VIA ELECTRONIC FILING

September 22, 2025

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Martin A. Makary, M.D., M.P.H.
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Dear Commissioner Makary,

Enclosed is a Citizen Petition filed by Informed Consent Action Network ("**ICAN**") regarding safety-related labeling changes for the use of over-the-counter acetaminophen-containing drug products during pregnancy. This petition raises exigent concerns that demand your immediate attention.

ICAN looks forward to receiving a timely decision. As counsel to the petitioners, we remain available to answer questions and provide any relevant additional information.

Very truly yours,

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UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION REQUIRING SAFETY-RELATED LABELING CHANGES FOR OVER-THE-COUNTER ACETAMINOPHEN-CONTAINING DRUG PRODUCTS	**:**	**Docket No._____**

CITIZEN PETITION

This petition for administrative action is submitted on behalf of Informed Consent Action Network[1] ("**Petitioner**") pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, to request that the Commissioner of Food and Drugs (the "**Commissioner**") require a labeling change for over-the-counter acetaminophen-containing drug products. Specifically, Petitioner requests that the Warnings for these products be revised to reflect the potential risks of frequent prenatal acetaminophen use on fetal neurodevelopment, including an increased risk of autism spectrum disorder ("**ASD**") and attention-deficit/hyperactivity disorder ("**ADHD**").[2]

Because of the urgent public health implications and the need to ensure that pregnant consumers receive accurate and timely information, **Petitioner respectfully requests that FDA act on the instant Petition forthwith.**

[1] Including, but not limited to, on behalf of its members and employees.

[2] As set forth in this Petition, Petitioner notes that acetaminophen appears to be one of potentially numerous causes of both ASD and ADHD.

A. ACTION REQUESTED

1. It is hereby requested that the Food and Drug Administration ("**FDA**") require revisions to the labeling for all over-the-counter acetaminophen-containing drug products marketed under the Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use monograph (OTC Monograph M013): (i) a revision to the "Warnings" subsection, currently found at M013.50(c)(1)(iii) in the Labeling section; and (ii) a revision to the "Pregnancy" subsection within the "Drug Interactions" subsection currently found at M013.95 in the Professional Labeling section.

2. Petitioner requests that the following warning be added to the "Pregnancy or Breastfeeding" section (as specified in 21 C.F.R. § 201.63(a)) of all such drug products:

> **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.**

3. Petitioner requests that the following warning be added to the "Pregnancy" subsection within the "Drug Interactions" subsection:

> **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**

4. Petitioner further requests that FDA require these labeling changes under its authority to revise drug labeling, 21 U.S.C. § 355(o)(4), to ensure that it accurately reflects known and emerging safety data, including information about potential risks to fetal development associated with the use of acetaminophen during pregnancy.

B. STATEMENT OF GROUNDS

5. Petitioner submits that there is substantial evidence, developed over a decade, demonstrating that prenatal acetaminophen exposure may pose a risk to fetal neurodevelopment. The evidence supporting this position includes:

a. Internal epidemiology and pharmacology reviews conducted by FDA between 2014 and 2023;[3]

[3] See the following FDA internal reviews: Lockwood G. Taylor, *Epidemiology Review of Study on Acetaminophen Use in Pregnancy And Risks of ADHD in Offspring* FDA CDER Office of Pharmacovigilance and Epidemiology (May

b. meta-analyses, and large-scale cohort studies identifying an association between prenatal acetaminophen exposure and neurodevelopmental outcomes, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD);[4]

c. expert reports and causality analyses applying established criteria (e.g., Bradford Hill, Navigation Guide) supports a potential causal relationship;[5]

d. preclinical animal and mechanistic studies that demonstrate biological plausibility;[6] and

