 'Clean Medicine' Brands. Medical Experts Are Worried*, STAT NEWS (Oct. 7, 2025), https://www.statnews.com/2025/10/07/tylenol-alternatives-surge-after-trump-autism-claims/.

risks directing pregnant women either to unsafe alternatives to manage their pain or fever or to forego therapeutic options altogether, a choice that may be harmful in itself.

B. Additional Public Health Rationales Support Using Existing Pregnancy Warning

In addition, it would not serve public health to give subjective dosing recommendations (i.e., "use the lowest effective dose for the shortest possible time and at the lowest possible frequency") as opposed to the current—and more conservative—approach of directing pregnant women to consult their health professionals, as provided in acetaminophen's Drug Facts Label. FDA has long required that acetaminophen—and other OTC drugs "intended for systemic absorption"—include the following warning: "**If pregnant or breast-feeding**, ask a health professional before use."[114] This is for good reason. The concepts of "lowest" and "shortest" already are enshrined in the current standard of medical care. How these concepts are effectively applied in care during pregnancy is best left to discussions between the pregnant woman and her doctor, who is best positioned to determine whether any use—and, if so, which use—is best suited for that individual. Adding additional language that departs from the current and conservative warning to "ask a health care professional before use" deters users from consulting their health professional.

These concepts have been long recognized and underly the regulatorily required pregnancy warning. The general pregnancy warning was promulgated by FDA in 1982, in part, in response to California's adoption of a pregnancy warning requirement. Expressing "concern[s] that a proliferation of [] State requirements may weaken FDA's efforts to develop comprehensive national labeling and other requirements for OTC drugs,"[115] FDA created a "single national warning."[116] FDA "acknowledged lack of specific information on the effects of most OTC drugs on developing fetuses or on breast-fed infants"[117] and therefore believed that a pregnant woman would be "best advised on whether to use a particular OTC drug by a knowledgeable health professional who is either familiar with her medical history or readily available to her and capable of assessing her situation with respect to a particular drug."[118] The existing warning therefore acknowledges the variability in patient circumstances and entrusts health professionals to provide advice tailored to each pregnant woman's needs and medical history. It also preserves the practice of medicine for healthcare practitioners and acknowledges that FDA's role does not include the regulation of medical practice.

Although health professionals already have a framework for understanding and evaluating these considerations in context,[119] for consumers, this proposed labeling lacks the necessary clarity and creates a risk that pregnant women may not discuss their circumstances with a health

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[114] 21 C.F.R. § 201.63(a).
[115] 47 Fed. Reg. 54750, 54756 (Dec. 3, 1982).
[116] *Id*.
[117] *Id.* at 54751.
[118] *Id*.
[119] *See, e.g.*, *ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy*, *supra* note 80 (recognizing that "what is already done by obstetrician-gynecologists when prescribing acetaminophen for a given clinical condition" is to consider "as always, [that] any medication taken during pregnancy should be used only as needed, in moderation, and after the pregnant patient has consulted with their doctor").

professional, thereby undermining the long-required regulatory warning that a health professional be consulted before use in pregnancy.

First, clinical guidelines generally recommend a nuanced range of different dosages of acetaminophen for different circumstances. For example, according to the *Physicians Desk Reference*, for fever as well as treatment of mild pain, or temporary relief of headache, myalgia, back pain, musculoskeletal pain, or dental pain, adults typically may take 325 to 650 mg of immediate-release oral acetaminophen every four to six hours or 1,000 mg every six hours as needed. By contrast, for osteoarthritis, adults typically may take 1,300 mg (extended release) every eight hours; and for acute treatment of migraine, 1,000 mg once.[120] There is substantial doubt that merely instructing consumers to "use the lowest effective dose for the shortest possible time and at the lowest possible frequency" would adequately convey these nuances and, on the contrary, this language may have potential unintended consequences such as medication errors (misuse) or ineffective dosing, as described below.

The additional language proposed in the Citizen Petition also could have a number of potentially harmful consequences. For example, pregnant woman with migraines might interpret "lowest" to mean 325 mg, which would not be a sufficient dose to treat a migraine (which normally requires 1,000 mg dosing). Such a consumer would be unlikely to achieve pain relief and could turn to alternatives that carry significant risks to mother or child or embark on an extended course of low-dose treatment that fails to adequately address the underlying migraine pain. Sending pregnant patients to their health professional also has the benefit of giving the provider an opportunity to assess whether a patient's pain is an indication of some other underlying medical condition that may require medical intervention.

Second, as noted above, the existing pregnancy warning recognizes that health professionals are in a unique position to address individual patient conditions, medical histories, and other considerations. The health professionals are therefore well-positioned to weigh these variables and provide tailored medical advice. This is all the more important for pregnant women who may have pre-existing conditions or who are taking other medications that could interact. In addition, some pregnant women may be taking several medications at the same time, and the consequences of drug-drug interaction may be more potentially significant due to pregnancy.[121] For these patients, clinical evaluation and advice from a medical professional is appropriate. ACOG's existing clinical guidelines recommend "[j]udicious use at the lowest effective dose for the shortest necessary duration, in consultation with an obstetrician-gynecologist or other obstetric

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[120] *See Tylenol Muscle Aches & Pain*, PHYSICIAN'S DESK REFERENCE, https://www.pdr.net/drug-summary/?drugLabelId=Tylenol-8HR-acetaminophen-2799 (last visited Oct. 16, 2025).

[121] *See, e.g.*, Ronald A. Black & D. Ashley Hill, *Over-the-Counter Medications in Pregnancy*, 67 AM. FAM. PHYSICIAN 2517, 2520 (2003), https://www.aafp.org/pubs/afp/issues/2003/0615/p2517.pdf ("[A]dverse drug interactions that do not occur in nonpregnant patients may occur in pregnant patients"); *see also* Thiago de Lima Pessoa et al., *Drug Interactions in Maternal Intensive Care: Prevalence, Risk Factors, and Potential Risk Medications*, 17 EINSTEIN 1, 2 (2019), https://pmc.ncbi.nlm.nih.gov/articles/PMC6533079/pdf/2317-6385-eins-17-03-eAO4521.pdf ("The use of drugs in maternal ICU presents some peculiarities. Physiology changes during pregnancy, leading to modified actions of medications on the body. [] Pregnant women present significant pharmacokinetic changes"); Maged M. Costantine, *Physiologic and Pharmacokinetic Changes in Pregnancy*, 5 FRONTIERS IN PHARMACOLOGY 1, 4 (2014), https://pmc.ncbi.nlm.nih.gov/articles/PMC3982119/pdf/fphar-05-00065.pdf ("Profound physiologic and anatomic changes occur in virtually every organ system during pregnancy. These have significant consequences on the pharmacokinetic and pharmacodynamic properties of various medications when used by pregnant women.").

care professional" for acetaminophen use in pregnant women,[122] and indeed, a consultation with a healthcare provider is crucial in determining the appropriate usage depending on the condition being treated and the individual's medical profile.

In sum, without guidance from their health professionals, pregnant women may not know which acetaminophen dosage is appropriate in their situation. The Petitioner's proposal, however, discourages pregnant women from taking acetaminophen even when needed for pain or fever without discussing with their healthcare providers and could potentially result in unsafe outcomes.

