Children's Health Defense

852 Franklin Ave., Suite 511
Franklin Lakes, NJ 07417

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Kyle Diamantas, J.D., Acting Commissioner
5630 Fishers Lane, Room 1061
Rockville, MD 20852

August 10, 2026

Dear Acting Commissioner:

Enclosed is a Citizen Petition filed on behalf of Children's Health Defense by Mary S. Holland, Esq., Chief Executive Officer, Brian S. Hooker, Ph.D., Chief Scientific Officer, Kim Mack Rosenberg, General Counsel, and Ray L. Flores II, Senior Outside Counsel, requesting that FDA take critical steps regarding Infants' Tylenol, Children's Tylenol, and other products containing acetaminophen. Specifically, we ask that Infants' Tylenol and similar products no longer be available over the counter and that Children's Tylenol and similar products contain new, more stringent warnings.

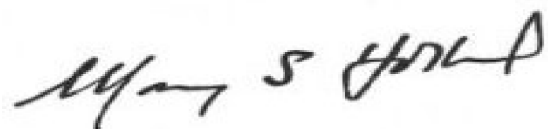
This Citizen Petition incorporates William Parker, Ph.D.'s results, findings, and conclusions concerning acetaminophen use in infants and children. Dr. William Parker holds a PhD in Chemistry and is best known for the discovery of the function of the human vermiform appendix (a safe-house for beneficial gut bacteria). He was an Associate Professor and researcher in fields including biochemistry, microbiology and immunology at Duke University where he worked for almost 30 years before starting WPLab in 2021. WPLab is a private non-profit research and education corporation. Dr. Parker has published more than 150 peer-reviewed papers, and his work also includes education and outreach regarding the risks of acetaminophen exposure during critical phases of neurodevelopment. He has spent more than a decade studying the impact of acetaminophen combined with oxidative stress on neurodevelopment. He has published work evaluating the role of acetaminophen in the induction of autism in journals such as Clinical and Experimental Pediatrics, the European Journal of Pediatrics, PLoS One, and Minerva Pediatrics, and other peer reviewed journals.

The petition contains conclusions of WPLab scientists that a significant portion of all cases of regressive Autism Spectrum Disorder are chemically induced and exposure of susceptible babies

and children to acetaminophen is one such exposure that may play a significant role. Of course, this is not the only risk with these products but this association is one that has been ignored for too long.

Mary S. Holland, Esq., and Brian S. Hooker, Ph.D., are available to answer questions and to provide any additional relevant information. We look forward to your timely review of this petition.

Sincerely,



Mary S. Holland, Esq., Chief Executive Officer

Brian S. Hooker, Ph.D., Chief Science Officer

Kim Mack Rosenberg, CHD General Counsel

Ray Flores, Senior Outside Counsel

cc: William Parker, Ph.D.

VIA ELECTRONIC FILING

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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

PETITION FOR ADMINISTRATIVE ACTION REGARDING ACETAMINOPHEN	**DOCKET NUMBER: _____**

On behalf of Children's Health Defense, the undersigned submit this petition under 21 C.F.R. § 10.20, § 10.30, § 50.23, § 201.57 § 600 – 680, § 601.2, 21 U.S.C. § 352, and § 553(e) of the Administrative Procedure Act since Tylenol and other products containing acetaminophen pose danger to newborns, infants, and children under six years of age. Petitioner asks that FDA remove from the market Infants' Tylenol and other acetaminophen-containing products marketed to infants and small children under two years of age and that Children's Tylenol and similar products provide more stringent warnings. Petitioner makes this request since mounting scientific evidence links newborn, infant, and early-childhood exposure to acetaminophen with Autism Spectrum Disorder ("ASD"). According to the FDA, "more than 600 medications – both prescription and nonprescription (over-the-counter ("OTC")) – contain acetaminophen."[1] Tylenol is the number one doctor-recommended pain reliever.[2]

[1] FDA https://www.fda.gov/consumers/consumer-updates/dont-overuse-acetaminophen (May 1, 2024) (last viewed July 1, 2026).
[2] Tylenol Website https://www.tylenol.com/products/adult-pain-reliever-comparison-chart (last viewed May 30, 2026).

Susceptibility to acetaminophen-induced injury is imposed by a range of genetic, epigenetic, and environmental factors associated with oxidative stress, and is apparently the greatest immediately after birth. Susceptibility then decreases until about six years of age, which is outside of the developmental window in which regression into ASD typically occurs. Given continued use of acetaminophen during labor and delivery, and routine use during infancy and early childhood including for indications such as circumcision, vaccination, and some chronic medical conditions, FDA action is much needed.

To be blunt, for infants and young children, there is no safe dose of Tylenol products and, most particularly, there is no safe dose for neonates and infants under two. Contrary to reasonable and necessary actions demanded by these important scientific observations, parents and doctors are not warned that Tylenol products pose a risk of ASD for infants and young children who take the drug even when administered in the *recommended* dosage. To compound the problem, OTC Infants' Tylenol doesn't provide any recommended dosage for young infants (under two or under 24 pounds). Instead, a consumer is advised to "Ask a Doctor." This sets up a dangerous scenario for potential overdosing since a prescription is not necessary for purchase. Further, Tylenol continues to be used during labor and delivery with no warning to the parent(s). Infants and young children are given Tylenol products based on the understanding that there is no risk when given in the "proper" dosage. This is untrue. Tylenol's active ingredient acetaminophen can cause ASD in infants and children when they ingest the drug even at doses indicated on the label/box.

Long-standing evidence indicates that acetaminophen is associated with many cases of regressive autism.[3] [4] [5] As a result, caregivers should be warned about associations between regression into autism and acetaminophen use during the period when regression is possible – at least until a child's sixth birthday.

---

[3] Parker W, Anderson LG, Jones JP, Anderson R, Williamson L, Bono-Lunn D, et al. The Dangers of Acetaminophen for Neurodevelopment Outweigh Scant Evidence for Long-Term Benefits. Children. 2024;11(1):44. PubMed PMID: doi:10.3390/children11010044. https://pmc.ncbi.nlm.nih.gov/articles/PMC10814214/pdf/children-11-00044.pdf (last viewed May 28, 2026).

[4] Schultz ST, Klonoff-Cohen HS, Wingard DL, Akshoomoff NA, Macera CA, Ji M. Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder. The results of a parent survey. Autism. 2008;12(3):293-307. https://pubmed.ncbi.nlm.nih.gov/18445737/ (last viewed May 30, 2026).

[5] Jones III JP, Konsoula Z, Williamson L, Anderson R, Meza-Keuthen S, Parker W. An Update on the Connection Between Acetaminophen and Autism: Expanding Evidence and Misinterpreted Sibling Control Studies. Preprints: Preprints; 2026. https://www.preprints.org/manuscript/202501.0319 (last viewed May 30, 2026).

Neonates lack an important metabolic machinery to safely metabolize acetaminophen, and this pathway does not mature until almost two years of age. This results in very strong associations between acetaminophen use during labor and delivery and autism, with associated risks of more than 300%. Further, a) long-standing evidence indicates that acetaminophen is associated with many cases of regressive autism; (b) most regression occurs before two years of age; and (c) use of acetaminophen during this time has never proven to be lifesaving. Acetaminophen use during the first two years of life should be prohibited, and Infants' Tylenol and similar products should be taken off the market. Children's Tylenol and similar products should come with a boxed warning, and FDA must warn health care professionals not to use acetaminophen containing products during labor and delivery.

On September 23, 2025, President Trump announced: "Since 2000, autism rates have surged by much more than 400 percent."[6] President Trump also asserted: "Don't take Tylenol if you're pregnant, and don't give Tylenol to your child."[7] President Trump stood beside Health and Human Services Secretary Robert F. Kennedy Jr. for what he called a "historic" announcement on autism. "If you're pregnant, don't take Tylenol, and don't give it to the baby after the baby is born," Trump said. "There are certain groups of people that don't take vaccines and don't take any pills that have no autism," he added. "They pump so much stuff into those beautiful little babies, it's a disgrace."[8]

HHS recognized Tylenol's association with ASD and ADHD when it announced, "HHS will act on acetaminophen. Today, the FDA will issue a physician notice and begin the process to initiate a safety label change for acetaminophen (Tylenol and similar products). HHS will launch a nationwide public service campaign to inform families and protect public health."[9] Up until this press release, the HHS willfully ignored the science that early-childhood exposure to acetaminophen products can cause ASD in children.

---

[6] UCSB, The American Presidency Project (September 22, 2025) https://www.presidency.ucsb.edu/documents/remarks-childrens-health-and-exchange-with-reporters (last viewed May 30, 2026).

[7] NPR When it comes to Tylenol, what are parents to do? (September 23, 2025) https://www.npr.org/sections/shots-health-news/2025/09/23/nx-s1-5551228/acetaminophen-tylenol-autism-trump-explainer (last viewed May 30, 2026).

[8] KFF Health News 'Sick to My Stomach': Trump Distorts Facts on Autism, Tylenol, and Vaccines, Scientists Say (September 22, 2025) https://kffhealthnews.org/public-health/trump-autism-announcement-rfk-tylenol-pregnancy-vaccines/ (last viewed May 30, 2026).

[9] Press Release, 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 (last viewed May 30, 2026).

This petition takes the HHS's announcement one step further. We ask that the FDA ban OTC Infants' Tylenol and other similar products containing acetaminophen. This petition also requests that the Commissioner require boxed warnings for use during labor and delivery and, for Children's Tylenol, and other similar products containing acetaminophen, up to a child's 6th birthday. It is time for the Commissioner to take the requested, decisive action.

The request is also based on HHS's Key Findings:[10]

- 1 in 31 U.S. children (3.2%) born in 2014 are diagnosed with ASD.
- This is a sharp increase from 1 in 36 just two years earlier.
- Prevalence is nearly 5 times higher than when the CDC began tracking in 2000 (1 in 150).
- Boys are disproportionately affected: 1 in 20 (5%).
- California has the highest prevalence: 1 in 12.5 boys.

Up until now, much of the focus has been on the dangers of Tylenol use during pregnancy. While several studies show significant associations between ASD and *frequent* use of acetaminophen during pregnancy, with risks of ASD increasing by more than 50% in the most robust study,[11] [12] that is not the topic of this Citizen Petition. The fetus is apparently not as susceptible to acetaminophen-mediated neurodevelopmental injury (particularly with sporadic exposure to acetaminophen) as is the neonate, probably due at least in part to protection from the mother's liver.

Since acetaminophen's real danger begins once the umbilical cord is severed, Petitioner requests that action be taken to eliminate the real dangers to neonates, infants and children under six years of age.

I. ACTIONS REQUESTED

Petitioner asks the Commissioner to:

---

[10] HHS Autism Announcement Fact Sheet (September 22, 2025) https://www.hhs.gov/press-room/autism-announcement-fact-sheet.html (last viewed May 30, 2026).