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15, 2014), https://archive.org/details/fda-acetaminophen-taylor-2014 [hereinafter Taylor FDA 2014]; Andrew D. Mosholder, *Epidemiology: Review of Published Study - Acetaminophen Use in Pregnancy and ADHD in Offspring,* FDA CDER Office of Pharmacovigilance and Epidemiology (March 18, 2015), https://archive.org/details/fda-acetaminophen-mosholder-2015 [hereinafter Mosholder FDA 2015]; Andrew D. Mosholder, *Epidemiology: Review of Published Study - Neurodevelopmental Outcomes Following Prenatal Acetaminophen Exposure*, FDA CDER Office of Pharmacovigilance and Epidemiology (October 14, 2016), https://archive.org/details/fda-acetaminophen-mosholder-2016 [hereinafter Mosholder FDA 2016]; Andrew D. Mosholder, *Epidemiology: Comparison of Multiple Studies or Literature Review - Urogenital Outcomes with in Utero Acetaminophen Exposure*, FDA CDER Office of Pharmacovigilance and Epidemiology, (January 7, 2019), https://archive.org/details/fda-acetaminophen-mosholder-2019 [hereinafter Mosholder FDA 2019]; Danielle Abraham & Andrew D. Mosholder, *Epidemiology: Review of Published Studies - Functional Neurobehavioral Outcomes and Urogenital Outcomes Associated with Prenatal Acetaminophen Exposure*, FDA CDER Office of Pharmacovigilance and Epidemiology (July 15, 2022), https://archive.org/details/fda-acetaminophen-abraham-2022 [hereinafter Abraham FDA 2022]; Danielle Abraham, *Epidemiology: Literature Review - Updated Literature Review of Studies That Examine the Association Between Acetaminophen Exposure During Pregnancy and Neurobehavioral or Urogenital Outcomes*, FDA CDER Office of Pharmacovigilance and Epidemiology, (March 10, 2023), https://archive.org/details/fda-acetaminophen-abraham-2023 [hereinafter Abraham FDA 2023].

[4] *See* Jong Hwan Kim et al., *Environmental Risk Factors, Protective Factors, and Peripheral Biomarkers for ADHD: An Umbrella Review*, 7 Lancet Psychiatry 955 (Nov. 2020), https://pubmed.ncbi.nlm.nih.gov/33069318; Silvia Alemany et al., *Prenatal and Postnatal Exposure to Acetaminophen in Relation to Autism Spectrum and Attention-Deficit and Hyperactivity Symptoms in Childhood: Meta-Analysis in Six European Population-Based Cohorts*, 36 Eur. J. Epidemiology 993 (May 28, 2021), https://pubmed.ncbi.nlm.nih.gov/34046850; Cristian Ricci et al., *In Utero Acetaminophen Exposure and Child Neurodevelopmental Outcomes: Systematic Review and Meta-Analysis*, Paediatr. & Perinat. Epidemiology (July 2023), https://pubmed.ncbi.nlm.nih.gov/36939050; Eivind Ystrom et al., *Prenatal Exposure to Acetaminophen and Risk of ADHD*, 140 Pediatrics e20163840 (Nov. 2017), https://pubmed.ncbi.nlm.nih.gov/29084830; Yuelong Ji et al., *Association of Cord Plasma Biomarkers of in Utero Acetaminophen Exposure with Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood*, 77 JAMA Psychiatry 180 (2020), https://pubmed.ncbi.nlm.nih.gov/31664451/; Zeyan Liew et al., *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168 JAMA Pediatrics 313 (2014), https://pubmed.ncbi.nlm.nih.gov/24566677.

[5] *See* Andrea Baccarelli, *Expert Report of Andrea Baccarelli, MD, PhD, MPH* (June 23, 2023) https://archive.org/details/baccarelli-expert-report-acetaminophen-asd-adhd [hereinafter Baccarelli Expert Report] (applies both the Bradford Hill criteria and the Navigation Guide methodology, concluding that 8 of 9 Hill factors are met and that acetaminophen is "known to be toxic" with respect to neurodevelopmental disorders). *See also* Robert M. Cabrera, *Expert Report of Robert M. Cabrera, PhD* (June 22, 2023) https://archive.org/details/cabrera-expert-report-acetaminophen [hereinafter Cabrera Expert Report] (applies the Bradford Hill criteria and concludes that therapeutic doses of APAP are sufficient to cause ASD and ADHD). *See also* Haotian Wu, *Export Report of Dr. Haotian Wu, PhD* (February 5, 2025) https://archive.org/details/wu-expert-report-acetaminophen (applies the Bradford Hill criteria and finds the evidence strongly supports a causal association).

[6] *See* Cabrera Expert Report *supra* note 5, at 13-15, 38-67; Brandon Pearson, *Expert Report of Brandon Pearson, MS, PhD* (June 21, 2023) https://archive.org/details/pearson-expert-report-acetaminophen [hereinafter Pearson Expert

e. international regulatory actions, including labeling updates required by the European Medicines Agency (EMA).[7]

6. The collective weight of this evidence supports the need for a labeling amendment that warns consumers of the potential neurodevelopmental risks associated with frequent acetaminophen use during pregnancy. Petition submits that this revision is necessary to fulfill FDA's obligation to protect public health and to ensure that pregnant individuals receive adequate and timely risk information.