C. Proposed Labeling Revisions Risk "Overwarning" And Confusing Consumers And May Cause Meaningful Information To Lose Significance

There is significant value—as repeatedly recognized by FDA—in keeping OTC labeling warnings concise, easily understandable, and grounded upon hazards that are not merely theoretical.

FDA has repeatedly cautioned about the potential dangers of overwarning. For example, FDA has underscored the public health importance of easily understandable warnings when finalizing the general pregnancy warning at 21 C.F.R. § 201.63(a). The pregnancy warning was intentionally kept short, simple, and conservative: "ask a health professional before use." The language is straightforward and designed to help prevent consumer confusion. FDA emphasized that this warning should be provided in its exact form, stating, "the final rule will not provide for the use of substantially similar language or for the voluntary addition of words to the warning."[123] Here, too, the pregnancy warning was intentionally kept simple: "ask a health professional before use." FDA received a number of comments suggesting edits to the language or seeking to combine the pregnancy warning with other warnings, but the Agency rejected them.

The Agency has echoed similar views numerous times throughout its rulemaking of OTC monographs, stating that "concisely and consistently worded warnings are essential to the safe use of an OTC drug product" and "permitting flexibility in this section of labeling could put consumers at risk in terms of safe use of an OTC drug product."[124] Indeed, as the Agency has stated, "[i]n all of its decisions on labeling, the agency seriously considers the consumer's comprehension of the intended message in the labeling" and invites—and considers—comments from the public on its proposed labeling language, to ensure that consumers understand the warning.[125] FDA voiced comparable concerns when it finalized standardized format and content requirements for OTC drug product labeling in 1999 ("Drug Facts Rule"). Noting research supporting the "use of less complex terminology" and discouraging labeling that "presents a 'cognitive load, such as the task of reading densely worded consumer information," the Agency emphasized that "[f]or consumers

[122] *See, e.g.*, *Acetaminophen Use in Pregnancy and Neurodevelopmental Outcomes: Practice Advisory*, *supra* note 103; *see also ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy*, *supra* note 90 (recognizing that "what is already done by obstetrician-gynecologists when prescribing acetaminophen for a given clinical condition" is to consider "as always, [that] any medication taken during pregnancy should be used only as needed, in moderation, and after the pregnant patient has consulted with their doctor").
[123] 47 Fed. Reg. at 54753.
[124] 51 Fed. Reg. 16258, 16263 (May 1, 1986).
[125] 53 Fed. Reg. 46204, 46208 (Nov. 16, 1988).

to gain the greatest benefit from these [OTC] products, relevant information must be easy to find, readable, readily understood, noted, and acted upon."[126]

Because of the consumer-facing labeling of nonprescription drugs, FDA requires label comprehension studies and/or self-selection studies, in certain cases, to assess consumer understanding of major communication elements and to ensure that consumers can apply the label information to their personal medical situations and make correct decisions about appropriate use of the product, respectively.[127] The overall intent is to confirm that consumers can safely and effectively use these drugs.

Most recently in the context of direct-to-consumer advertising, FDA has stated that "[o]verwarning is the concept that individuals are exposed to so many warnings in the course of daily life that they are less likely to pay attention to any one particular warning . . . . In terms of presenting risk information, detailing too many risks may lead consumers to discount all risks, or miss the most important risk information."[128] In the context of the adverse reaction section in prescription drug labeling, FDA in guidance has recommended that "[e]xhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or *not plausibly related to drug therapy* should be avoided . . . . Such lists are not informative and tend to obscure the more clinically meaningful information."[129]

Taken together, the Agency has consistently worked to ensure that consumers can understand and apply the information on OTC drug labels, and therefore safely and effectively use these products, through carefully crafted language.[130] Petitioner's labeling proposals fail when examined through this lens. Petitioner's labeling changes not only undermine the current conservative language to consult with a health professional before use, but also would add unsubstantiated, speculative information regarding causation between acetaminophen and autism and ADHD to the label, generate confusion among users who may not appreciate the nuance of the scientific evidence, and cause other important concepts in the label to lose their significance.

III. ADOPTION OF THE PROPOSED LABELING REVISIONS WOULD BE ARBITRARY, CAPRICIOUS, AND CONTRARY TO LAW

The proposed labeling changes in the Citizen Petition should be rejected because their adoption would be arbitrary, capricious, and contrary to law.

First, Petitioner's proposed labeling changes are not supported by scientific evidence. Since 2014, FDA has consistently concluded that the scientific evidence does not support a causal association between use of acetaminophen during pregnancy and neurological disorders, such as

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[126] 64 Fed. Reg. 13254, 13255, 13277 (Mar. 17, 1999).
[127] *See* FDA, *Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products* (Aug. 2010), https://www.fda.gov/files/drugs/published/Label-Comprehension-Studies-for-Nonprescription-Drug-Products.pdf.
[128] 82 Fed. Reg. 27842, 27844 (June 19, 2017).
[129] FDA, *Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Jan. 2006), https://www.fda.gov/media/72139/download.
[130] *See* FDA, *Guidance for Industry: Self-Selection Studies for Nonprescription Drug Products* (Apr. 2013), https://www.fda.gov/media/81141/download; FDA, *Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products* (Aug. 2010), https://www.fda.gov/files/drugs/published/Label-Comprehension-Studies-for-Nonprescription-Drug-Products.pdf.

ASD and ADHD. FDA updated and repeated that finding in 2023, and again most recently this year. As such, the consumer labeling change sought by Petitioner runs contrary to the evidence before the Agency.[131]

Second, adopting the Petitioner's proposed labeling changes cannot be reconciled with FDA's repeated determinations that the scientific evidence does not support a causal association between acetaminophen use during pregnancy and ASD or ADHD. In particular, the requirement that an agency provide reasoned explanation for its action (1) "would ordinarily demand that it display awareness that it is changing position" and (2) requires the agency to "show that there are good reasons for the new policy."[132] Here, FDA would be unable to show either.[133]

Third, the proposed labeling change should be rejected because it would have adverse effects on public health. The Petition does not address the impact on pregnant women who may not seek treatment for fever and pain during pregnancy or who seek out alternatives to acetaminophen with known adverse health risks. The proposed labeling change in the Citizen Petition should be rejected because it fails to consider or address this aspect of a change to long-established labeling.[134]

Fourth, the Citizen Petition process should not be used in this instance to circumvent the administrative order process set forth in section 505G(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). Under the CARES Act, Congress directed that changes to a final monograph, including changes to warnings, should follow the steps set forth in section 505G(b). Specifically, FDA is required to (i) make reasonable efforts to notify sponsors of the drug that will be subject to the administrative order, (ii) issue a proposed administrative order on FDA's website and explain the grounds for the issuance of the order, (iii) publish a notice of availability in the Federal Register, (iv) provide for a public comment period of no less than 45 days, and (v) issue a final administrative order in the Federal Register.[135] This process may be initiated by FDA or at the request of a requestor.[136] Both processes mandate that the public and interested parties become

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[131] *See Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); *Fred Myer Stores, Inc. v. NLRB*, 865 F.3d 630, 638 (D.C. Cir. 2017) (ruling that challenged action was arbitrary and capricious because "it evidences a complete failure to reasonably reflect upon the information contained in the record and grapple with contrary evidence—disregarding entirely the need for reasoned decisionmaking").