[11] Ahlqvist VH, Sjöqvist H, Dalman C, Karlsson H, Stephansson O, Johansson S, et al. Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability. Jama. 2024;331(14):1205-14. Epub 2024/04/09. doi: 10.1001/jama.2024.3172. PubMed PMID: 38592388; PubMed Central PMCID: PMCPMC11004836. (April 9, 2024) https://jamanetwork.com/journals/jama/fullarticle/2817406 (last viewed May 31, 2026).

[12] Jones JP, 3rd, Williamson L, Konsoula Z, Anderson R, Reissner KJ, Parker W. Evaluating the Role of Susceptibility Inducing Cofactors and of Acetaminophen in the Etiology of Autism Spectrum Disorder. Life (Basel, Switzerland). 2024;14(8). Epub 2024/08/31. doi: 10.3390/life14080918. PubMed PMID: 39202661; PubMed Central PMCID: PMCPMC11355895. https://pmc.ncbi.nlm.nih.gov/articles/PMC11355895/pdf/life-14-00918.pdf (last viewed May 28, 2026).

1. Withdraw OTC approval for Infants' Tylenol and other products containing acetaminophen approved for use with children under two;

2. Require a "box warning" and other safety information concerning severe risk of ASD for Children's Tylenol and other products containing acetaminophen for children under six; and,

3. Require that the FDA issue a "box warning" for Tylenol and other products containing acetaminophen relevant to labor and delivery.

1) **The undersigned request that the Commissioner of Food and Drugs remove Infants' Tylenol and other products containing acetaminophen approved for use with children under two from the Over-the-Counter monograph M013.**

According to the FDA, "Under the process set forth in section 505G(b) of the FD&C Act, FDA has the authority to issue an administrative order (proposed and final) that adds, removes, or changes generally recognized as safe and effective (GRASE) conditions for an OTC drug monograph. Either FDA or a requestor can initiate the administrative order process."[13]

In addition to the danger Tylenol and other products containing acetaminophen poses to children as set forth herein, there is no standard dosage for infants (under two years of age). The label merely alerts the consumer that a healthcare provider should be contacted. The makers of acetaminophen already acknowledge severe liver damage in the event of an overdose – but with no standard dose on the label for infants, the risk of overdose increases. Additionally, the scientific data contained in this petition show the danger of ASD is much greater for children under two years of age. Even with the dosage provided by a licensed prescriber these acetaminophen-containing products are still dangerous. That is why OTC status should be withdrawn for Infants' Tylenol and other infant products containing acetaminophen.

This is not the first time acetaminophen dosage has been an issue. Prior to 2011, acetaminophen for babies and children was packaged in two very different concentrations, and, as a result, parents were making mistakes with dosing.[14] Babies got sick – some even died. So in 2011, at the urging of the Food and Drug Administration, the maker of brand-name Tylenol announced that Infants' Tylenol would be the same concentration as Children's Tylenol.

---

[13] FDA OTC Drug Review Process | OTC Drug Monographs (October 19, 2023) https://www.fda.gov/drugs/otc-drug-review-process-otc-drug-monographs (last viewed May 30, 2026).

[14] PMC Acetaminophen in children, Ran D. Goldman (October 2013) https://pmc.ncbi.nlm.nih.gov/articles/PMC3796971/ (last viewed June 30, 2026).

Manufacturers changed the concentration of acetaminophen in medicines for infants since the earlier dosage was three times stronger.[15]

However, even though the syringe now allows a parent to accurately measure the dosage, ascertaining the correct dosage requires consultation with a medical professional. Given the fact that acetaminophen already poses a danger to infants, the potential for overdosing still exists.

The evidence presented demands that the Commissioner uses its authority to issue an order to remove Infants' Tylenol from the OTC monograph.

2) **The Commissioner should require box warnings on Children's Tylenol for children under six and for obstetricians during labor and delivery**.

Box warnings are described in the Code of Federal Regulations (CFR) under "Warnings (21CFR 201.57 (e)):"

> Labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved…. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration…

The Commissioner has the authority to act. Based on the statement of grounds (below) a Boxed Warning should be issued for use by obstetricians during labor and delivery and administration to children under six.

The FDA routinely requires information of risk on OTC labels. Liver damage is listed, but HHS fails to notify parents of the risk that giving their infants and young children Tylenol could lead to ASD. HHS has never required an appropriate warning.

II. STATEMENT OF GROUNDS

More than 30 lines of evidence from different scientific studies **cited in this document** indicate that exposure of susceptible babies and children to acetaminophen can trigger autism. Multiple studies confirm that children with autism are poor metabolizers of

[15] NPR Tylenol For Infants (May 27, 2019) https://www.npr.org/sections/health-shots/2019/05/27/726327937/tylenol-for-infants-and-children-is-the-same-why-does-1-cost-3-times-more (last viewed May 30, 2026).

acetaminophen. [16] [17] [18] [19] Acetaminophen is much more toxic in children who metabolize the drug poorly. This toxicity is due to excess formation of the toxic metabolite of acetaminophen, called NAPQI. [20]

The fields of pharmacology and toxicology yield the most abundant sources of evidence, with clinical and epidemiological observations, numerous miscellaneous observations, and studies in laboratory animal models providing conclusive support. This narrative review summarizes that evidence, and discusses recent work with sibling control analysis that has been unfortunately misinterpreted as a result of incorrect assignment of interacting variables as confounding factors. Susceptibility to acetaminophen-induced injury is imposed by a range of genetic, epigenetic, and environmental factors associated with oxidative stress, and is apparently the greatest immediately after birth. Susceptibility then decreases until about six years of age, which is outside of the developmental window in which regression into ASD typically occurs. Although associations between heavy use of acetaminophen during pregnancy and ASD suggest some risk may be present during pregnancy, insufficient evidence is available to know if sporadic use of acetaminophen during pregnancy poses any risks. Given continued use of acetaminophen during labor and delivery, and routine use during infancy and early childhood, including for indications such as circumcision, vaccination, and some chronic medical conditions, a course correction in clinical practice is much needed.

A. INTRODUCTION

---

[16] Stein TP, Schluter MD, Steer RA, Ming X. Autism and phthalate metabolite glucuronidation. J Autism Dev Disord. 2013;43(11):2677-85. Epub 2013/04/12. doi: 10.1007/s10803-013-1822-y. PubMed PMID: 23575644; PubMed Central PMCID: PMCPMC3797149. https://pmc.ncbi.nlm.nih.gov/articles/PMC3797149/pdf/nihms466807.pdf (last viewed May 28, 2026).

[17] Geier DA, Kern JK, Garver CR, Adams JB, Audhya T, Geier MR. A prospective study of transsulfuration biomarkers in autistic disorders. Neurochem Res. 2009;34(2):386-93. Epub 2008/07/10. doi: 10.1007/s11064-008-9782-x. PubMed PMID: 18612812. https://pubmed.ncbi.nlm.nih.gov/18612812/ (last viewed May 30, 2026).

[18] Pagan C, Benabou M, Leblond C, Cliquet F, Mathieu A, Lemière N, et al. Decreased phenol sulfotransferase activities associated with hyperserotonemia in autism spectrum disorders. Translational Psychiatry. 2021;11(1):23. doi: 10.1038/s41398-020-01125-5. https://www.nature.com/articles/s41398-020-01125-5 (last viewed May 28, 2026).

[19] Alberti A, Pirrone P, Elia M, Waring RH, Romano C. Sulphation deficit in "low-functioning" autistic children: a pilot study. Biol Psychiatry. 1999;46(3):420-4. Epub 1999/08/06. doi: 10.1016/s0006-3223(98)00337-0. PubMed PMID: 10435209. https://pubmed.ncbi.nlm.nih.gov/10435209/ (last viewed May 30, 2026).

[20] Zhao L, Jones J, Anderson L, Konsoula Z, Nevison C, Reissner K, et al. Acetaminophen causes neurodevelopmental injury in susceptible babies and children: no valid rationale for controversy. Clinical and experimental pediatrics. 2023. Epub 2023/06/16. doi: 10.3345/cep.2022.01319. PubMed PMID: 37321575. https://pubmed.ncbi.nlm.nih.gov/37321575/ (last viewed May 28, 2026).

Abundant evidence has led us to conclude, without reasonable doubt, that exposure of susceptible babies and children to acetaminophen causes neurodevelopmental injury, contributing to a significant portion of cases of autism spectrum disorder (ASD).[21] [22] [23] [24] Evidence also demonstrates that a wide range of genetic, epigenetic and environmental factors associated with oxidative stress create susceptibility to acetaminophen-induced injury. Furthermore, the developmental period of greatest susceptibility appears to be at the time of birth, with susceptibility diminishing over time and ending almost completely by about six years of age.[25] A current summary of evidence that, when considered together, demonstrates the induction of ASD in susceptible individuals by acetaminophen is shown in Tables 1-5**.** The 31 lines of evidence shown in the tables are divided into five categories separated into tables based on the nature of that evidence. No attempt is made to "grade" the evidence or rank the evidence in relative terms. Any such effort would involve comparing very different lines of evidence, for example one line of evidence derived from over a dozen studies in laboratory animal models versus another line of evidence derived from many dozens of studies regarding risk factors associated with ASD and their impact on the metabolism of acetaminophen. Any attempt at such comparisons would be highly subjective at best, and arbitrary to at least some extent.

Importantly, no line of evidence alone is sufficient to arrive at any conclusion regarding a causal relationship between acetaminophen exposure and ASD. It is the weight of total evidence, taken together, which is overwhelmingly conclusive. Evidence is numbered sequentially starting with line of evidence #1 in the beginning of Table 1 and ending with line of evidence #31 at the end of Table 5. The 5 categories are as follows:

- Pharmacology/toxicology related evidence (Table 1; 9 lines of evidence, #1 through #9)
- Associations between ASD and acetaminophen use (Table 2; 5 lines of evidence; #10 through #14)
- Laboratory animal studies (Table 3; 4 lines of evidence; #15 through #18)
- Miscellaneous observations (Table 3; 8 lines of evidence; #19 through #26)
- Associations in place and time (Table 5; 5 lines of evidence; #27 through #31**)**

Throughout the text, particular lines of evidence will be referenced according to their number assigned in Tables 1-5. For example, the fact that fetal alcohol spectrum disorder shares

---

[21] *Id.* at n. 20.
[22] Patel E, Jones III JP, 3rd, Bono-Lunn D, Kuchibhatla M, Palkar A, Cendejas Hernandez J, et al. The safety of pediatric use of paracetamol (acetaminophen): a narrative review of direct and indirect evidence. Minerva pediatrics. 2022;74(6):774-88. Epub 2022/07/14. doi: 10.23736/s2724-5276.22.06932-4. PubMed PMID: 35822581. https://pubmed.ncbi.nlm.nih.gov/35822581/ (last viewed May 28, 2026).
[23] *Id.* at n. 3.
[24] *Id.* at n. 12.
[25] *Id.* at n. 3.

many similarities with ASD is listed in Table 4 as the 24th line of evidence, and will be listed in the text as line of evidence #24. Again, no single line of evidence is used to make a "leap" to any conclusion, but rather it is the weight of total evidence that is used to draw conclusions.