7. OTC Monograph M013 was finalized under the CARES Act in 2020. Both before and after that time, FDA has conducted multiple safety reviews of prenatal acetaminophen exposure in response to emerging literature and epidemiological studies. While no labeling change has been implemented to date, FDA's internal assessments reflect an increasingly consistent pattern of concern.

8. Petitioner submits that failure to act on this request will result in irreparable harm to the public. Millions of pregnant individuals use acetaminophen each year without awareness of the emerging safety data. The continued absence of a warning label deprives consumers of the ability to make informed decisions about use during pregnancy and may result in preventable yet catastrophic neurodevelopmental harm to exposed fetuses.

9. Furthermore, granting this petition is undoubtedly in the public's interest. FDA has a responsibility to update drug labeling to reflect known or emerging risks, particularly when use during pregnancy is widespread and alternatives may not be clearly safer. Amending the label to reflect the current body of evidence aligns with FDA's mandate to protect the public health and ensures that consumers are provided with the best available information to guide their decisions.

C. SUMMARY OF EVIDENCE

(i) Epidemiological Evidence

10. Between 2016 and 2022, researchers published more than two dozen epidemiological studies examining the relationship between prenatal acetaminophen exposure and the risk of neurodevelopmental outcomes in children.[8] The majority of these studies reported

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Report]; D. Charles Thompson, FDA, CDER Office of Nonprescription Drugs, *Memorandum to File - TSI 1355: Review of Nonclinical Published Literature* (Feb. 8, 2016) https://archive.org/details/fda-acetaminophen-thompson-2016 [hereinafter Thompson FDA 2016]; and D. Charles Thompson, FDA, CDER Office of Nonprescription Drugs, *Memorandum to File - TSI 1355: Review #2 of Nonclinical Published Literature* (Dec. 4, 2017) https://archive.org/details/fda-acetaminophen-thompson-2017.

[7] *See* European Medicines Agency, Pharmacovigilance Risk Assessment Comm., *PRAC Recommendations on Signals*, EMA/PRAC/157165/2019 (Apr. 8, 2019), https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-12-15-march-2019-prac-meeting_en.pdf (recommending updated product labeling for paracetamol-containing medicines to reflect conflicting epidemiological findings related to potential neurodevelopmental risks).

[8] *See* Abraham FDA 2022, *supra* note 3, at 6-7; Abraham FDA 2023, *supra* note 3, at 6-7 (these reviews evaluated a combined total of 27 epidemiological studies).

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).[9] These findings are consistent across diverse populations, study designs, and geographic regions.[10]

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.[11]

12. Sznajder et al. (2022) identified a statistically significant association between acetaminophen exposure and attention and sleep problems in children at age 3.[12] Theunissen et al. (2022) reported elevated depressive symptoms in 8-year-olds with prenatal exposure to acetaminophen.[13]

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 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.[14]

(ii) Dose-Responsive Relationship

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.[15]

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[9] *See* Abraham FDA 2022, *supra* note 3, at 9-12 (a majority of the studies reviewed reported statistically significant associations between frequent or prolonged prenatal acetaminophen use and later diagnoses or symptoms of attention deficit hyperactivity disorder and autism spectrum disorder).

[10] *See* Abraham FDA 2022, *supra* note 3, at 6-7.

[11] *See* Rami Masarwa et al., *Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies*, 187 Am. J. Epidemiol. 1817, 1817-27 (2018), https://doi.org/10.1093/aje/kwy086; and Xiaoyun Gou et al., *Association of Maternal Prenatal Acetaminophen Use with the Risk of Attention Deficit/Hyperactivity Disorder in Offspring: A Meta-Analysis*, 53 Austl. & N.Z. J. Psychiatry 195 (2019), https://pubmed.ncbi.nlm.nih.gov/30654621.

[12] K. Sznajder et al., *Maternal Use of Acetaminophen During Pregnancy and Neurobehavioral Problems in Offspring at 3 Years: A Prospective Cohort Study*, 17 PLOS One e0272593 (2022), https://pubmed.ncbi.nlm.nih.gov/36170224/.