[132] *FCC v. Fox Television*, 556 U.S. 502 (2009); *Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 221 (2016); *American Wild Horse Preservation v. Perdue*, 873 F.3d 914 (D.C. Cir. 2017); *Mistick PBT v. Chao*, 440 F.3d 503, 512 (D.C. Cir. 2006) ("Where an agency departs from established precedent without a reasoned explanation, its decision will be vacated as arbitrary and capricious.").

[133] *See Tummino v. Hamburg*, 936 F. Supp. 2d 162, 169 (E.D.N.Y. 2013) (striking down HHS Secretary Sebelius's reversal of FDA's considered view with respect to Plan B, given that "[HHS Secretary's] directive to the FDA to reject [regulatory action] forced the agency to ride roughshod over the policies and practices that it has consistently applied"); *see also Bus. Roundtable v. SEC*, 647 F.3d 1144, 1155 (D.C. Cir. 2011) (rejecting agency rule based upon agency assertion that was "an ipse dixit, without any evidentiary support"); *Nat'l Tire Dealers & Retreaders Ass'n v. Brinegar*, 491 F.2d 31, 40 (D.C. Cir. 1974) (refusing to accept "agency's mere ipse dixit"); *Prevor v. FDA*, 895 F. Supp. 2d 90, 98 (D.D.C. 2012) (rejecting agency ipse dixit).

[134] *See State Farm*, 463 U.S. at 43 (agency action is arbitrary and capricious where the agency's conclusion fails to consider "important aspect[s] of the problem"); *Lilliputian Sys., Inc. v. Pipeline & Hazardous Materials Safety Admin.*, 741 F.3d 1309, 1313 (D.C. Cir. 2014) (agency action is arbitrary and capricious where it failed to engage with facts and comments going against the agency's conclusion).

[135] 21 U.S.C. § 355h(b)(2).

[136] 21 U.S.C. § 355h(b)(2), (5).

aware of the proposed change and have an opportunity to participate in that process. These procedural guardrails therefore help avoid unfounded scientific conclusions from being announced without proper review and process. It requires emphasis that when a citizen petition was submitted seeking amendment to an OTC monograph in 2022, after the enactment of the CARES Act, FDA denied the petition, in part because the Agency "would need to proceed via the order process":

> In order to categorically amend the conditions under which OTC external analgesic drug products in PPP dosage forms are legally marketed under the OTC monograph (e.g., to narrow or expand permissible indications for use), FDA would need to proceed via the order process described in section 505G(b)(1) of the FD&C Act. Alternatively, requestors seeking to modify the conditions of marketing with respect to OTC external analgesics may submit a request under section 505G(b)(5)(B) of the FD&C Act to initiate administrative order proceedings. . . .[137]

A significant reason for OTC drug reform, enacted by Congress in the CARES Act, was to move away from the cumbersome, often delayed citizen petition process and provide for efficiency through the new administrative order process, while providing the necessary protections for interested stakeholders to engage. If, as a result of the Petition, FDA should decide to entertain some label changes for this product, it would have to initiate such changes through the 505G(b) process, including the procedures mandated by the CARES Act.

In addition, to the extent that the Citizen Petition attempts to modify the general pregnancy warning for acetaminophen product labeling under 21 C.F.R. § 201.63(d)—and the petition is unclear on whether it is suggesting such modification—the plain language of the regulation makes this unavailable to the Petitioner. As the regulatory provision makes clear, the citizen petition pathway available in § 201.63(d) is intended for OTC drug manufacturers seeking an exemption *from* the general pregnancy warning requirement in § 201.63(a)—akin to the categories of OTC drugs already granted exemption under § 201.63(c). That would only be implemented through notice-and-comment rulemaking. To replace the general pregnancy warning with a "specific warning . . . for a particular drug product," however, one must follow the regulatory process set forth in § 201.63(b), namely, "in the NDA" (for drugs subject to an approved application) or as part of the "final OTC drug monograph" (for monograph drugs not subject to an approved application).[138] In the latter case, as reviewed above, 505G(b) must be followed.

Fifth, the Citizen Petition relies on an incorrect statutory provision, section 505(o)(4) of the FDCA, and as a result, fails to invoke the proper legal authority necessary for FDA to revise the labeling at issue. FDA's authority to seek a safety labeling change for a drug under this provision does not extend to OTC drugs.[139] As FDA has explained, "Section 505(o)(4) ***does not***

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[137] *See* FDA, Response from Patrizia Cavazzoni, Dir., Center for Drug Evaluation and Research to Nancy E. Taylor, Greenberg Traurig, Dkt. No. FDA-2022-P-0896 (May 2, 2023), https://www.regulations.gov/document/FDA-2022-P-0896-0005; *see also* Consumer Healthcare Products Association's (CHPA) Comment to Greenberg Traurig Citizen Petition, Dkt. No. FDA-2022-P-0896 (Aug. 10, 2022), https://www.regulations.gov/comment/FDA-2022-P-0896-0003 ("Rather than responding to this Citizen Petition, CHPA recommends FDA follow the processes established under the OTC Monograph User Fee Act of 2020 (OMUFA). Under this new process, FDA can update rules for OTC drug products regulated under the Monograph system.").

[138] 21 C.F.R. § 201.63(b).

[139] *See* 21 U.S.C. § 355(o)(2) (defining "responsible person" to be the holder of a "covered application" and defining "covered application" to be limited to prescription drugs subject to 21 U.S.C. §353(b)).

apply to nonprescription (over-the-counter) drugs approved under an NDA or ANDA or to marketed unapproved drugs."[140]

Finally, the proposed labeling changes should be rejected as they would intervene in the practice of medicine. The law is long settled that FDA lacks authority to regulate the practice of medicine. As the Supreme Court recently has reaffirmed, "States have traditionally exercised primary responsibility over 'matters of health and safety,' including the regulation of the practice of medicine."[141] As such, "direct control of medical practice in the States is beyond the power of the Federal Government."[142] Here, the proposed labeling change directs: "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." Likewise, the proposed labeling recommends that "Pregnant women should only take acetaminophen if, in consultation with her doctor, she determines it is strictly necessary." But, as the Fifth Circuit has explained, FDA has no authority to "endorse, denounce, or advise" consumers to take or avoid particular drugs,[143] or to substitute its judgment for that of a trained healthcare provider, because FDA is not "a healthcare professional responsible for a patient's care."[144]

FDA should deny the Citizen Petition. Acceptance of Petitioner's requests would be contrary to and unsupported by existing scientific evidence, and would constitute a marked and fundamental departure from existing policy regarding acetaminophen use during pregnancy. As such, to do so would be arbitrary and capricious, and as a result, is unlawful. In addition, procedurally, FDA would not be able to modify the labeling for acetaminophen merely by responding to the Citizen Petition, without undergoing the administrative order process established by Congress in section 505G(b). Moreover, FDA cannot modify the labeling for acetaminophen under section 505(o)(4) as the Petitioner requests.