A very brief summary of all evidence is shown in Figure 1. The numbering in Figure 1 corresponds with the numbers shown in Tables 1-5. This list of evidence (Tables 1-5 and Figure 1) is an update from previously published lists. It is important to note, however, that additions to the list do not involve new evidence reported for the first time in this review. Rather, the updated list incorporates existing, previously published evidence into the list for the first time.

Each of the 31 lines of evidence shown in the tables was derived independently, with some lines of evidence being corroborated by multiple research groups. However, in compiling evidence, some information that is discrete and derived independently has been combined into a single category for the sake of clarity and ease of communication. For example, studies examining the effect of acetaminophen on learning in mice are combined with studies of the effect of acetaminophen on social behavior in rats, forming a single line of evidence (line of evidence #15). As another example, the association of ASD with deficiencies in two distinct metabolic pathways involved in the non-toxic metabolism of acetaminophen (line of evidence #4) are lumped into a single category. That line of evidence is summarized in Figure 2, which brings together several lines of pharmaceutical evidence (lines of evidence #1, #3, #4, and #8). Thus, the evidence provided could be divided into more than 31 lines of evidence while maintaining the requirement that each line of evidence remain discrete and independent, and the number of lines of evidence that could be considered discrete and independent exceeds 31. With this in mind, the number 31 should not be considered a precise tabulation of evidence, and will be considered a conservative tally of discrete and independently derived evidence for the sake of this review.

The most recent previously published tally of evidence from our group listed 22 lines of evidence from clinical observations, pharmacokinetic considerations, laboratory animal studies, and other fields of inquiry.[26] Since that list of evidence was published in 2023, additional lines of evidence were described in the literature in 2024, including the numerous similarities between ASD and fetal alcohol spectrum disorder,[27] which demonstrate that a single drug, interacting with environmental and genetic factors, can cause a complex spectrum disorder. In addition, prenatal exposure to valproate, a drug commonly used as an anti-seizure medication, can also induce a spectrum disorder.[28] Of note is the fact that acetaminophen,[29 30] alcohol,[31 32] and

---

[26] *Id.* at n. 3.
[27] *Id.* at n. 12.
[28] Clayton-Smith J, Bromley R, Dean J, Journel H, Odent S, Wood A, et al. Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability. Orphanet journal of rare diseases. 2019;14(1):180. Epub 2019/07/22. doi: 10.1186/s13023-019-1064-y. PubMed PMID: 31324220; PubMed Central PMCID: PMCPMC6642533.

valproate[33] are all metabolized by the human body via cytochrome P450 enzymes to produce a toxic metabolite in the reactive electrophile class.

Another example of evidence newly added to the list connecting acetaminophen with neurodevelopmental problems, including ASD, is a study by Graeca and Kulesza showing that exposure of laboratory rats to acetaminophen in utero leads to problems with auditory processing later in life.[34] As reviewed by the authors,[35] some degree of auditory dysfunction is seen in the majority of individuals with ASD. However, it remains unknown whether the acetaminophen-induced auditory dysfunction observed in laboratory rats is related to auditory dysfunction observed in individuals with ASD. Thus, this line of evidence, by itself, does not lead to the conclusion that acetaminophen can act as a trigger for the induction of ASD. Nevertheless, the study by Graeca and Kulesza adds to an already overwhelming body of evidence connecting

---

https://pmc.ncbi.nlm.nih.gov/articles/PMC6642533/pdf/13023_2019_Article_1064.pdf (last viewed May 28, 2026).

[29] Albano E, Rundgren M, Harvison PJ, Nelson SD, Moldéus P. Mechanisms of N-acetyl-p-benzoquinone imine cytotoxicity. Mol Pharmacol. 1985;28(3):306-11. Epub 1985/09/01. PubMed PMID: 4033631. https://pubmed.ncbi.nlm.nih.gov/4033631/ (last viewed May 30, 2026).

[30] Luo G, Huang L, Zhang Z. The molecular mechanisms of acetaminophen-induced hepatotoxicity and its potential therapeutic targets. Exp Biol Med (Maywood). 2023;248(5):412-24. Epub 2023/01/22. doi: 10.1177/15353702221147563. PubMed PMID: 36670547; PubMed Central PMCID: PMCPMC10281617.
https://pmc.ncbi.nlm.nih.gov/articles/PMC10281617/pdf/10.1177_15353702221147563.pdf (last viewed May 28, 2026).

[31] Zakhari S. Overview: how is alcohol metabolized by the body? Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism. 2006;29(4):245-54. Epub 2007/08/28. PubMed PMID: 17718403; PubMed Central PMCID: PMCPMC6527027 interests.
https://pmc.ncbi.nlm.nih.gov/articles/PMC6527027/pdf/245-255.pdf (last viewed May 28, 2026).

[32] LoPachin RM, Gavin T. Molecular mechanisms of aldehyde toxicity: a chemical perspective. Chem Res Toxicol. 2014;27(7):1081-91. Epub 2014/06/10. doi: 10.1021/tx5001046. PubMed PMID: 24911545; PubMed Central PMCID: PMCPMC4106693.
https://pmc.ncbi.nlm.nih.gov/articles/PMC4106693/pdf/tx5001046.pdf (last viewed May 28, 2026).

[33] Shnayder NA, Grechkina VV, Khasanova AK, Bochanova EN, Dontceva EA, Petrova MM, et al. Therapeutic and Toxic Effects of Valproic Acid Metabolites. Metabolites. 2023;13(1). Epub 2023/01/22. doi: 10.3390/metabo13010134. PubMed PMID: 36677060; PubMed Central PMCID: PMCPMC9862929.
https://pmc.ncbi.nlm.nih.gov/articles/PMC9862929/pdf/metabolites-13-00134.pdf (last viewed May 28, 2026).

[34] Graeca M, Kulesza R. Impaired brainstem auditory evoked potentials after in utero exposure to high dose paracetamol exposure. Hear Res. 2024;454:109149. Epub 2024/11/18. doi: 10.1016/j.heares.2024.109149. PubMed PMID: 39550993. (December 2024)
https://pubmed.ncbi.nlm.nih.gov/39550993/ (last viewed May 30, 2026).

[35] *Id.*

acetaminophen with developmental problems and the induction of ASD in particular, and therefore should be included in an updated tally of evidence (line of evidence #17). Another line of evidence that has been included involves the relationships between arachidonic acid metabolism and acetaminophen,[36] [37] and between arachidonic acid metabolism and ASD.[38] [39] These studies, taken together, suggest that arachidonic acid could be involved in the acetaminophen-mediated induction of ASD by mechanisms that have yet to be elucidated, and constitute yet another link between acetaminophen and ASD (line of evidence #7).

The current summary of evidence demonstrating the induction of ASD in susceptible individuals by acetaminophen conservatively entails 31 lines of discrete and independent evidence (Tables 1-5, Figure 1). Despite this overwhelming evidence, acetaminophen continues to be used in the pediatric population. For example, although acetaminophen is not generally recommended for vaccinations by the World Health Organization,[40] three doses of acetaminophen are now recommended for use with each dose of the vaccine against meningococcal serogroup B (MenB), administered to 2, 4, and 12 months of age (see discussion below). Given the existence of this policy and of the ongoing acceptance of acetaminophen use

---

[36] Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J. 2008;22(2):383-90. Epub 2007/09/22. doi: 10.1096/fj.07-8506com. PubMed PMID: 17884974. (February 2028) https://pubmed.ncbi.nlm.nih.gov/17884974/ (last viewed May 30, 2026).

[37] Hogestatt ED, Jonsson BA, Ermund A, Andersson DA, Bjork H, Alexander JP, et al. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem. 2005;280(36):31405-12. Epub 2005/07/01. doi: 10.1074/jbc.M501489200. PubMed PMID: 15987694. (September 2005) https://pubmed.ncbi.nlm.nih.gov/15987694/ (last viewed May 30, 2026).

[38] El-Ansary A, Alfawaz HA, Bacha AB, Al-Ayadhi LY. Combining Anti-Mitochondrial Antibodies, Anti-Histone, and PLA2/COX Biomarkers to Increase Their Diagnostic Accuracy for Autism Spectrum Disorders. Brain Sci. 2024;14(6):576. PubMed PMID: doi:10.3390/brainsci14060576. https://pmc.ncbi.nlm.nih.gov/articles/PMC11201962/pdf/brainsci-14-00576.pdf (last viewed May 28, 2026).

[39] Hirai T, Umeda N, Harada T, Okumura A, Nakayasu C, Ohto-Nakanishi T, et al. Arachidonic acid-derived dihydroxy fatty acids in neonatal cord blood relate symptoms of autism spectrum disorders and social adaptive functioning: Hamamatsu Birth Cohort for Mothers and Children (HBC Study). Psychiatry and clinical neurosciences. 2024;78(9):546-57. Epub 2024/07/23. doi: 10.1111/pcn.13710. PubMed PMID: 39041066; PubMed Central PMCID: PMCPMC11488600. https://pmc.ncbi.nlm.nih.gov/articles/PMC11488600/pdf/PCN-78-546.pdf (last viewed May 28, 2026).

[40] WHO. Reducing pain at the time of vaccination: WHO position paper, September 2015-Recommendations. Vaccine. 2016;34(32):3629-30. Epub 2015/11/17. doi: 10.1016/j.vaccine.2015.11.005. PubMed PMID: 26571310. (September 24, 2015) https://www.who.int/publications/i/item/who-wer9039 (last viewed May 30, 2026).

during early development, one obvious question remains; is there enough evidence of harm from acetaminophen to change practice regarding its use?

1. How much evidence is enough?

Although randomized, blinded, placebo-controlled experiments to obtain absolute proof that acetaminophen induces ASD in humans might seem worthwhile at first glance, such experiments would be both impractical and unethical. In terms of trial design, acetaminophen effectively treats fevers, so study subjects would be able to effectively guess their study group, making a blinded placebo control difficult. In addition, even without a blinded placebo control, exposure would need to be controlled from conception to age 5 in thousands of individuals, consuming vast amounts of time and resources for the trial. Even more important is the fact that evidence (Tables 1-5) already conclusively demonstrates that acetaminophen is a developmental neurotoxin. Thus, exposure of any fetus, baby, or child to the drug for the sake of research is unethical.