[13] G. Theunissen et al., *Prenatal Determinants of Depressive Symptoms in Childhood: Evidence from Growing up in New Zealand*, 302 J. Affect. Disord. 41 (2022), https://doi.org/10.1016/j.jad.2022.01.076.

[14] *See* Baccarelli Expert Report, *supra* note 5, at 106 (Brandlistuen et al. (2013) reported a twofold increase in ADHD-like behaviors among children exposed to acetaminophen for more than 28 days during pregnancy, compared to unexposed siblings).

[15] *See* Taylor FDA 2014, *supra* note 3, at 9-10 (Liew et al. (2014) found that longer duration and higher frequency of prenatal acetaminophen use were associated with increased risk of ADHD-like behaviors, hyperkinetic disorder, and ADHD medication use).

15. For example, 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.[16] Similarly, Liew et al. (2014) found that the duration and frequency of use were strongly correlated with increased risk across ADHD-like behaviors, hyperkinetic disorder diagnoses, and ADHD medication use.[17]

(iii) Biological Mechanisms of Harm

16. Scientific literature supports multiple mechanistic pathways through which acetaminophen could disrupt fetal brain development.[18] Studies show that:

a. Acetaminophen crosses the placenta and accumulates in fetal tissue;[19]

b. It induces oxidative stress and depletes fetal glutathione, a key antioxidant required during brain development;[20]

c. It interferes with prostaglandin signaling and pregnancy hormone regulation—both critical to healthy neurodevelopment;[21]

d. It disrupts neurotransmitter systems, particularly dopamine and serotonin;[22] and

e. It induces epigenetic modifications, changing gene expression patterns necessary for fetal brain maturation.[23]

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[16] *See* Baccarelli Expert Report, *supra* note 5, at 21-22.

[17] *See* Taylor FDA 2014, *supra* note 3, at 2-9.

[18] *See* Cabrera Expert Report, *supra* note 5, at 38-67; and Pearson Expert Report, *supra* note 6, at 9-13, 46-66 (these reports describe multiple mechanistic pathways through which acetaminophen may disrupt fetal brain development, including oxidative stress, hormone disruption, neurotransmitter interference, and mitochondrial dysfunction). *See also* Thompson FDA 2016, *supra* note 6, at 2-4.

[19] *See* Pearson Expert Report, *supra* note 6, at 10-12; and Cabrera Expert Report, *supra* note 5, at 58-59 (these reports document that acetaminophen crosses the placenta and enters fetal circulation, with studies detecting the compound and its metabolites in fetal tissue, including the brain). *See also* Mosholder FDA 2016, *supra* note 3, at 4.

[20] *See* Pearson Expert Report, *supra* note 6, at 9-10, 51-53; and Cabrera Expert Report, *supra* note 5, at 40-41 (both reports describe how acetaminophen produces NAPQI, a toxic metabolite that depletes glutathione—a key antioxidant necessary for fetal brain development—and induces oxidative stress).

[21] *See* Pearson Expert Report, *supra* note 6, at 65-66; and Cabrera Expert Report, *supra* note 5, at 25-26, 52-53 (both reports describe how acetaminophen inhibits cyclooxygenase (COX) enzymes, leading to reduced prostaglandin synthesis—critical for fetal brain development). *See also* Walter Lichtensteiger, et al., *Differential Gene Expression Patterns in Developing Sexually Dimorphic Rat Brain Regions Exposed to Antiandrogenic, Estrogenic, or Complex Endocrine Disruptor Mixtures: Glutamatergic Synapses As Target*, 156(4) Endocrinology 1477 (Apr. 2015), https://pubmed.ncbi.nlm.nih.gov/25607892/.

[22] *See* Pearson Expert Report, *supra* note 6, at 25-27; and Cabrera Expert Report, *supra* note 5, at 47-51 (both reports describe how acetaminophen alters the function and availability of key neurotransmitters, including dopamine and serotonin, which are related to emotional regulation, attention, and impulse control).

[23] *See* Pearson Expert Report, *supra* note 6, at 60-61; and Cabrera Expert Report, *supra* note 5, at 178-181 (both reports detail how acetaminophen induces epigenetic modifications, including DNA methylation changes and altered

These converging pathways provide strong biological plausibility for the neurodevelopmental effects observed in human studies.