CONCLUSION

For these reasons, the Citizen Petition should be denied. Kenvue has continuously evaluated the science on acetaminophen use in pregnancy and neurodevelopmental disorders and has found no causal association. FDA, leading health authorities, and medical organizations around the world have independently reviewed this topic and have reached this same conclusion on multiple occasions. The current warning—which directs pregnant women to consult their health

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[140] FDA, *Guidance for Industry, Safety Labeling Changes – Implementation of Section 505(o)(4) of the [Food, Drug, and Cosmetic] Act* at 2 (September 2025), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-labeling-changes-implementation-section-505o4-federal-food-drug-and-cosmetic-act (emphasis in original).

[141] *See Medina v. Planned Parenthood South Atlantic*, 145 S. Ct. 2219, 2227 (2025).

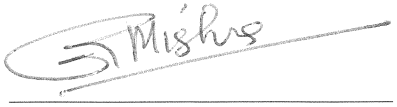
[142] *See Linder v. United States*, 268 U.S. 5, 18 (1925); *see also Medina*, 145 S. Ct. at 2227 (citing *Linder*); *Apter v. Dep't of Health & Hum. Servs.*, 80 F.4th 579, 589 (5th Cir. 2023) (explaining that FDA has no authority to "endorse, denounce, or advise" consumers to take or avoid particular medications); *cf. Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (ruling that FDA may not "intrud[e] upon decisions statutorily committed to the discretion of health care professionals."); *Louisiana Pub. Serv. Comm'n v. F.C.C.*, 476 U.S. 355, 357 (1986) (ruling that an "agency literally has no power to act . . . unless and until Congress confers power upon it").

[143] *See Apter v. Dep't of Health & Hum. Servs.*, 80 F.4th 579, 589 (5th Cir. 2023).

[144] *Noel v. Bayer Corp.*, 481 F. Supp. 3d 1111, 1121 (D. Mont. 2020) (citing *Conklin v. Medtronic, Inc.*, 431 P.3d 571, 577 (Ariz. 2018) ("The FDA is not a health care provider and does not prescribe anything for patients.")).

professionals before use—is the most conservative and appropriate approach based on the current scientific evidence and in the interest of public health.

Respectfully submitted,



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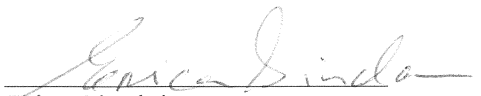

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APPENDIX A

Paragraph in Citizen Petition	Kenvue's Response
Paragraph 10: "The majority of these studies reported statistically significant associations between frequent or prolonged prenatal acetaminophen use and later diagnoses or symptoms consistent with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). These findings are consistent across diverse populations, study designs, and geographic regions."[145]	• The majority of studies assessing ASD diagnosis do not report a statistically significant increased risk after adjusting for relevant confounders (Ji et al. 2018, Saunders et al. 2019, Mkhitaryan et al. 2024, Ahlqvist et al. 2024, and Okubo et al. 2025).[146] • There are twelve studies that assess the relationship between maternal use of acetaminophen and diagnosed ADHD. The studies reporting a positive association, however, have significant limitations (e.g., internally inconsistent data, insufficient adjustment for key confounders such as indication of use and genetics/familial factors, exposure assessment derived from data of uncertain relevance to maternal acetaminophen use, and small samples sizes). Similar to the literature assessing ASD, the most methodologically robust studies provided evidence the reported associations were due to confounding. (Gustavson 2021, Ahlqvist 2024, and Okubo 2025).[147] • While several studies assessing symptoms associated with ADHD or ASD report at least one statistically significant result, the studies are highly inconsistent. For example: o Tronnes et al. 2020 reported no statistically significant results at all for communication problems assessed by the Ages and Stages Questionnaire ("ASQ") or externalizing problems assessed by the Child Behavior Checklist ("CBCL"),[148] whereas Brandlistuen et al. 2013 found significant associations in the same domains.[149] o Vlenterie et al. 2016 found a significant association between acetaminophen use and motor milestone delay, but no associations with any other behavioral or temperamental problems as measured by the ASQ.[150]

[145] *See* Citizen Petition, *supra* note 1, at 4.
[146] *See generally* Ji et al., *supra* note 81; Saunders et al., *supra* note 81; Mkhitaryan et al., *supra* note 81; Ahlqvist et al., *supra* note 24; Okubo et al., *supra* note 67. Ji et al. 2020 as well, after accounting for the flaw in exposure data and using the supplemental table that adjusts for maternal ADHD, depression, and anxiety. *See generally* Ji et al., *supra* note 82.
[147] *See generally* Gustavson et al., *supra* note 84; Ahlqvist et al., *supra* note 24; Okubo et al., *supra* note 67.
[148] *See generally* Johanne N. Tronnes et al., *Prenatal Paracetamol Exposure and Neurodevelopmental Outcomes in Preschool-Aged Children*, 34 PEDIATRIC & PERINATAL EPIDEMIOLOGY 246 (2020).
[149] *See generally* Brandlistuen et al., *supra* note 85.
[150] *See generally* Richelle Vlenterie et al., *Neurodevelopmental Problems at 18 Months Among Children Exposed to Paracetamol* In Utero*: A Propensity Score Matched Cohort Study*, 45 INT'L J. EPIDEMIOLOGY 1998 (2016).

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	○ Tovo-Rodrigues et al. 2020 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 suggest a protective effect.[151] ○ Liew et al. 2016 found one statistically significant association among 36 reported outcomes. Some of the reported outcomes in that study had risk ratios below 1, and all but one were statistically insignificant.[152] ○ Several studies (Avella-Garcia et al. 2016, Parker et al. 2020, Thompson et al. 2014) found different results depending on who administered the questionnaire.[153]
Paragraph 11: "A 2018 meta-analysis by Masarwa et al. (2018) pooled seven cohort studies and found a relative risk (RR) of 1.34 (95% CI: 1.21–1.47) for ADHD and 1.19 (95% CI: 1.14–1.25) for ASD. Similarly, Gou et al. (2019) found a similar association, with an ADHD RR of 1.25 (95% CI: 1.17–1.34) in prenatal exposure groups."[154]	• The authors of Masarwa et al. 2018[155] performed a subsequent study, Masarwa et al 2020,[156] to assess bias and concluded that their "[b]ias analysis suggests that the previously reported association between acetaminophen use during pregnancy and an increased risk of ADHD in the offspring may be due to unmeasured confounding." • The Gou et al 2019 authors caution against concluding that this association is causal, "because potentially unidentified or inadequately controlled confounding factors in the included studies may have unpredictable effects on the observed association."[157]

[151] *See generally* Luciana Tovo-Rodrigues, *Low Neurodevelopmental Performance and Behavioural/Emotional Problems at 24 and 48 Months in Brazilian Children Exposed to Acetaminophen During Foetal Development*, 34 PEDIATRIC & PERINATAL EPIDEMIOLOGY 278 (2020).
[152] *See generally* Liew et al., *supra* note 82.
[153] *See generally* Claudia B. Avella-Garcia et al., *Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Functions and Autism Spectrum Symptoms*, 45 INT'L J. EPIDEMIOLOGY 1987 (2016); Samantha E. Parker et al., *Maternal Acetaminophen Use During Pregnancy and Childhood Behavioural Problems: Discrepancies Between Mother- and Teacher-Reported Outcomes*, 34 PEDIATRIC & PRENATAL EPIDEMIOLOGY 299 (2020); John M. D. Thompson et al., *Associations Between Acetaminophen Use During Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years*, PLOS ONE, Sept. 2014.
[154] *See* Citizen Petition, *supra* note 1, at 5.
[155] *See generally* Reem 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 of Cohort Studies*, 187 AM. J. EPIDEMIOLOGY 1817 (2018).
[156] *See generally* Reem Masarwa, *Acetaminophen Use During Pregnancy and the Risk of Attention Deficit Hyperactivity Disorder: A Causal Association or Bias?*, 34 PEDIATRIC & PERINATAL EPIDEMIOLOGY 309 (2020).
[157] *See generally* Xiaoyun Gou et al., *Association of Maternal Prenatal Acetaminophen Use with the Risk of Attention Deficit/Hyperactivity Disorder in Offspring: A Meta-Analysis*, 53 AUSTRALIAN & NEW ZEALAND J. PSYCHIATRY 195 (2019).