Changes in clinical practice should not require enough evidence to conclude without any reasonable doubt that exposure of susceptible children to acetaminophen is associated with many cases of ASD. In general, the "precautionary principle" should prevail, which requires only that a threat be "reasonable and plausible" to be avoided.[41]

Only a few lines of evidence are required to conclude that acetaminophen exposure may reasonably and plausibly be connected with neurodevelopmental problems. For example, the facts that, (a) children with ASD are deficient in a metabolic pathway (sulfation) that is necessary for safe metabolism of acetaminophen (a part of line of evidence #4); (b) relatively low doses acetaminophen in early life cause long-term brain dysfunction in laboratory mice and rats (line of evidence #15); and (c) acetaminophen cannot be used in some domestic animals because they are deficient in the same pathway (glucuronidation) that is deficient in all newborn babies (line of evidence #5) should have been sufficient to remove the drug entirely from the pediatric market more than a decade ago.

From another perspective, the 2008 study by Schultz and colleagues[42] should have been sufficient to have the safety of acetaminophen for pediatric use completely and immediately reevaluated. That study provided the initial red flag pointing toward the role of acetaminophen in the induction of ASD. However, further analysis reveals that there was sufficient evidence available to scientists prior to 2008 that, if the red flag had been taken seriously, would have quickly led to the conclusion that acetaminophen was very likely involved in the induction of

---

[41] Resnik DB. The precautionary principle and medical decision making. The Journal of medicine and philosophy. 2004;29(3):281-99. Epub 2004/10/30. doi: 10.1080/03605310490500509. PubMed PMID: 15512973. (June 2004) https://pubmed.ncbi.nlm.nih.gov/15512973/ (last viewed May 30, 2026).

[42] *Id.* at n. 4.

ASD.[43] For example the rationale underlying the widespread but erroneous belief that acetaminophen was proven safe for use in babies and children was not critically evaluated until more than a decade later, in 2022[44] (line of evidence #19).

The bottom line is that evidence sufficient to drive regulatory changes and changes in clinical practice has long been ignored. Further, proof without reasonable doubt that exposure of susceptible children to acetaminophen can and does cause ASD exceeds what should be required to remove the drug entirely from the pediatric market. Suspicion of danger should be sufficient. At this point, the evidence (Tables 1-5, Figure 1) leads to a level of certainty that far exceeds suspicion.

2. A single line of easily misconstrued evidence dominates the current discussion.

Observational studies assessing acetaminophen use and neurological outcomes have dominated the medical literature and public discourse surrounding the link between acetaminophen and ASD. More than 30 studies assessing the connection between prenatal acetaminophen use and ASD (line of evidence #11a), and one study assessing the connection between postnatal acetaminophen use and ASD (line of evidence #11b) have been published. Such studies can provide insight into potential causality. Indeed, if no association exists, causality is not likely.

The "raw analysis" from observational studies generally shows a strong connection between acetaminophen use and ASD. However, using statistical methods to adjust for factors that the authors believe might confound the conclusions, the associations between acetaminophen and ASD usually found in the raw analysis can be diminished or even removed entirely. For example, in the widely publicized study published by Ahlqvist and colleagues in 2024,[45] the raw data showed a strong connection between high levels of acetaminophen use during pregnancy and ASD (Figure 3). The relationship was dose-dependent, with high doses of acetaminophen associated with a hazard ratio of 1.87 (C.I.:1.71-2.06) and statistically significant associations ($p < 0.001$) at low, medium, and high doses of acetaminophen. These associations are particularly concerning given the high prevalence of acetaminophen use in some populations. As has been previously discussed,[46] a combination of the hazard ratio associated with a given factor and the prevalence of that factor in the population dictates the potential impact of that

[43] *Id.* at n. 20.
[44] Cendejas-Hernandez J, Sarafian J, Lawton V, Palkar A, Anderson L, Lariviere V, et al. Paracetamol (Acetaminophen) Use in Infants and Children was Never Shown to be Safe for Neurodevelopment: A Systematic Review with Citation Tracking. . Eur J Pediatr. 2022;181:1835-57. doi: 10.1007/s00431-022-04407-w. https://pmc.ncbi.nlm.nih.gov/articles/PMC9056471/pdf/431_2022_Article_4407.pdf (last viewed May 28, 2026).
[45] *Id.* at n. 11.
[46] *Id.* at n. 22.

factor on public health. Thus, for something as common as acetaminophen use, any statistically significant risk for ASD is probably unacceptable.

However, the conclusion of the widely publicized paper by Ahlqvist noted above [47] was that "Acetaminophen use during pregnancy was not associated with children's risk of autism…."

The conclusion reached by Ahlqvist and colleagues[48] that acetaminophen use during pregnancy is not associated with ASD, was based on the application of statistical "correction" for confounding factors that are, in fact, associated with oxidative stress, a cofactor rather than a confounding factor in the induction of ASD. Any pharmacologist familiar with the metabolism of acetaminophen will be able to confirm that acetaminophen interacts with oxidative stress to create toxicity. The effect of correction for cofactor-associated variables in the Ahlqvist study is shown in Figure 3. As can be seen, the data published by Ahlqvist are exactly as expected if indeed acetaminophen, combined with a wide range of genetic, epigenetic and environmental factors related to oxidative stress, trigger the induction of ASD. As previously pointed out,[49] [50] [51] the results of such corrections, while informative, cannot be used to determine whether associations are clinically important. Such an error in drawing conclusions from such studies will be evident to professional statisticians, suggesting that experts on the Ahlqvist study team performing statistical tests may have been unaware of the pharmacokinetics of acetaminophen, including interactions of the drug with factors related to inflammation and oxidative stress. In effect, Ahlqvist and colleagues catalogued the conditions under which acetaminophen is dangerous for neurodevelopment. They did not determine that the drug is safe for neurodevelopment. The same problem can be identified in a study by Tovo-Rodrigues and colleagues,[52] who also adjusted their analysis using numerous factors related to oxidative stress.

A formal demonstration of the problem of statistical correction for cofactors (aka, predisposing factors or interacting variables) is shown in Figure 3 and Table 6. The table shows the results of a computer simulation in which 50 % of all cases of ASD were caused by a combination of oxidative stress and exposure to acetaminophen during an arbitrary time period.

---

[47] *Id.* at n. 11.
[48] *Id.*
[49] *Id.* at n. 22.
[50] *Id.* at n. 12.
[51] Baker BH, Bammler TK, Barrett ES, Bush NR, Collett BR, Derefinko KJ, et al. Associations of maternal blood biomarkers of prenatal APAP exposure with placental gene expression and child attention deficit hyperactivity disorder. Nature Mental Health. 2025. doi: 10.1038/s44220-025-00387-6. https://pmc.ncbi.nlm.nih.gov/articles/PMC12439753/pdf/nihms-2110227.pdf (last viewed May 28, 2026).
[52] Tovo-Rodrigues L, Carpena MX, Martins-Silva T, Santos IS, Anselmi L, Barros AJD, et al. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. Paediatr Perinat Epidemiol. 2020;34(3):278-86. Epub 2020/03/21. doi: 10.1111/ppe.12649. PubMed PMID: 32196712. (May 2020) https://pubmed.ncbi.nlm.nih.gov/32196712/ (last viewed May 30, 2026).

In this computer simulation, the raw ("uncorrected" analysis) shows a hazard ratio for ASD with acetaminophen use of 2.55 (CI 2.41-2.71, $p = 2 \times 10^{-16}$), close to the actual hazard ratio of 2.667 built into the model. However, after correcting for 100 % of the factors that account for all susceptibility to acetaminophen-mediated injury, the calculated hazard ratio for ASD with acetaminophen use is 0.85 (CI 0.80-0.90; $p = 2 \times 10^{-7}$). Thus, when oxidative stress factors are treated as confounding factors, acetaminophen is "shown" to be protective from ASD despite the fact that it actually caused 50 % of all ASD cases in this computer simulation.

One particularly egregious comedy of errors related to associations between ASD and acetaminophen use during pregnancy occurred with the publication of a study by Prahm and colleagues based on the Danish National Birth Cohort.[53] In that study, the authors found that the "crude incidence rate" of ASD (diagnoses per 10,000 person years) was 31.2 for heavy users of acetaminophen during pregnancy, compared to 23.1 for nonusers of acetaminophen during pregnancy. The 35% greater prevalence of ASD in children whose mothers were heavy users of acetaminophen was negated by adjustment for interacting variables, as in other studies, resulting in a hazard ratio of 1.01 (CI 0.88-1.14). This error was identical to errors in other studies. However, release of the information to the public resulted in an additional error.

Prahm and colleagues[54] collected data for maternal acetaminophen prescriptions during pregnancy and on ASD diagnoses for children born between January 1, 1997, and July 31, 2022. They stopped collecting data on July 31, 2023, which means that some of their patients had only one year of follow-up time. Two of the main factors affecting their data were, first, that acetaminophen prescriptions for pregnant women in Denmark drastically increased in 2014, and 2015 due to a change in over-the-counter drug regulation in Denmark.[55] Thus, over-the-counter purchases of acetaminophen prior to 2014, were replaced by prescriptions for acetaminophen after 2014. This resulted in a more than 10-fold increase in acetaminophen prescriptions from 2015 to 2023 relative to the pre-2014 period. Second, the average age of diagnosis of ASD is more than five years of age. [56]

---

[53] AMA, Acetaminophen Exposure During Pregnancy and the Risk of Autism in Offspring, Prahm KP, Chen P, Rode L. https://jamanetwork.com/journals/jamapediatrics/article-abstract/2847695 (April 13, 2026) (last viewed July 1, 2026).

[54] *Id.*

[55] Pflugfelder S, Gram EB, Damkier P. Acetaminophen in Pregnancy: A Population-Level Drug-Utilization Study of Prescription-Based Acetaminophen Use Among Pregnant Women in Denmark From 2001 to 2023. Basic Clin Pharmacol Toxicol. 2025;136(6):e70048. Epub 2025/05/02. doi: 10.1111/bcpt.70048. PubMed PMID: 40313013; PubMed Central PMCID: PMCPMC12046276. https://pmc.ncbi.nlm.nih.gov/articles/PMC12046276/pdf/BCPT-136-0.pdf (last viewed May 28, 2026).

[56] Van't Hof M, Tisseur C, van Berckelear-Onnes I, van Nieuwenhuyzen A, Daniels AM, Deen M, Hoek HW, Ester WA. Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. Autism. 2021 May;25(4):862-873. doi:

Thus, during the period of the study when the vast majority of the acetaminophen was prescribed, autism was not completely diagnosed, and during the period of the study when autism was more completely diagnosed, acetaminophen was seldomly prescribed because over-the-counter medications were favored. The result was as might be expected: 1.8% of children exposed to acetaminophen as a fetus were diagnosed with ASD, compared to 3.0% of unexposed children. The authors had attempted to adjust for this problem in their analysis by converting their data into diagnoses per year, as described above. However, the ensuing media coverage, involving articles in numerous reputable media outlets, including JAMA,[57] MedPage Today,[58] Reuters,[59] the University of Minnesota (under the topic "anti-science"),[60] and Contemporary OB/GYN,[61] reported the raw numbers determined by Prahm and colleagues. These raw numbers, showing 40 % less ASD with fetal acetaminophen exposure, gave the false impression that fetal exposure to acetaminophen offers significant protection from ASD.