(iv) Preclinical and Toxicological Evidence

17. Animal studies further support the potential for acetaminophen to interfere with neurodevelopment. Viberg et al. (2014) found that neonatal mice exposed to acetaminophen exhibited impaired spatial learning and altered locomotor activity.[24] Blecharz-Klin et al. (2015) reported neurotransmitter changes and behavioral alterations in rats following perinatal exposure.[25] Isling et al. (2014) identified neurodevelopmental disruption in rodent models exposed to endocrine-disrupting chemical mixtures that included acetaminophen.[26] These findings, while preclinical, align with the biological mechanisms described above and further establish a biologically plausible pattern of harm, strengthening the case for regulatory precaution.

(v) FDA Internal Evaluations (2014-2023)

18. Over the past decade, FDA has conducted a series of internal reviews of the emerging evidence linking prenatal acetaminophen exposure to neurodevelopmental harm. These reviews span epidemiological data, toxicological evidence, and regulatory policy discussions. Collectively, they reflect a pattern of consistent concern, increasing evidence of harm, and repeated decisions not to update product labeling despite that evidence.

19. On May 15, 2014, FDA's Division of Epidemiology I ("**DEPI-I**") reviewed a study by Liew et al. published in *JAMA Pediatrics*, which found a statistically significant association between prenatal acetaminophen exposure and an increased risk of hyperkinetic disorder (a severe form of ADHD) and ADHD medication usage.[27] The review acknowledged the potential confounding variables and limitations of the study design but ultimately concluded that the findings merited further monitoring. No regulatory action was taken at that time.

20. In September 2014, a study by Thompson et al., which analyzed behavioral outcomes in children up to age 11, found an association between prenatal acetaminophen exposure and elevated behavioral symptom scores, particularly in areas linked to emotional problems and impulse control.[28]

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expression of genes essential to fetal brain development. Cabrera discusses Carter & Blizard (2016) which identified ninety-two autism susceptibility genes significantly affected by prenatal exposure to acetaminophen).

[24] *See* Cabrera Expert Report, *supra* note 5, at 82-83; and Thompson FDA 2016, *supra* note 6, at 2.

[25] *See* Pearson Expert Report, *supra* note 6, at 63, 86-88; and Thompson FDA 2016, *supra* note 6, at 3.

[26] *See* Thompson FDA 2016, *supra* note 6, at 3.

[27] *See* Lockwood FDA 2014, *supra* note 3.

[28] 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. 24, 2014), https://pubmed.ncbi.nlm.nih.gov/25251831/.

21. On January 9, 2015, FDA issued a Drug Safety Communication, stating that the data are "too limited to make any recommendations" at this time, and that FDA "recommendations on how pain medicines are used during pregnancy will remain the same at this time."[29]

22. On March 18, 2015, DEPI-I reviewed the Thompson et al. study.[30] Again, the agency recommended no immediate changes to labeling.

23. On February 8, 2016, at the request of the Office of Surveillance and Epidemiology, FDA's pharmacology and toxicology reviewers evaluated animal studies published between 2010 and 2015. Although there was no validated animal model for ADHD, the studies demonstrated changes in behavior, learning, and neurotransmitter levels in rodents exposed to acetaminophen during key periods of brain development.[31] The review concluded that additional animal studies would be unlikely to clarify causality.

24. On March 2, 2016, the agency formally closed its Tracked Safety Issue file (TSI 1355), originally opened in response to the Liew study. The FDA stated that "data do not support a causal association" and that the agency should resume normal surveillance.[32]

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.[33] Yet, FDA took no action.

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.[34] Despite the growing consistency of findings, FDA again chose not to update labeling, citing the need for stronger causal evidence.[35]

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[29] FDA, *FDA Drug Safety Communication: FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy* (Jan. 9, 2015), https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy.

[30] *See* Mosholder FDA 2015, *supra* note 6, at 6-8.

[31] *See* Thompson FDA 2016, *supra* note 6, at 1-4.

[32] *See* Tracked Safety Issue Integrated Review Memorandum from the FDA Division of Nonprescription Drug Products, at 1–2 (Mar. 2, 2016), https://archive.org/details/fda-acetaminophen-pratt-2016.

[33] *See* Mosholder FDA 2016, *supra* note 3.