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Paragraph 12: "Sznajder et al. (2022) identified a statistically significant association between acetaminophen exposure and attention and sleep problems in children at age 3. Theunissen et al. (2022) reported elevated depressive symptoms in 8-year-olds with prenatal exposure to acetaminophen."[158]	• As to Sznajder et al. 2022, the usefulness of the results of the study is limited by likely reporting bias with respect to exposure reporting, as the mothers studied were only asked once (at week 35 of gestation) about acetaminophen use.[159] In addition, the outcome measure is based on CBCL parent report, not a clinical diagnostic assessment of ASD or ADHD. • While Sznajder et al. 2022 does report an increased risk for "attention problems and sleep problems," these results are inconsistent with other studies that utilized the CBCL as an outcome measurement.[160] • As to Theunissen et al. 2022, the study has limited relevance to ASD/ADHD, and with regard to depression, must be replicated with more robust information on relevant confounders.[161] Notably, the study authors admit, "no previous study has directly examined the effects of prenatal [acetaminophen] use and depressive symptoms in children" and the effect sizes were "modest."
Paragraph 13: "Importantly, several of these studies relied on biomarkers such as cord blood and meconium samples to objectively verify exposure and reduce the risk of	• First and foremost, the citation for this statement is Brandlistuen et al. 2013, which is not a biomarker study. • Presuming that the biomarker studies Petitioner intends to refer to are the Ji et al. 2020[163] and Baker et al. 2020,[164] in its July 15, 2022 review, FDA stated that "[a]lthough the use of direct measures of APAP levels is a novel contribution to the literature in this area, the

[158] *See* Citizen Petition, *supra* note 1, at 5.
[159] *See generally* Kristin K. Sznajder et al., *Maternal Use of Acetaminophen During Pregnancy and Neurobehavioral Problems in Offspring at 3 Years: A Prospective Cohort Study*, PLOS ONE, Sept. 2022.
[160] *See, e.g.,* Woodbury et al. 2024 (finding that of the twenty exposures and outcomes assessed, the only significant associations were for externalizing problems in the second trimester and total problems score in the second trimester); Sznajder et al. 2022 (finding significant associations for two of seven CBCL items assessed (attention problems aOR 1.23, 95% CI 1.01, 1.51); (aggressive behavior aOR 1.21, 95% CI 1.01, 1.45)); Tronnes et al. 2020 (evaluating CBCL items with two aggregated subscales to measure externalizing and with 3 aggregated subscales to measure internalizing and finding one significant association for internalizing problems was reported for acetaminophen use in all three trimesters. No association was reported for one trimester or two trimesters of use.); Tovo-Rodrigues et al. 2020 (finding no associations were reported for 8 CBCL items assessed and no associations were reported for two measures aggregating these items (externalizing and internalizing) or totaling all items at 48 months in adjusted models); Parker et al. 2020 (finding associations were reported when adjusted for indication or illness); Vlenterie et al. 2016 (finding no associations were present for short term use and no associations were present for nine of 10 CBCL items assessed for greater than 28 days of acetaminophen exposure. Only significant association was for "motor milestone.").
[161] Gisela Theunissen et al., *Prenatal Determinants of Depressive Symptoms in Childhood: Evidence from* Growing Up in New Zealand, 302 J. AFFECTIVE DISORDERS 41 (2022).
[163] *See generally* Ji et al., *supra* note 82.
[164] *See generally* Brennan H. Baker et al*., supra* note 83.

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recall bias inherent in self-reported data. These studies continued to demonstrate consistent associates between verified exposure and adverse behavioral or cognitive outcomes in children."[162]	measurement methods in the studies reviewed do not reflect APAP exposure throughout pregnancy and may not be valid[.]" • These studies also suffer from numerous limitations, including insufficiently accounting for confounding by indication of use and genetics/familial factors.
Paragraph 14: "A critical threshold in establishing causality is the presence of a dose-response pattern—and multiple studies precisely demonstrate that. Risk appears to increase with higher cumulative exposure across multiple trimesters."[165]	• Liew et al. 2014[166] has insufficient data on key confounders and does not have actual data on dose—exposure was measured by trimesters of use and weeks of use. Additionally, this analysis ignores the results from more recent studies that saw associations for the highest users attenuate to the null after a sibling control analysis (Gustavson et al. 2021, Ahlqvist et al. 2024, and Okubo et al. 2025).[167]
Paragraph 15: "Brandlistuen et al. (2013) found that children exposed to acetaminophen for more than twenty-eight days during pregnancy had a significantly increased risk of developing ADHD-like behaviors compared to unexposed siblings"[168]	• The authors note, however, that "because clinical assessments with diagnostic tools were not available in this study, we could not determine the clinical importance of the difference observed. Future studies should seek to include clinical diagnoses of neurodevelopmental and behavioural diagnoses, to explore whether there is an increased risk of, for example, attention deficit hyperactivity disorder (ADHD) or language disorders after exposure to long-term paracetamol use during pregnancy."[169] • Following their own recommendation, several authors from this team conducted a similar study, Gustavson et al. 2021, using the same cohort, but with diagnosis for ADHD. There, the increased risk of 2.02 for greater than 28 days of use was attenuated to 1.06 and no longer statistically significant after a sibling control analysis.[170]

[162] *See* Citizen Petition, *supra* note 1, at 5.
[165] *See* Citizen Petition, *supra* note 1, at 5.
[166] *See generally* Liew et al., *supra* note 83.
[167] *See generally* Gustavson et al., *supra* note 84; Ahlqvist et al., *supra* note 24; Okubo et al., *supra* note 67.
[168] Citizen Petition, *supra* note 1, at 6.
[169] *See generally* Brandlistuen et al., *supra* note 85.
[170] *See generally* Gustavson et al., *supra* note 84.