Another problem with analyses of healthcare databases is that such analyses do not take into account that oxidative stress may be associated with genetic, epigenetic, or persistent environmental factors, causing persistence of susceptibility in an individual. The resulting effect is that assessment of acetaminophen exposure versus oxidative-stress-related variables at a given time (e.g., during pregnancy or during infancy) may miss important injury-inducing exposure to acetaminophen that happened at a different time (e.g., during labor and delivery). The net result of this situation is that the analysis can identify associations between oxidative-stress related variables but not acetaminophen, even under ideal circumstances. That is to say, even if, hypothetically, 100 % of acetaminophen exposures are documented in a given study period, the

---

10.1177/1362361320971107. Epub 2020 Nov 19. PMID: 33213190. https://pubmed.ncbi.nlm.nih.gov/33213190/ (last viewed July 20, 2026).

[57] Anderer S. New Study Finds No Link Between Acetaminophen Use in Pregnancy and Autism. JAMA. 2026. doi: 10.1001/jama.2026.2130. (May 8, 2026) https://jamanetwork.com/journals/jama/article-abstract/2849017 (last viewed May 30, 2026).

[58] Everyday Health Group. George J. Does Tylenol Increase Autism Risk? A New Study Has Answers - No link emerged in Danish cohort, with or without sibling comparisons. MedPage Today. 2026 Accessed: May 12, 2026. Available from: https://www.medpagetoday.com/neurology/autism/120766 (last viewed May 28, 2026).

[59] Reuters. Lapid N. Tylenol in pregnancy not linked with autism, Danish study finds. 2026 Accessed: May 12, 2026. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/tylenol-pregnancy-not-linked-with-autism-danish-study-finds-2026-04-13/. (last viewed May 30, 2026).

[60] University of Minnesota. Van Beusekom M. Tylenol during pregnancy not tied to increased risk of autism in children. CIDRAP. 2026 Accessed: May 12, 2026. Available from: https://www.cidrap.umn.edu/anti-science/tylenol-during-pregnancy-not-tied-increased-risk-autism-children (last viewed May 28, 2026).

[61] Fitch J. Danish study finds acetaminophen exposure not associated with increased autism risk. Contemporary OB/GYN. 2026 Accessed: May 12, 2026. Available from: https://www.contemporaryobgyn.net/view/danish-study-acetaminophen-exposure-not-associated-increased-autism-risk (last viewed May 28, 2026).

net effect of limiting the study period (e.g., to prenatal or postnatal exposure) is that only a fraction of potentially important acetaminophen exposures will be documented. The only way to avoid this problem would be to assess all exposures to acetaminophen which might trigger ASD, from conception to age 5. Although such an approach is not feasible, sufficient evidence is already available (Tables 1-5) to draw conclusions for clinical practice. Therefore, the fact that ideal observational studies are not feasible should be of little concern.

A more recent analysis of sibling-controlled data from Taiwan, according to the authors of the study, identified "unaddressed sources of bias and prevents firm conclusions from being drawn using the sibling design."[62] In short, a positive association between autism and acetaminophen use (HR 1.75; 95% CI, 1.29-2.36) was observed when only the older sibling was exposed to acetaminophen. Potential sources of bias in the data include the fact that parents may halt reproduction after having a child with ASD,[63] [64] although this effect can be complex and possibly dependent on the population studied.[65] Another source of potential bias is rooted in the fact that pregnancy is not the period of greatest risk for acetaminophen-induced induction of ASD,[66] and individuals who have older siblings without ASD are expected to be, on average, less sensitive to the induction of ASD than are individuals with older siblings who do have ASD. Thus, individuals who have older siblings without ASD are, in theory, relatively less likely to experience ASD induction during pregnancy, when risk is relatively low compared to the immediate post-partum period and to very early childhood. However, the biases affecting current

---

[62] Lee PC, Chuang YH, Hu YH, Lin CN, Li CY, Chen YY, et al. Maternal Acetaminophen Use and Child Neurodevelopment. JAMA pediatrics. 2026. Epub 2026/03/09. doi: 10.1001/jamapediatrics.2026.0071. PubMed PMID: 41801232; PubMed Central PMCID: PMCPMC12973218. (May 1, 2026) https://pubmed.ncbi.nlm.nih.gov/41801232/ (last viewed May 30, 2026).

[63] Hoffmann TJ, Windham GC, Anderson M, Croen LA, Grether JK, Risch N. Evidence of reproductive stoppage in families with autism spectrum disorder: a large, population-based cohort study. JAMA Psychiatry. 2014;71(8):943-51. Epub 2014/06/20. doi: 10.1001/jamapsychiatry.2014.420. PubMed PMID: 24942798. (August 2014) https://pubmed.ncbi.nlm.nih.gov/24942798/ (last viewed May 30, 2026).

[64] Power RA, Kyaga S, Uher R, MacCabe JH, Långström N, Landen M, et al. Fecundity of Patients With Schizophrenia, Autism, Bipolar Disorder, Depression, Anorexia Nervosa, or Substance Abuse vs Their Unaffected Siblings. JAMA Psychiatry. 2013;70(1):22-30. doi: 10.1001/jamapsychiatry.2013.268. (January 2013) https://pubmed.ncbi.nlm.nih.gov/23147713/ (last viewed May 30, 2026).

[65] Kuja-Halkola R, Larsson H, Lundström S, Sandin S, Chizarifard A, Bölte S, et al. Reproductive stoppage in autism spectrum disorder in a population of 2.5 million individuals. Molecular autism. 2019;10:45. Epub 2019/12/21. doi: 10.1186/s13229-019-0300-6. PubMed PMID: 31857873; PubMed Central PMCID: PMCPMC6907273. https://pmc.ncbi.nlm.nih.gov/articles/PMC6907273/pdf/13229_2019_Article_300.pdf (last viewed May 28, 2026).

[66] *Id.* at n. 3.

sibling control studies remain unknown, and errors underlying the assumptions employed in the analysis, described above and illustrated in Figure 3, stand out as the obvious flaw.

Misconstrued analyses of healthcare databases can be influential. An example of placing heavy emphasis on a misconstrued line of evidence is found in Graeca and Kulesza's groundbreaking work showing acetaminophen-induced developmental problems related to auditory function.[67] The overreliance on observational studies as a basis for understanding the connection between acetaminophen and ASD is evident in the Introduction of that paper:

> Specifically, in utero (but not postnatal) exposure to paracetamol results in a 19% increased risk of ASD (Masarwa et al., 2018; Alemany et al., 2021; Khan et al., 2022).

The studies by Masarwa et al. in 2018[68] and by Khan et al. in 2022[69]cited by Graeca and Kulesza address only prenatal exposure. Therefore, Graeca and Kulesza base their conclusion that postnatal exposure to acetaminophen (paracetamol) is not associated with ASD solely on the study by Alemany and colleagues in 2021.[70] However, Alemany and colleagues did not conclude that postnatal acetaminophen use is not associated with ASD. Rather, they concluded that postnatal use of acetaminophen is not associated with "autism spectrum condition symptoms," which has a prevalence from 6 % to 13 % of the samples they evaluated, much higher than the prevalence of ASD in their study population. However, more than 80 % of Alemany's sample (48,161 out of 58,006 total individuals) came from the Danish National Birth Cohort (DNBC), and ASD, not autism spectrum condition symptoms, was measured in that cohort. In Alemany's analysis of the connection between postnatal acetaminophen use and ASD in the DNBC, they found a positive association (OR = 1.30, CI 1.02-1.66). Given that the DNBC dramatically

---

[67] *Id.* at n. 34.

[68] Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. 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. Am J Epidemiol. 2018;187(8):1817-27. Epub 2018/04/25. doi: 10.1093/aje/kwy086. PubMed PMID: 29688261. (August 2018) https://pubmed.ncbi.nlm.nih.gov/29688261/ (last viewed May 30, 2026).

[69] Khan FY, Kabiraj G, Ahmed MA, Adam M, Mannuru SP, Ramesh V, et al. A Systematic Review of the Link Between Autism Spectrum Disorder and Acetaminophen: A Mystery to Resolve. Cureus. 2022;14(7):e26995. doi: 10.7759/cureus.26995. https://www.researchgate.net/publication/362872615_A_Systematic_Review_of_the_Link_Between_Autism_Spectrum_Disorder_and_Acetaminophen_A_Mystery_to_Resolve (last viewed May 28, 2026).

[70] Alemany S, Avella-García C, Liew Z, García-Esteban R, Inoue K, Cadman T, 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. Eur J Epidemiol. 2021;36(10):993-1004. Epub 2021/05/29. doi: 10.1007/s10654-021-00754-4. PubMed PMID: 34046850. https://pmc.ncbi.nlm.nih.gov/articles/PMC8542535/pdf/10654_2021_Article_754.pdf (last viewed May 28, 2026).

underreports acetaminophen use[71] and given that the authors corrected for oxidative stress-related variables in an invalid fashion (see discussion above), the odds ratio of 1.30 is probably underestimated dramatically. Nevertheless, an odds ratio of 1.30 is profoundly concerning given the high prevalence of acetaminophen exposure. However, when reporting overall results, for example in the abstract of the paper, Alemany and colleagues combined results from analysis of ASD in the DNBC with results from analysis of smaller databases that reported only autism spectrum condition symptoms.[72] In their combined analysis, they counted (weighed) the very concerning results from the DNBC as only 31.84 % of the total, despite the facts that it contained more than 80 % of the total individuals, was the only database to contain measures of ASD, and was the only database which yielded statistically significant results in the analysis. Alemany and colleagues provided no explanation for the weighting scheme or for the lack of emphasis on the very concerning results from their analysis of the DNBC.

In short, analysis of associations between prenatal acetaminophen use and ASD (Table 2, line of evidence #11a) and associations between postnatal acetaminophen use and ASD (Table 2, line of evidence #11b) are informative and useful, but those lines of evidence have been fraught with misinformation, miscalculation, and misinterpretation. Recently:[73]

> It is concluded that risks of acetaminophen use for neurodevelopment obtained from multivariate analysis of cohort data depend on underlying assumptions in the analyses, and that other evidence, both abundant and robust, demonstrate the critical role of acetaminophen in the etiology of ASD.

In a recent article in *Environmental Health*,[74] Prada et al. assess evidence related to acetaminophen use during pregnancy and neurodevelopmental injury, including autism spectrum disorder (ASD). Prada et al, unlike other investigators, cited the formal mathematical proof [75] that treating critical and interacting variables as confounding factors will erroneously eliminate the contribution of acetaminophen to the induction of autism in the final analysis. Unfortunately, Prada et al.,[76] dismissed the mathematical proof as "speculative" without supporting "direct evidence."