[34] *See* FDA CDER Medical Policy and Program Review Council Meeting Notes, *Discuss Tracked Safety Issue 1355 for Acetaminophen and Effects During Pregnancy*, at 3-5 (January 24, 2018) https://archive.org/details/fda-meeting-acetaminophen-pratt-2018,

[35] *See* FDA CDER Medical Policy and Program Review Council Meeting Notes, *Follow-up Discussion of Tracked Safety Issue 1355 for Acetaminophen and Effects During Pregnancy*, at 1-2 (October 3, 2018), https://archive.org/details/fda-meeting-2-acetaminophen-pratt-2018.

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 FDA consider communicating this message to healthcare providers and pregnant women.[36]

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).[37] The agency still declined to issue new labeling requirements.

29. On July 15, 2022, FDA issued a report reviewing twenty-four studies, including five meta-analyses, published between 2016 and 2021. The review acknowledged that the findings across studies were increasingly consistent, and that a dose-response relationship had been observed in several studies.[38] The review highlighted confounding variables as a continued concern but did not dispute the presence of a safety signal. Still, no regulatory action was recommended.

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 childhood.[39] Nevertheless, the agency concluded that the evidence of causality was still insufficient to warrant a label change.

(vi) International Regulatory Context

31. In 2018, the European Medicines Agency ("**EMA**") required updated product labeling for paracetamol to acknowledge the uncertain but concerning data regarding neurodevelopmental harm.[40]The EMA advised caution during pregnancy and emphasized the need

[36] *See* Andrew D. Mosholder, FDA, CDER Office of Pharmacovigilance and Epidemiology, *Epidemiology: Comparison of Multiple Studies or Literature Review - Urogenital Outcomes with in Utero Acetaminophen Exposure*, at 3-6, 18-19 (January 7, 2019).

[37] *See* Valerie Pratt, FDA, CDER Office of Nonprescription Drugs, *Newly Identified Safety Signal (NISS) Integrated Review Memorandum - Acetaminophen - Maternal Exposure During Pregnancy* (May 1, 2020), https://archive.org/details/fda-acetaminophen-pratt-2020 [hereinafter Pratt FDA 2020].

[38] *See* Abraham FDA 2022, *supra* note 3, at 6-19.

[39] *See* Abraham FDA 2023, *supra* note 3, at 7-17.

[40] *See* FDA Pratt 2020, *supra* note 37 (noting that on November 19, 2018, the European Medicines Agency required updated product labeling for paracetamol-containing medicines to reflect conflicting epidemiological findings).

for further investigation—an action the FDA has not yet mirrored, despite reviewing the same evidence.

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, 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.

D. CONCLUSION

33. In August 2025, a rigorous new study by Prada et al. found the evidence supports a positive association of prenatal acetaminophen use with ADHD, ASD, or NDDs in offspring. The study found that a "causal relationship is plausible" due to the consistency of the results and that it is consistent with temporal trends, as rates of ADHD and ASD have risen alongside acetaminophen use during pregnancy over the past several decades.[42]

34. In light of the growing body of epidemiological, mechanistic, and regulatory evidence, as well as FDA's own history of internal safety reviews, Petitioner respectfully submits that a labeling change for acetaminophen-containing products is both warranted and urgently needed. The absence of a warning regarding potential neurodevelopmental risks during pregnancy deprives consumers—particularly pregnant individuals—of the information necessary to make informed decisions. Given the widespread use of this drug during pregnancy and the consistency of the emerging safety signal, the requested labeling revision aligns with FDA's responsibility to protect public health and ensure that product labeling reflects current scientific knowledge.

E. ENVIRONMENTAL IMPACT

35. The undersigned hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. §§ 25.30 and 25.31.

F. ECONOMIC IMPACT

36. Economic impact information will be submitted upon request of the commissioner.

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[41] Ann Z. Bauer et al., *Paracetamol Use During Pregnancy—A Call for Precautionary Action*, Nature Reviews Endocrinology 757 (2021), https://doi.org/10.1038/s41574-021-00553-7.

[42] Diddier Prada et al., *Evaluation of the Evidence on Acetaminophen Use and Neurodevelopmental Disorders Using the Navigation Guide Methodology*, 24 Environmental Health (2025) https://ehjournal.biomedcentral.com/articles/10.1186/s12940-025-01208-0.

G. CERTIFICATION

37. The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

38. The Petitioner therefore respectfully urges that this request be granted forthwith.

Respectfully submitted,

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