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Paragraph 16(b): "[Acetaminophen] induces oxidative stress and depletes fetal glutathione, a key antioxidant required during brain development."[171]	• Oxidation is one of the three pathways by which the liver metabolizes acetaminophen. The others, glucuronidation and sulfation, are responsible for processing 85–95% of acetaminophen. • Through oxidation, CYP2E1 reacts with acetaminophen forms the metabolite N-acetyl-p-benzoquinone imine (NAPQI). At therapeutic levels, NAPQI generally is harmless, as the body contains an antioxidant (glutathione) that immediately neutralizes it. High, non-therapeutic levels, however, can result in excess NAPQI that can deplete glutathione levels and lead to oxidative stress and potential liver cell injury. • There is no evidence that NAPQI can be formed in the human brain at sufficient levels—if any—to cause oxidative stress. Scientific research and reputable databases such as the Human Protein Atlas confirm that CYP2E1 levels in the brain are non-existent to one thousand times less than the CYP2E1 concentration of the liver; the human brain therefore has little to no capacity to form NAPQI. But the human brain's glutathione concentration levels, on the other hand, are fairly comparable to those in the liver. Based on this CYP2E1-to-glutathione ratio, the brain has far lower (or no) capacity to produce NAPQI and high capacity to neutralize whatever negligible NAPQI could form in the brain, if any. • As a result, the brain cannot produce NAPQI at sufficient levels, if any, to cause oxidative stress or otherwise cause neurotoxicity. This was confirmed in Ali et al. 2025,[172] which found that glutathione was not depleted in mouse brains, even when the mice were exposed to high, hepatotoxic levels of acetaminophen. Likewise, studies such as Klein et al. 2020[173] and Rigobello et al. 2021[174] have confirmed that prenatal doses of acetaminophen do not result in reduced levels of glutathione in the rodent brain.
Paragraph 16(c): "[Acetaminophen] interferes with prostaglandin signaling and	• The sources the Petitioner cites do not provide affirmative evidence for this proposed mechanism. For example, Dean et al. 2012 is an unreplicated study of twelve rats that found higher spinophilin levels in those exposed to acetaminophen, but with no

[171] Citizen Petition, *supra* note 1, at 6.
[172] *See generally* Nyera A. Ali et al., *NAPQI Is Absent in the Mouse Brain After Sub-Hepatotoxic and Hepatotoxic Doses of Acetaminophen*, 205 TOXICOLOGICAL SCIS. 274 (2025).
[173] *See generally* Rodrigo Moreno Klein et al., *Gestational Exposure to Paracetamol in Rats Induces Neurofunctional Alterations in the Progeny*, 77 NEUROTOXICOLOGY & TERATOLOGY (2020).
[174] *See generally* Camila Rigobello et al., *Perinatal Exposure to Paracetamol: Dose and Sex-Dependent Effects in Behaviour and Brain's Oxidative Stress Markers in Progeny*, 408 BEHAVIOURAL BRAIN RSCH. (2021).

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pregnancy hormone regulation—both critical to healthy neurodevelopment."[175]	explanation or rationale as to how higher spinophilin levels are relevant to ASD or ADHD. [176] • Additionally, other analgesics and antipyretics likely have similar effects on prostaglandins, but they are not associated with neurodevelopmental injuries, further undermining this proposed mechanism.
Paragraph 16(d): "[Acetaminophen] disrupts neurotransmitter systems, particularly dopamine and serotonin."	• There is no reliable evidence that acetaminophen results in the described effects.
Paragraph 16(e): "[Acetaminophen] induces epigenetic modifications, changing gene expression patterns necessary for fetal brain maturation."[177]	• None of the studies (Gervin et al. 2017, Eslamimehr et al. 2022, and Spildrejorde et al. 2022) that could plausibly explain the potential epigenetic effect of acetaminophen have been replicated.[178] When the study authors attempted to replicate Gervin et al. 2017 by increasing the sample numbers, they observed no impact by acetaminophen and explicitly stated that they "did not replicate [their] previous results."
Paragraph 17: "Animal studies further support the potential for acetaminophen to interfere with neurodevelopment."[179] Viberg et al. (2014) found that neonatal mice exposed to acetaminophen exhibited impaired spatial	• Animal studies on neurodevelopment have limited clinical applicability. Animals cannot be given the uniquely human diagnosis of ASD or ADHD, even if one were to identify multiple behavioral changes that have so-called face validity for ASD or ADHD. • Despite numerous subsequent studies examining these types of outcomes,[182] their results have rarely been replicated and are inconsistent with other subsequent studies. For example, studies that employed the open field test (to measure locomotor activity) reported

[175] Citizen Petition, *supra* note 1, at 6.
[176] *See generally* Shannon L. Dean et al., *Prostaglandin E2 Is an Endogenous Modulator of Cerebellar Development and Complex Behavior During a Sensitive Period*, 35 EUROPEAN J. NEUROSCIENCE 1218 (2012).
[177] *See* Citizen Petition, *supra* note 1, at 6.
[178] *See generally* Kristina Gervin et al., *Long-Term Prenatal Exposure to Paracetamol Is Associated with DNA Methylation Differences in Children Diagnosed with ADHD*, 9 CLINICAL EPIGENETICS (2017); Shakiba Eslamimehr et al., *Association of Prenatal Acetaminophen Use and Acetaminophen Metabolites with DNA Methylation of Newborns: Analysis of Two Consecutive Generations of the Isle of Wight Birth Cohort*, 8 ENV'T EPIGENETICS (2022); Mari Spildrejorde et al., *Multi-omics Approach Reveals Dysregulated Genes During hESCs Neuronal Differentiation Exposure to Paracetamol*, ISCIENCE, Oct. 2023.
[179] Citizen Petition, *supra* note 1, at 6.
[182] *Id.* at 7 ("Viberg et al. (2014) found that neonatal mice exposed to acetaminophen exhibited impaired spatial learning and altered locomotor activity.").

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learning and altered locomotor activity. Blecharz-Klin et al. (2015) reported neurotransmitter changes and behavioral alterations in rats following perinatal exposure.[180] Isling et al. (2014) identified neurodevelopmental disruption in rodent models exposed to endocrine-disrupting chemical mixtures that included acetaminophen. These findings, while preclinical, align with the biological mechanisms described above and further establish a biologically plausible pattern of	no effect (Dean et al. 2012, Harshaw and Warner 2022),[183] a reduced effect (Saeedan et al. 2018, Rigobello et al. 2021, Baker et al. 2023),[184] or internally inconsistent results (Klein et al. 2020, Philippot et al. 2018, Philippot et al. 2022).[185] • The Thompson 2016 Memo cited in the Citizen Petition noted that these findings are "limited in their ability to address the question at hand" because (1) "the study design did not incorporate prenatal exposure or exposure of juvenile animals of ages corresponding to human prenatal exposure"; (2) "the justification for the selected dose levels was not adequate, given that the administered dose appeared to be less than maximal based on typical BSA [body surface area] scaling factors and approved dosing levels for APAP in children under 12 years"; and (3) "the animal numbers employed and the endpoints evaluated in the study design were not adequate in comparison with Agency guidance for pre-/postnatal and juvenile animal study designs."[186] • The citation to Blecharz-Klin et al. 2015[187] refers to two different publications from the same team in 2015, discussed in parallel in the Thompson 2016 Memo. The Thompson 2016 Memo comments that "the clinical relevance of these findings is unclear." Both studies (and all of the Blecharz-Klin series of studies) dosed the animals well into adulthood to postnatal day 60, and then immediately conducted the testing on day 60,

[180] Based on the citations in the Citizen Petition, this collectively refers to two different 2015 studies by Blecharz-Klin et al., discussed below.

[183] *See generally* Dean et al., *supra* note 176; Christopher Harshaw & Anna G. Warner, *Interleukin-1β-Induced Inflammation and Acetaminophen During Infancy: Distinct and Interactive Effects on Social-Emotional and Repetitive Behavior in C57BL/6J Mice*, 22 PHARMACOLOGY, BIOCHEMISTRY & BEHAVIOR (2022).