Support for the interaction between acetaminophen and oxidative stress in neurodevelopmental injury, particularly autism spectrum disorder (ASD) has been the subject of

---

[71] *Id.* at n. 22.
[72] *Id.* at n. 70.
[73] *Id.* at n. 12.
[74] Prada D, Ritz B, Bauer AZ, Baccarelli AA. Evaluation of the evidence on acetaminophen use and neurodevelopmental disorders using the Navigation Guide methodology. Environmental Health. 2025;24(1):56. doi: 10.1186/s12940-025-01208-0. (August 2025) https://pubmed.ncbi.nlm.nih.gov/40804730/ (last viewed May 30, 2026).
[75] *Id.* at n. 12.
[76] *Id.* at n. 74.

extensive review,[77] and will not be described in detail here. However, as Prada et al., briefly reviewed themselves,[78] studies in laboratory animals indicate that oxidative stress is a hallmark of acetaminophen-mediated neurological injury. More importantly, children with ASD are known to have an impaired ability to metabolize acetaminophen via phase II metabolic pathways,[79] [80] leading to the shunting of acetaminophen down a phase I pathway that involves a toxic intermediate (N-acetyl-p-benzoquinone imine; (NAPQI).[81] [82] NAPQI binds directly to cellular proteins, inducing toxicity, and it may also lead to other reactions that create further toxicity.[83] As noted in our current list of evidence (Table 1, line of evidence #3), enzymes that produce NAPQI are present during the induction of ASD or associated in some way with ASD. Further, neutralization of NAPQI is dependent on the "master antioxidant" in the human body, glutathione. Low concentrations of available (active, reduced state) glutathione are frequently used as an indicator of oxidative stress resulting from a vast number of stimuli. With these factors in mind, it is abundantly clear that oxidative stress will indeed enhance the toxicity of acetaminophen, and it is therefore difficult to understand why Prada et al., would dismiss warnings about treating oxidative stress-related factors as confounding factors. Indeed, they provided no justification for their dismissal.

3. Plausible mechanism

Given that the metabolism of acetaminophen yields a toxic metabolite, NAPQI (a reactive electrophile, similar to that produced by the metabolism of ethanol) especially under conditions associated with ASD, and given that the toxic metabolite affects mitochondrial and

---

[77] Parker W, Hornik CD, Bilbo S, Holzknecht ZE, Gentry L, Rao R, et al. The role of oxidative stress, inflammation and acetaminophen exposure from birth to early childhood in the induction of autism. J Int Med Res. 2017;45(2):407-38. (March 16, 2017) https://pubmed.ncbi.nlm.nih.gov/28415925/ (last viewed May 30, 2026).
[78] *Id.* at n. 74.
[79] *Id.* at n. 19.
[80] *Id.* at n. 17.
[81] *Id.* at n. 77.
[82] Du K, Ramachandran A, Jaeschke H. Oxidative stress during acetaminophen hepatotoxicity: Sources, pathophysiological role and therapeutic potential. Redox biology. 2016;10:148-56. Epub 2016/10/17. doi: 10.1016/j.redox.2016.10.001. PubMed PMID: 27744120; PubMed Central PMCID: PMCPMC5065645. https://pmc.ncbi.nlm.nih.gov/articles/PMC5065645/pdf/main.pdf (last viewed May 28, 2026).
[83] Chan JCY, Soh ACK, Kioh DYQ, Li J, Verma C, Koh SK, et al. Reactive Metabolite-induced Protein Glutathionylation: A Potentially Novel Mechanism Underlying Acetaminophen Hepatotoxicity. Mol Cell Proteomics. 2018;17(10):2034-50. Epub 2018/07/15. doi: 10.1074/mcp.RA118.000875. PubMed PMID: 30006487; PubMed Central PMCID: PMCPMC6166671. https://pmc.ncbi.nlm.nih.gov/articles/PMC6166671/pdf/zjw2034.pdf (last viewed May 28, 2026).

neuronal function, the induction of ASD by acetaminophen under conditions of oxidative stress is plausible from a mechanistic perspective (lines of evidence #1-5). The observation that ASD is similar in many regards to fetal alcohol spectrum disorder (line of evidence #24) demonstrates that a single chemical does, in fact, have the means to produce a complex developmental spectrum disorder.

The observation that acetaminophen affects social function in adults (line of evidence #20) demonstrates that the drug does indeed have a propensity to affect aspects of brain function involved in all ASD phenotypes. This view is corroborated by studies in laboratory animals[84] showing acetaminophen-mediated damage to cortical neurons (line of evidence #18), a cell type apparently involved in ASD phenotypes.

Although use of acetaminophen is frequently undocumented,[85] evidence suggests that most individuals throughout the US and Europe are exposed to the drug both in utero and during early childhood,[86] indicating that acetaminophen does indeed have the opportunity to induce ASD. As previously discussed,[87] despite low levels (< 10 % of the population) of exposure to acetaminophen reported in the Danish and Swedish databases, assessments of acetaminophen use in those populations indicate that more than 50 % of those populations are exposed. [88] [89] Further, factors associated with oxidative stress, which determine sensitivity to acetaminophen-mediated injury,[90] are connected with reasons for using acetaminophen. Such factors include infection, antibiotic use, and headaches. Thus, exposure to acetaminophen of individuals susceptible to acetaminophen-mediated neurological injury is almost certainly higher than in the population as a whole, increasing risk. Also convincing is the direct measurement of acetaminophen

---

[84] Posadas I, Santos P, Blanco A, Muñoz-Fernández M, Ceña V. Acetaminophen induces apoptosis in rat cortical neurons. PLoS One. 2010;5(12):e15360. Epub 2010/12/21. doi: 10.1371/journal.pone.0015360. PubMed PMID: 21170329; PubMed Central PMCID: PMCPMC3000821. https://pmc.ncbi.nlm.nih.gov/articles/PMC3000821/pdf/pone.0015360.pdf (last viewed May 28, 2026).

[85] *Id.* at n. 20.

[86] *Id.*

[87] *Id*. at n. 22.

[88] Ertmann RK, Møller JJ, Waldorff FB, Siersma V, Reventlow S, Söderström M. The majority of sick children receive paracetamol during the winter. Danish medical journal. 2012;59(12):A4555. Epub 2013/01/08. PubMed PMID: 23290291. https://content.ugeskriftet.dk/sites/default/files/scientific_article_files/2018-12/a4555.pdf (last viewed May 28, 2026).

[89] Bornehag CG, Reichenberg A, Hallerback MU, Wikstrom S, Koch HM, Jonsson BA, et al. Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry. 2018;51:98-103. Epub 2018/01/15. doi: 10.1016/j.eurpsy.2017.10.007. PubMed PMID: 29331486. (June 2018) https://pubmed.ncbi.nlm.nih.gov/29331486/ (last viewed May 30, 2026).

[90] *Id.* at n. 77.

metabolites in humans,[91] [92] [93] which demonstrates widespread exposure to the drug during neurodevelopment in the populations assessed.

4. An implausible hypothesis: acetaminophen does not play a critical role in the induction of ASD

A useful exercise of scientific reasoning is to consider the "null hypothesis." In this case, what if acetaminophen does NOT play a critical role in the induction of ASD? If that is the case, several observations would be very difficult to explain.

- Why did Schultz find that acetaminophen exposure was the common denominator among children with regressive ASD (line of evidence #12)?
- Why did Ji and colleagues find very strong correlations between acetaminophen use during labor and delivery and ASD (line of evidence #13)?
- Why is acetaminophen a potent neurodevelopmental toxin in laboratory rats and especially mice (line of evidence #15), but not humans?
- Why is acetaminophen safe in human neonates who have the same metabolic deficiency that makes acetaminophen dangerous in domestic cats (line of evidence #5)?
- Why is the circumcision procedure associated with adverse effects on social function later in life (line of evidence #10)?
- What is the explanation for the unusual prevalence of autism among Orthodox Jews (line of evidence #14), individuals with cystic fibrosis (line of evidence #22), and individuals in some Scandinavian countries (line of evidence #28)?
- Why is acetaminophen safe for human neonates even though it alters nerve development in tissue culture (Table 3, line of evidence #21)?

---

[91] *Id.* at n. 51.

[92] Ji Y, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, 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. JAMA Psychiatry. 2020;77(2):180-9. Epub 2019/10/31. doi: 10.1001/jamapsychiatry.2019.3259. PubMed PMID: 31664451; PubMed Central PMCID: PMCPMC6822099. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2753512 (last viewed May 28, 2026).

[93] Baker BH, Lugo-Candelas C, Wu H, Laue HE, Boivin A, Gillet V, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. JAMA pediatrics. 2020;174(11):1073-81. Epub 2020/09/29. doi: 10.1001/jamapediatrics.2020.3080. PubMed PMID: 32986124; PubMed Central PMCID: PMCPMC7522774. https://pmc.ncbi.nlm.nih.gov/articles/PMC7522774/ (last viewed May 28, 2026).

Several other observations must be "coincidental" in the sense that they do not reflect any connection between acetaminophen and ASD. For example:

- The formation of a toxic metabolite by acetaminophen in the presence of oxidative stress, which is associated with ASD (lines of evidence #1 through #4), must be coincidental.
- Similarities between FASD and ASD (line of evidence #24) must be coincidental or due to an unknown factor.
- Similarities between the effects of acetaminophen on adults and the hallmarks of the ASD phenotype (line of evidence #20) must be coincidental.
- The association of both acetaminophen and ASD with altered gut function (line of evidence #6) must be coincidental.
- The association of both acetaminophen and ASD with arachidonic acid metabolism (line of evidence #7), alterations in hearing and smell (line of evidence #17), and impaired Ca++ and mitochondrial function (line of evidence #9) must all be coincidental.
- The correlations in time between ASD prevalence and acetaminophen use must be coincidental (lines of evidence #27, #29, and #30).

