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Docket: FDA 2025 N 3774 — Pediatric Advisory Committee — Written Testimony

To Whom It May Concern:

I respectfully urge the Pediatric Advisory Committee to place on a near term agenda a focused review of prenatal acetaminophen exposure and child neurodevelopmental outcomes, specifically autism spectrum disorder and attention deficit hyperactivity disorder, and to recommend interim precautionary updates to consumer and professional communications while higher certainty evidence is generated. This topic is squarely within the Committee’s remit because the Pediatric Advisory Committee advises the Food and Drug Administration on pediatric safety, labeling, and research matters across drugs, biologics, and devices, and it is routinely convened to evaluate post marketing pediatric focused safety issues and to provide advice that informs agency communications and labeling actions. A potential prenatal exposure with plausible implications for child neurodevelopment is directly relevant to pediatric risk management and labeling clarity, and the Federal Register notice and advisory calendar for the November thirteen meeting confirm the public process by which this Committee receives input

and provides advice that can shape agency action on pediatric safety issues, including the receipt of written comments in this docket by November twelve at eleven fifty nine in the evening Eastern time (Food and Drug Administration, 2025a; Food and Drug Administration, 2025b).

The current evidence base justifies Committee attention but does not establish causation. The highest quality human evidence to date comprises nationwide sibling control analyses from Sweden that compared exposed and unexposed siblings and found no association between prenatal acetaminophen use and autism spectrum disorder or attention deficit hyperactivity disorder once shared familial genetics and environment were accounted for, which indicates that earlier signals were likely driven by confounding rather than a drug effect and that causal inference from prior observational associations is not warranted at this time (Ahlqvist et al., 2024). In contrast, earlier cohort reports that observed associations often relied on maternal recall of medication use and therefore remained vulnerable to recall bias and to confounding by indication such as fever, infection, and pain, although some work attempted to strengthen inference using umbilical cord blood biomarkers of acetaminophen adducts and reported dose response patterns that merit continued scientific scrutiny rather than policy conclusions (Ji et al., 2020). The biomarker literature itself invites careful interpretation because adduct levels may reflect not only drug dose but also maternal and fetal physiology such as oxidative stress and metabolic variation, and thus even objective exposure measures do not by themselves resolve all confounding concerns. Given these uncertainties, causal triangulation across methods that include sibling comparisons, negative control analyses, and designs that better address indication is essential before concluding that a true drug effect exists in humans.

The widely promoted Harvard associated review summarized dozens of observational studies using a qualitative Navigation Guide framework and concluded that the weight of evidence favored an association. However, this review did not perform a quantitative meta analysis because of heterogeneity, and instead relied on a form of vote counting across studies with similar vulnerabilities, without resolving familial confounding and without conducting

quantitative bias analysis to measure the impact of confounding by indication and exposure misclassification. This approach can inflate apparent consistency when multiple studies share the same structural limitations, and it weakens any causal interpretation advanced on that basis. The Harvard communications amplified the qualitative conclusion without fully engaging the direct contradiction posed by sibling control findings where the association disappears when family level factors are controlled, which is a critical omission in policy facing messaging that should place the strongest causal designs at the top of the evidentiary hierarchy (Prada et al., 2025; Harvard T. H. Chan School of Public Health, 2025; Ahlqvist et al., 2024). By contrast, a comprehensive review in The British Medical Journal concluded that existing evidence does not clearly link maternal paracetamol use with autism spectrum disorder or attention deficit hyperactivity disorder once study quality and confounding are carefully weighed, and leading obstetric guidance has emphasized that association does not equal causation and that undertreatment of maternal fever and pain can itself harm mothers and fetuses (Thangaratinam et al., 2025; American College of Obstetricians and Gynecologists, 2021). A multidisciplinary consensus statement in Nature Reviews Endocrinology has for several years recommended precaution in pregnancy with use only when medically indicated at the lowest effective dose for the shortest necessary duration, a stance that preserves needed care while avoiding routine or chronic use absent a clear indication (Bauer et al., 2021).

The regulatory context further supports Committee engagement. On September 22, 2025, the Food and Drug Administration announced that it had initiated a process to update acetaminophen safety labeling for pregnancy and issued a Notice to Physicians acknowledging evidence of an association in some studies while emphasizing that causation has not been established and that clinical judgment remains essential. The agency explained that the labeling process would proceed through established mechanisms and that expert input would be sought. A pediatric focused public deliberation at this Committee can accelerate clarity for agency communications and ensure that pediatric risk management and benefit risk considerations are

addressed transparently, including the potential for a joint session with the Drug Safety and Risk Management Advisory Committee and the Nonprescription Drugs Advisory Committee so that pediatric implications, over the counter labeling, and real world use can be evaluated together in one public forum (Food and Drug Administration, 2025c; Food and Drug Administration, 2025d). At the same time, high visibility media messaging around this topic has at moments been inconsistent and has risked overstating causation, which can deter appropriate fever treatment in pregnancy and thereby create its own fetal risks. Major news coverage on September twenty one and September twenty two documented specific assertions and immediate caution from clinicians and public health experts who warned that undermining the safest recommended antipyretic in pregnancy without clear causal evidence can cause harm through undertreatment of maternal fever. This divergence between political or media messaging and the agency's measured scientific communication created avoidable confusion in a high volume exposure setting, which underscores the value of this Committee's role in providing precise and balanced advice grounded in the state of the evidence rather than in rhetoric or speculation (Abutaleb et al., 2025a; Abutaleb et al., 2025b).

For these reasons I ask the Pediatric Advisory Committee to recommend that the Food and Drug Administration schedule a dedicated session to review prenatal acetaminophen exposure and child neurodevelopment with presentation of objective biomarker data, large registry analyses employing sibling comparison and negative control designs, and updated systematic reviews, with explicit consideration of confounding by indication including maternal fever. I further ask the Committee to advise the agency to implement near term precautionary messaging that is simple, balanced, and reversible. For consumer Drug Facts labels under the pregnancy and breastfeeding statement, the agency should advise language that encourages use only when medically needed at the lowest effective dose for the shortest time and consultation with a clinician before repeated or prolonged use. For clinicians the agency should issue a Dear Health Care Professional communication and update its pregnancy focused web

pages to summarize the evidence, to explicitly distinguish association from causation, to emphasize appropriate treatment of clinically meaningful fever and pain, and to discourage routine or chronic use in pregnancy without a clear indication. Finally I ask the Committee to advise the agency to set a specific research roadmap that includes prospective pregnancy cohorts with serial biospecimens for validated acetaminophen exposure biomarkers, sibling comparison and negative control strategies, and where feasible Mendelian randomization, with defined milestones for the Center for Drug Evaluation and Research to report progress back to the Pediatric Advisory Committee in public session. These steps are proportionate and targeted to protect pediatric health while better evidence accumulates and they are needed to anchor pregnancy communications in transparent pediatric safety science.

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