[184] *See generally* Abdulaziz S. Saeedan et al., *Effect of Early Natal Supplementation of Paracetamol on Attenuation of Exotoxin/Endotoxin Induced Pyrexia and Precipitation of Autistic Like Features in Albino Rats*, 26 INFLAMMOPHARMACOLOGY 951 (2018); Rigobello et al., *supra* note 174; Brennan H. Baker et al., *Sex-Specific Neurobehavioral and Prefrontal Cortex Gene Expression Alterations Following Developmental Acetaminophen Exposure in Mice*, 177 NEUROBIOLOGY OF DISEASE (2023).

[185] *See generally* Klein et al., *supra* note 173; Gaetan Philippot et al., *A Cannabinoid Receptor Type 1 (CB1R) Agonist Enhances the Developmental Neurotoxicity of Acetaminophen (Paracetamol)*, 166 TOXICOLOGICAL SCIS. 203 (2018); Gaetan Philippot et al., *Paracetamol (Acetaminophen) and Its Effect on the Developing Mouse Brain*, FRONTIERS IN TOXICOLOGY, Mar. 2022. Viberg et al. 2014 also reported diminished spatial learning in exposed animals, after reaching adulthood. This finding has never been replicated. Additionally, it is not a common test used for attempting to model autism in rodents. *See generally* Henrik Viberg et al., *Paracetamol (Acetaminophen) Administration During Neonatal Brain Development Affects Cognitive Function and Alters Its Analgesic and Anxiolytic Response in Adult Male Mice*, 138 TOXICOLOGICAL SCIS. 139 (2014). The authors reported no effect at the low dose and no effect in females, but reported increased errors and total time to complete the maze for males at the high dose only. Viberg et al. 2014 contrasts with the findings of Blecharz-Klin et al. 2017, which found no evidence of altered special learning, except increased spatial learning among those exposed to low-dose acetaminophen.

[186] *See generally* Memorandum to File by D. Charles Thompson, Division of Nonprescription Drug Products (Feb. 8, 2016).

[187] *See* Citizen Petition, *supra* note 1, at 7 ("Blecharz-Klin et al. (2015) reported neurotransmitter changes and behavioral alterations in rats following perinatal exposure.").

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harm, strengthening the case for regulatory precaution."[181]	rendering it impossible to determine whether any effects were due to adult dosing close in time to the testing. The 2015a study ("Effect of prenatal and early life paracetamol exposure on the level of neurotransmitters in rats—Focus on the spinal cord") reported increased spinal cord levels of certain amino acids that have not been reported to have anything to do with ASD, but it also reported a multitude of negative findings that cut against the proposed mechanisms of action, including no changes in levels of Taurine, Alanine, GABA, Histidine, Noradrenaline, DOPAC, DOPAC/DA, HVA (at the higher dose),[188] HVA/DA, 3-MT/DA, 5-HT, and 5-HIAA/5-HT.[189] The 2015b study ("Developmental exposure to paracetamol causes biochemical alterations in medulla oblongata") reported decreased monoamines (neurotransmitters such as dopamine, norepinephrine, and serotonin) in the medulla oblongata in rat subjects.[190] Nine out of 22 endpoints were statistically significant, though some reported increases and others reported decreases, with no clear clinical relevance. Other rodent studies, including others by the Blecharz-Klin team, reported contradictory results for those same monoamines. • Isling et al. 2014[191] ("neurodevelopmental disruption in rodent models exposed to endocrine-disrupting chemical mixtures that included acetaminophen") did not isolate the effects of acetaminophen (versus the other eight or twelve chemicals in the cocktails), nor did it examine neurodevelopmental outcomes.[192] The Isling authors dosed two groups of rats with "a mixture of 13 anti-androgenic and estrogenic chemicals including phthalates, pesticides, u.v.-filters, bisphenol A, parabens, and the drug paracetamol [acetaminophen]," with another two groups with a mixture of nine anti-androgenic chemicals including acetaminophen. Among other non-neurodevelopmental changes, they reported changes in reproductive traits and increased rates of pituitary tumors and pituitary adenoma in the high-dose groups. The authors reported that "[m]ost of the observed effects only reached statistical significance in the [two high-dose groups]." The Thompson 2016 memo rejected

[181] *See* Citizen Petition, *supra* note 1, at 7.
[188] Changes at a low dose but not at a high dose contradict the presence of a dose-response and therefore indicate a risk of false positives.
[189] *See generally* Kamilla Blecharz-Klin et al., *Effect of Prenatal and Early Life Paracetamol Exposure on the Level of Neurotransmitters in Rats—Focus on the Spinal Cord*, 47 INT'L J. DEV. NEUROSCI. 133 (2015).
[190] *See generally* Kamilla Blecharz-Klin et al., *Developmental Exposure to Paracetamol Causes Biochemical Alterations in Medulla Oblongata*, 40 ENV'T TOXICOLOGY & PHARMACOLOGY 369 (2015).
[191] *See* Citizen Petition, *supra* note 1, at 7 ("Isling et al. (2014) identified neurodevelopmental disruption in rodent models exposed to endocrine-disrupting chemical mixtures that included acetaminophen.").
[192] *See generally* Louise Krag Isling et al., *Late-Life Effects on Rat Reproductive System After Developmental Exposure to Mixtures of Endocrine Disrupters*, 147 REPRODUCTION 465 (2014).

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	this study as irrelevant: "the study design employed does not address the potential for any association between prenatal exposure to APAP and development of ADHD in offspring."
Paragraph 25: "On October 14, 2016, DEPI-I completed a review of eight observational studies and concluded that seven of the eight showed some association with adverse neurodevelopmental outcomes. The authors recommended that FDA bring this issue to the attention of consumers and healthcare providers. Yet, FDA took no action."[193]	• In conjunction with this review, several different divisions at FDA also prepared their own reviews of the relevant literature—a maternal health memorandum by the Division of Pediatric and Maternal Health ("DPMH") signed on April 7, 2017, a February 10, 2017 memorandum of consultation by the Division of Bone, Reproductive, and Urologic Products ("DBRUP"), and a December 4, 2017 review of nonclinical published literature by the Division of Nonprescription Drug Products ("DNDP"). • After considering each division's positions and recommendations, the Medical Policy and Program Review Council determined that a revised label was not appropriate. o *"The nonclinical teams from DNDP and DAAAP [Division of Anesthesiology, Addiction Medicine, and Pain Medicine] presented options for nonclinical testing, in addition to concerns raised by the NAS. A decision was made to take this issue before the OND Medical Policy Team. This meeting is currently scheduled for 24 January 2018."*
Paragraph 26: "On January 24, 2018, a presentation was given to the Medical Policy and Program Review Council (MPPRC), discussing a broad review of twelve observational studies. Eleven of the twelve studies reported associations between prenatal acetaminophen exposure and adverse neurodevelopmental outcomes, including delays in language and motor development, and increased symptoms of ADHD and ASD. Despite the growing consistency of findings,	• The MPPRC did not conclude the findings of the observational studies were consistent, nor was this the extent of the MPPRC's involvement in this issue. On October 3, 2018, the MPPRC recommended the following: o "The Council agreed with the Division and did not suggest making labeling changes." o "[G]iven the uncertainty as to whether there is a causal association, issuing a communication at present would not add substantively to the prior DSC that counseled caution in use of any pain medication dining pregnancy." o The MPPRC recommended that the teams involved in managing TSI-1355 come back to the MPPRC with a proposal for additional analyses or studies and further requested that they return within six months to update the Council.