Recently, Fluegge and Fluegge argue that ASD is "specifically induced from environmental emissions of nitrous oxide (N_2O)" rather than acetaminophen. In this view, increases in atmospheric nitrous oxide that result from use of synthetic nitrogen fertilizers, which began in the mid-1910s,[94] are responsible for the pandemic of ASD. Their conclusions are not reconcilable with many of the observations described above, and were based on the argument that acetaminophen was first brought to market in 1954, over a decade after ASD was first described in 1943 by Leo Kanner.[95] According to Fluegge and Fluegge, the description of autism more than a decade before acetaminophen was introduced into the commercial market "considerably weakens the argument of causation" connecting acetaminophen with ASD. The authors were apparently unaware that acetaminophen was, for practical intents and purposes, introduced into commercial use in 1886. Both acetanilide (introduced in 1886 [96]) and phenacetin

[94] Frink CR, Waggoner PE, Ausubel JH. Nitrogen fertilizer: retrospect and prospect. Proc Natl Acad Sci U S A. 1999;96(4):1175-80. Epub 1999/02/17. doi: 10.1073/pnas.96.4.1175. PubMed PMID: 9989997; PubMed Central PMCID: PMCPMC33552. https://pmc.ncbi.nlm.nih.gov/articles/PMC33552/pdf/pq001175.pdf (last viewed May 28, 2026).
[95] Kanner L. Autistic disturbances of affective contact. Nervous child. 1943;2(3):217-50. https://autismtruths.org/pdf/Autistic%20Disturbances%20of%20Affective%20Contact%20-%20Leo%20Kanner.pdf (last viewed May 28, 2026).
[96] Mahmud S, Rosen N. History of NSAID Use in the Treatment of Headaches Pre and Post-industrial Revolution in the United States: the Rise and Fall of Antipyrine, Salicylic Acid, and Acetanilide. Current pain and headache reports. 2019;23(1):6. Epub 2019/01/24. doi:

(introduced in 1887 [97] [98]) are prodrugs that are converted into acetaminophen by the human body. This undermines the principle argument put forth by Fluegge and Fluegge, although it does not diminish the potential for nitrous oxide to contribute to the induction of ASD because of its tendency to induce oxidative stress.[99] [100] Finally, it should be noted that ASD was first described in considerable detail by Grunya Sukhareva in 1925,[101] [102] not by Kanner in 1943, although this fact would not affect the argument by Fluegge and Fluegge.

The idea that ASD is genetic is fraught with additional incompatibility with available evidence. If the disorder is genetic, then its incidence cannot have changed dramatically over time.

- Why were early investigators oblivious to the high prevalence of ASD (line of evidence #30)?
- Since specific genes responsible for most cases of ASD cannot be found despite obvious heritability, why does the principle of missing heritability *not* apply (line of evidence #23)?

10.1007/s11916-019-0744-6. PubMed PMID: 30673879. (January 2019) https://pubmed.ncbi.nlm.nih.gov/30673879/ (last viewed May 30, 2026).

[97] Clissold SP. Paracetamol and phenacetin. Drugs. 1986;32 Suppl 4:46-59. Epub 1986/01/01. doi: 10.2165/00003495-198600324-00005. PubMed PMID: 3552585. https://pubmed.ncbi.nlm.nih.gov/3552585/ (last viewed May 30, 2026).

[98] Phenacetin and Thallin for Children. Ind Med Gaz. 1889 Jul;24(7):215. PMID: 29000162; PMCID: PMC5141739. https://pmc.ncbi.nlm.nih.gov/articles/PMC5141739/ (last viewed July 31, 2026).

[99] Grzych G, Diesnis R, Dupré T, Niguet JP, Gernez E, Denimal D, et al. Addressing the Global Challenge of Nitrous Oxide Misuse Through a Multidisciplinary Approach: Example of the PROTOSIDE Network. Toxics. 2025;13(6). Epub 2025/06/25. doi: 10.3390/toxics13060466. PubMed PMID: 40559939; PubMed Central PMCID: PMCPMC12197755. https://pmc.ncbi.nlm.nih.gov/articles/PMC12197755/pdf/toxics-13-00466.pdf (last viewed May 28, 2026).

[100] Singh SK, Misra UK, Kalita J, Bora HK, Murthy RC. Nitrous oxide related behavioral and histopathological changes may be related to oxidative stress. Neurotoxicology. 2015;48:44-9. Epub 2015/03/15. doi: 10.1016/j.neuro.2015.03.003. PubMed PMID: 25766523. (May 2015) https://pubmed.ncbi.nlm.nih.gov/25766523/ (last viewed May 30, 2026).

[101] Manouilenko I, Bejerot S. Sukhareva--Prior to Asperger and Kanner. Nordic journal of psychiatry. 2015;69(6):479-82. Epub 2015/04/01. doi: 10.3109/08039488.2015.1005022. PubMed PMID: 25826582. (August 2015) https://pubmed.ncbi.nlm.nih.gov/25826582/ (last viewed May 30, 2026).

[102] Sher DA, Gibson JL. Pioneering, prodigious and perspicacious: Grunya Efimovna Sukhareva's life and contribution to conceptualising autism and schizophrenia. European child & adolescent psychiatry. 2023;32(3):475-90. Epub 2021/09/26. doi: 10.1007/s00787-021-01875-7. PubMed PMID: 34562153; PubMed Central PMCID: PMCPMC10038965. https://pmc.ncbi.nlm.nih.gov/articles/PMC10038965/pdf/787_2021_Article_1875.pdf (last viewed May 28, 2026).

- Why do numerous observations indicate that ASD is rare in the absence of modern medicine (line of evidence #31)?
- Why is some ASD infantile, and other ASD regressive?

5. Barriers to moving forward

Necessary changes in practice should be, for the most part, a matter of rethinking the accepted routines and habits of analgesic use given overwhelming evidence that acetaminophen is a neurodevelopmental toxin.[103] However, the currently widespread acceptance of a view that does not include acetaminophen as an important component in the etiology of ASD may be impeding progress. The "multifactorial model," in which a wide range of genetic, epigenetic and environmental factors contribute to the induction of ASD, is now widely accepted by investigators in the field.[104] [105] A wide range of genetic, epigenetic, and environmental factors are indeed associated with ASD. However, this fact should not be used to downplay the role of any single factor playing a significant role in the etiology of autism.[106]

Compelling evidence for a specific role of acetaminophen as a cause of ASD has mounted for years. The first study in laboratory mice showing long-term, profound (almost complete) loss of important aspects of cognitive function following early-life exposure to acetaminophen was published more than a decade ago, in 2013, by Viberg and colleagues.[107] In that study, two doses of 30 mg/kg acetaminophen were administered in one day. That dose is not exceedingly higher than the oral dosage of acetaminophen in babies and children, who can receive up to 4 doses of 14.7 mg/kg of acetaminophen on multiple, consecutive days. Given these results, acetaminophen could never be approved for pediatric use today, even in clinical trials, if it was evaluated using modern safeguards in place to prevent adverse drug reactions. The drug would not pass preclinical testing.

Shortly after Viberg's study in laboratory mice in 2013, Frisch and Simonsen, two Danish investigators, found more than double the risk of infantile ASD associated with

---

[103] *Id.* at n. 3.
[104] *Id.* at n. 12.
[105] Amaral DG. Examining the Causes of Autism. Cerebrum : the Dana forum on brain science. 2017;2017. Epub 2017/07/13. PubMed PMID: 28698772; PubMed Central PMCID: PMCPMC5501015. https://pmc.ncbi.nlm.nih.gov/articles/PMC5501015/pdf/cer-01-17.pdf (last viewed May 28, 2026).
[106] *Id.* at n. 77.
[107] Viberg H, Eriksson P, Gordh T, Fredriksson A. Paracetamol (Acetaminophen) Administration During Neonatal Brain Development Affects Cognitive Function and Alters Its Analgesic and Anxiolytic Response in Adult Male Mice. Toxicol Sci. 2013;138(1):139-47. doi: 10.1093/toxsci/kft329. (March 2014) https://pubmed.ncbi.nlm.nih.gov/24361869/ (last viewed May 30, 2026).

circumcision when assessing the Danish National Birth Cohort.[108] They initiated that investigation in part because Bauer had proposed that acetaminophen exposure during circumcision may induce ASD.[109] Although Frisch and Simonsen could not evaluate acetaminophen use during circumcision, their report did confirm the predictions of Bauer. Further, even if hospital records of acetaminophen administration had been available, these would have been of limited use. Parents are frequently told to administer acetaminophen at home following circumcision to help alleviate discomfort from the procedure that can last for several hours. Finally, a US study[110] found that male circumcision was associated with increased social aversion, corroborating the effects of circumcision on social function that were first observed by Frisch and Simonsen. Unfortunately, the Frisch and Simonsen study was largely ignored.[111]

6. Clinical implications

At the present time, no evidence supports the idea that the benefits of acetaminophen use outweigh the risks of neurodevelopmental injury. The drug has never been shown to be lifesaving or to provide any long-term benefits in any study. Fears over fevers tend to be unfounded, with no evidence supporting the view that acetaminophen can block adverse fever-associated events with long-term negative consequences. This topic has been reviewed in detail recently.[112] At the same time, acetaminophen exposure to babies and children seems to be performed with a cavalier attitude, likely due to the erroneous assumption that it is extremely safe because hepatoxicity is not generally induced, even at doses exceeding the recommended

---

[108] Frisch M, Simonsen J. Ritual circumcision and risk of autism spectrum disorder in 0- to 9-year-old boys: national cohort study in Denmark. J R Soc Med. 2015;108(7):266-79. Epub 2015/01/13. doi: 10.1177/0141076814565942. PubMed PMID: 25573114; PubMed Central PMCID: PMCPMC4530408. https://pmc.ncbi.nlm.nih.gov/articles/PMC4530408/pdf/10.1177_0141076814565942.pdf (last viewed May 28, 2026).

[109] Bauer A, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. Environmental Health. 2013;12(1):41. PubMed PMID: doi:10.1186/1476-069X-12-41. https://pmc.ncbi.nlm.nih.gov/articles/PMC3673819/pdf/1476-069X-12-41.pdf (last viewed May 28, 2026).

[110] Miani A, Di Bernardo GA, Højgaard AD, Earp BD, Zak PJ, Landau AM, et al. Neonatal male circumcision is associated with altered adult socio-affective processing. Heliyon. 2020;6(11):e05566. Epub 2020/12/11. doi: 10.1016/j.heliyon.2020.e05566. PubMed PMID: 33299934; PubMed Central PMCID: PMCPMC7702013. https://pmc.ncbi.nlm.nih.gov/articles/PMC7702013/pdf/main.pdf (last viewed May 28, 2026).

[111] Parker W, Corrigan PT, Anderson R, Jones I, J. P., Konsoula Z, Williamson L, et al. Evidence that acetaminophen triggers autism in susceptible individuals has been ignored and mishandled for more than a decade. Journal of the Academy of Public Health. 2025. https://publichealth.realclearjournals.org/literature-syntheses/2025/10/evidence-that-acetaminophen-triggers-autism-in-susceptible-individuals-has-been-ignored-and-mishandled-for-more-than-a-decade/ (last viewed May 28, 2026).