[193] Citizen Petition, *supra* note 1, at 8.

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FDA again chose not to update labeling, citing the need for stronger causal evidence."[194]	
Paragraph 27: "On January 7, 2019, FDA's Division of Epidemiology I (DEPI-I) issued a focused internal review evaluating the association between prenatal acetaminophen exposure and male urogenital abnormalities, including hypospadias, cryptorchidism, anogenital distance, and penile width. Several of the reviewed studies identified statistically significant associations with acetaminophen use during specific windows of pregnancy, particularly between gestational weeks eight and twenty-two. The review acknowledged the possibility of residual confounding variables due to the observational nature of the data but emphasized that biological plausibility was supported by toxicological evidence of endocrine-disrupting effects. The reviewers concluded that 'use during pregnancy is not necessarily free of risk to the fetus' and recommended that	• This review does not relate to neurodevelopmental disorders.

[194] *Id.*

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FDA consider communicating this message to healthcare providers and pregnant women."[195]	
Paragraph 28: "On May 1, 2020, an integrated review memorandum by the Division of Non-Prescription Drugs 1 (DNPD 1) revealed that FDA's National Center for Toxicological Research (NCTR) hypothesized that 'the adverse neurodevelopmental effects, if present, could be the result of constriction of the ductus arteriosus (thereby altering fetal blood flow and potentially impacting neuronal development).' The agency still declined to issue new labeling requirements."[196]	• This excerpt from the May 1, 2020 Integrated Review Memorandum is missing critical context, which establishes this hypothesis was based on an animal study, and which the MPPRC suggested was unreliable due to differences in peak periods of brain development across species.
Paragraph 30: "On March 10, 2023, the most recent FDA literature review evaluated three additional epidemiological studies. Two of the studies reinforced earlier concerns about neurodevelopmental impacts, including attention problems and depressive symptoms in early	• This is not FDA's most recent literature review. FDA's most recent literature review is dated May 27, 2025, wherein FDA reviewed observational studies published since its prior review and again concluded the literature prohibits a causal interpretation.

[195] *Id.* at 9.
[196] *Id.*

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childhood. Nevertheless, the agency concluded that the evidence of causality was still insufficient to warrant a label change."[197]	
Paragraph 31: "In 2018, the European Medicines Agency ('EMA') required updated product labeling for paracetamol to acknowledge the uncertain but concerning data regarding neurodevelopmental harm. The EMA advised caution during pregnancy and emphasized the need for further investigation—an action the FDA has not yet mirrored, despite reviewing the same evidence."[198]	• As noted above in Section I.A., FDA considered and rejected this approach.
Paragraph 32: "In 2021, an international group of ninety-one scientists, clinicians, and public health experts published a consensus statement in Nature Reviews Endocrinology calling for precautionary labeling and increased awareness regarding acetaminophen use during pregnancy.41 The authors concluded that growing evidence,	• Following the 2021 Nature Review article (the "consensus statement"), a number of highly-regarded international societies published statements refuting its claims: o September 2021 American College of Obstetricians and Gynecologists' ("ACOG") Response to Consensus Statement on Paracetamol Use During Pregnancy: *"*This consensus statement, and studies that have been conducted in the past, show no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any trimester and fetal developmental issues. . . . ACOG's clinical guidance remains the same and physicians should not change clinical practice until definitive prospective research is done. Most importantly, patients should not be frightened away from the many benefits of acetaminophen." [200] o October 4, 2021 European Network of Teratology Information Services' ("ENTIS") Official Position Statement: "ENTIS holds the position that the evidence supporting

[197] *Id.*
[198] *Id.* at 9-10.
[200] *ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy*, *supra* note 90.

Paragraph in Citizen Petition	Kenvue's Response
from both animal and human studies, supports the potential for neurodevelopmental, urogenital, and reproductive harm. They urged regulators and medical societies to update existing guidance and stated that pregnant women should forego acetaminophen use unless medically indicated and should minimize exposure by using the lowest effective dose for the shortest possible time."[199]	an increased risk of untoward fetal effects and childhood neurodevelopment, including ASD & ADHD following in utero exposure to paracetamol (acetaminophen) is weak, inconsistent and to a large extent fundamentally flawed."[201] ○ November 8, 2021 statement on the use of acetaminophen for analgesia and fever in pregnancy by the Society of Obstetricians and Gynaecologists of Canada ("SOGC"): "The position of SOGC, and a number of other international societies, is that the evidence for causality for this claim is weak and has many fundamental flaws. The SOGC recommends the use of acetaminophen as a first-line therapeutic option for fever and pain in pregnancy when medically indicated at recommended doses for the shortest duration required."[202] • The academic community also published two "consensus counterstatements" in response: ○ "Paracetamol use in pregnancy — caution over causal inference from available data" (Alwan 2022), which was "supported by 50 scientists, clinicians, epidemiologists and teratology information specialists affiliated with the Organization of Teratology Information Specialists and/or other partner organizations." ○ "Paracetamol use in pregnancy — neglecting context promotes misinterpretation" (O'Sullivan 2022), which was "signed by 16 organizations and 63 individual researchers and clinicians." The signatory organizations included International Federation of Obstetrics and Gynaecology, European Association of Perinatal Medicine, Royal College of Obstetricians and Gynaecologists (UK), American College of Obstetricians and Gynaecologists, and Society of Obstetricians and Gynaecologists of Canada. • The 2021 Nature Review article authors themselves expressly stated in a follow-on statement that:

[199] Citizen Petition, *supra* note 1, at 10.

[201] *OFFICIAL ENTIS POSITION STATEMENT: Paracetamol (acetaminophen, APAP) Use in Pregnancy*, EUROPEAN NETWORK OF TERATOLOGY INFORMATION SERVS. (Oct. 4, 2021), https://www.entis-org.eu/entis-news/official-entis-position-statement-paracetamol-acetaminophen-apap-use-in-pregnancy#:~:text=ENTIS%20holds%20the%20position%20that%20paracetamol%20%28acetaminophen%29%20is,lowest%20dose%20and%20for%20the%20shortest%20possible%20duration.

[202] Jamie R. Hutson, Graeme N. Smith, Elisabeth Codsi & Facundo Garcia-Bournissen, *Statement on the Use of Acetaminophen for Analgesia and Fever in Pregnancy*, SOGC.ORG (Nov. 8, 2021), https://sogc.org/en/en/content/featured-news/Statement_on_the_use_of_acetaminophen.aspx.

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	○ "limitations and uncertainties remain despite the large body of available data, therefore, [they] avoided any inference of causality."[203] • As detailed in Section I.D. above, multiple additional studies have come out since 2021: the most methodologically robust studies, Ahlqvist 2024 and Okubo 2025, reported no association; Mkhitaryan 2024 reported no significant association.

[203] Ann Z. 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 REVS. ENDOCRINOLOGY 192, 192 (2022).