[112] *Id.* at n. 3.

dose.[113] Hospital pharmacies, for example, generally recommend doses of acetaminophen up to 45 mg/kg when the drug is administered via the rectum,[114] [115] [116] three times more than the recommended oral dose. The recommended dose for rectal administration is greater than the recommended dose for oral administration because, on average, the rectally administered drug has less bioavailability than the orally administered drug. However, the bioavailability of the drug administered via the rectal route is variable among children and especially neonates, [117] [118] [119] [120] which could result in some babies and children receiving considerably more acetaminophen than is possible via the oral route. Further, it seems unlikely that acetaminophen use with circumcision in the first hours of life is always considered with the possibility that some acetaminophen might remain in the neonate's body as a result of the mother receiving the drug during labor and delivery. In addition, reports abound describing the common

---

[113] Rumack BH. Aspirin versus acetaminophen: a comparative view. Pediatrics. 1978;62(5 Pt 2 Suppl):943-6. Epub 1978/11/01. PubMed PMID: 569271. https://www.researchgate.net/publication/22573575_Aspirin_versus_acetaminophen_A_comparative_view (last viewed May 28, 2026).

[114] Chen L, Zhang M, Yung J, Chen J, McNair C, Lee KS. Safety of Rectal Administration of Acetaminophen in Neonates. The Canadian journal of hospital pharmacy. 2018;71(6):364-9. Epub 2019/01/11. PubMed PMID: 30626982; PubMed Central PMCID: PMCPMC6306189. https://pmc.ncbi.nlm.nih.gov/articles/PMC6306189/pdf/cjhp-71-364.pdf (last viewed May 28, 2026).

[115] Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. Anesthesiology. 2002;96(6):1336-45. Epub 2002/08/10. doi: 10.1097/00000542-200206000-00012. PubMed PMID: 12170045. https://journals.lww.com/anesthesiology/fulltext/2002/06000/acetaminophen_developmental_pharmacokinetics_in.11.aspx (last viewed May 28, 2026).

[116] Birmingham PK, Tobin MJ, Fisher DM, Henthorn TK, Hall SC, Coté CJ. Initial and subsequent dosing of rectal acetaminophen in children: a 24-hour pharmacokinetic study of new dose recommendations. Anesthesiology. 2001;94(3):385-9. Epub 2001/05/26. doi: 10.1097/00000542-200103000-00005. PubMed PMID: 11374595. https://journals.lww.com/anesthesiology/fulltext/2001/03000/initial_and_subsequent_dosing_of_rectal.1.aspx (last viewed May 28, 2026).

[117] *Id.* at n. 115.

[118] *Id.* at n. 116.

[119] Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45 mg.kg-1) rectal acetaminophen in children. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 1995;42(11):982-6. Epub 1995/11/01. doi: 10.1007/bf03011069. PubMed PMID: 8590508. https://link.springer.com/article/10.1007/BF03011069 (last viewed May 28, 2026).

[120] Coulthard KP, Nielson HW, Schroder M, Covino A, Matthews NT, Murray RS, et al. Relative bioavailability and plasma paracetamol profiles of Panadol suppositories in children. J Paediatr Child Health. 1998;34(5):425-31. Epub 1998/10/10. doi: 10.1046/j.1440-1754.1998.00267.x. PubMed PMID: 9767504. (October 1998) https://pubmed.ncbi.nlm.nih.gov/9767504/ (last viewed May 30, 2026).

occurrence of acetaminophen administration more frequently than recommended, at doses higher than recommended, and for reasons that are not recommended (for review, see Patel et al.[121]) supporting the view that a cavalier attitude exists toward the drug among medical health professionals and possibly other caregivers.

Acetaminophen use during sensitive periods of neurodevelopment continues to be recommended by medical authorities without apparent awareness of the risks. An excellent example of a policy that should be reconsidered is the recommendation of three doses of acetaminophen concurrent with the meningococcal group B (MenB) vaccine at 2, 4, and sometimes 12 months of life,[122] when acetaminophen-related induction of ASD is likely.[123] Fortunately, Australian and Canadian authorities have determined that the MenB vaccine can be given separate from other vaccines and without acetaminophen.[124] [125] It is this approach, in addition to avoidance of other acetaminophen exposures from the start of labor and delivery until after age five, that should be strongly recommended by medical authorities. The risk of acetaminophen exposure to the fetus during pregnancy, however, is presently uncertain, and parents-to-be should be made aware of this fact prior to pregnancy in order to make informed decisions and have plans in place to treat fever and pain during pregnancy.

Discontinuation of acetaminophen use during labor and delivery is perhaps the most impactful change that needs to be made immediately, and it also carries the least potential drawbacks. Other means of pain relief during labor and delivery are radically more effective than acetaminophen. The risks for ASD associated with acetaminophen at the time of birth are greater than at other times, and, based on pharmacological considerations, the time immediately post-partum carries the greatest risk of acetaminophen-mediated injury. This idea of sensitivity at the time of birth is not new. In his landmark treatise of 1964, instrumental in overturning the

---

[121] *Id.* at n. 22.
[122] Paracetamol use with Bexsero New Zealand: Immunisation Advisory Centre; 2018 [updated 2023; cited 2024 December 21]. Available from: https://www.immune.org.nz/factsheets/paracetamol-use-with-bexsero-r (last viewed May 28, 2026).
[123] *Id.* at n. 3.
[124] Meningococcal vaccines: Canadian Immunization Guide. In: Canada PHAo, editor.: Government of Canada; 2022. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-13-meningococcal-vaccine.html (last viewed August 3, 2026).
[125] Meningococcal disease. In: Care HaA, editor.: Australian Government; 2024. https://www1.health.gov.au/internet/main/publishing.nsf/Content/CA1DBF11D71F5F3ECA258ADE0019B036/$File/cdi-2024-48-52.pdf (last viewed May 28, 2026).

infamous "refrigerator mother hypothesis," Bernard Rimland[126] states (quotes and italics in the original):

> It may also be significant that "pure" cases of early infantile autism are almost invariably beautifully formed, having no stigmata. This suggests that the crippling factor takes its effect *very late* in the development of the infant—perhaps at birth or shortly after.

The fetus is apparently not as susceptible to neurodevelopmental injury as is the neonate, probably due, at least in part, to detoxification provided by the mother's liver. However, several studies show significant associations between autism and frequent use of acetaminophen during pregnancy, with risks of autism increasing by more than 50% in the most robust study.[127] Unfortunately, these risks associated with frequent use of acetaminophen are generally disregarded for reasons described previously,[128] but women should be warned prior to pregnancy about the potential risks, nonetheless. In contrast, insufficient data regarding the cost/benefit balance of the *occasional* use of acetaminophen for the treatment of fevers during pregnancy is available. Some data show low levels of risk of autism associated with low levels of acetaminophen exposure during pregnancy. (See, for example, the extremely robust Swedish data [129] before invalid adjustment for interacting variables.) On the other hand, some data suggest that occasional use of acetaminophen to treat a fever during pregnancy might even reduce the risk of autism.[130] [131] The concept is plausible. It is well known that "hormesis," or the response to very low levels of toxin, can result in adaptations which render the organism more resistant to further insult.[132] [133] In addition, mice,[134] rats,[135] and humans[136] [137] are thought to

---

[126] Rimland B. In: Elliott RM, Lindzey G, MacCorquodale K, editors. Infantile Autism. Century Psychology Series. New York: Meredith Publishing Company; 1964. p. 131. (April 5, 2026) https://books.google.com/books/about/Infantile_Autism.html?id=dtFsAAAAMAAJ (last viewed July 31, 2026).

[127] *Id.* at n. 11.

[128] *Id.* at n. 12.

[129] *Id.* at n. 11.

[130] Hornig M, Bresnahan MA, Che X, Schultz AF, Ukaigwe JE, Eddy ML, et al. Prenatal fever and autism risk. Mol Psychiatry. 2018;23(3):759-66. doi: 10.1038/mp.2017.119. https://pmc.ncbi.nlm.nih.gov/articles/PMC5822459/pdf/mp2017119a.pdf (last viewed May 28, 2026).

[131] Zerbo O, Iosif AM, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. J Autism Dev Disord. 2013;43(1):25-33. Epub 2012/05/09. doi: 10.1007/s10803-012-1540-x. PubMed PMID: 22562209; PubMed Central PMCID: PMCPMC3484245. https://pmc.ncbi.nlm.nih.gov/articles/PMC3484245/pdf/nihms381007.pdf (last viewed May 28, 2026).

[132] Wan Y, Liu J, Mai Y, Hong Y, Jia Z, Tian G, et al. Current advances and future trends of hormesis in disease. npj aging. 2024;10(1):26. Epub 2024/05/16. doi: 10.1038/s41514-024-

change metabolically after exposure to acetaminophen. This change may represent an adaptive response. Finally, blocking fevers with acetaminophen is a type of immunosuppression, and suppression of maternal immune activation, which can be detrimental to the fetus,[138] may be useful in some cases. However, again, insufficient data are available to make an evidence-based recommendation for or against occasional acetaminophen use during pregnancy to treat a fever. Most importantly, as discussed throughout this manuscript, pregnancy is not the time of greatest risk for acetaminophen-induced neurodevelopmental injury, and is thus not the time of greatest concern for action.

00155-3. PubMed PMID: 38750132; PubMed Central PMCID: PMCPMC11096327 commercial or financial relationships that could be construed as a potential conflict of interest. https://pmc.ncbi.nlm.nih.gov/articles/PMC11096327/pdf/41514_2024_Article_155.pdf (last viewed May 28, 2026).

[133] Calabrese EJ, Mattson MP. How does hormesis impact biology, toxicology, and medicine? NPJ aging and mechanisms of disease. 2017;3:13. Epub 2017/09/26. doi: 10.1038/s41514-017-0013-z. PubMed PMID: 28944077; PubMed Central PMCID: PMCPMC5601424. https://pmc.ncbi.nlm.nih.gov/articles/PMC5601424/pdf/41514_2017_Article_13.pdf (last viewed May 28, 2026).

[134] *Id.* at n. 107.

[135] Dungan AR, VanRyzin JW, Wood Ja, Patel E, Suda N, Jones JP, et al. Early Life Exposure to Acetaminophen Exerts Cohort-Dependent Effects on Nursing and Play Behavior in Sprague Dawley Rats. SSRN (Preprint). 2025;http://dx.doi.org/10.2139/ssrn.5223387. Dungan AR, VanRyzin JW, Wood Ja, Patel E, Suda N, Jones JP, et al. Early Life Exposure to Acetaminophen Exerts Cohort-Dependent Effects on Nursing and Play Behavior in Sprague Dawley Rats. SSRN (Preprint). 2025. http://dx.doi.org/10.2139/ssrn.5223387 (last viewed May 28, 2026).

[136] Schultz S, Gould GG, Antonucci N, Brigida AL, Siniscalco D. Endocannabinoid System Dysregulation from Acetaminophen Use May Lead to Autism Spectrum Disorder: Could Cannabinoid Treatment Be Efficacious? Molecules (Basel, Switzerland). 2021;26(7). Epub 2021/04/04. doi: 10.3390/molecules26071845. PubMed PMID: 33805951; PubMed Central PMCID: PMCPMC8037883. https://pmc.ncbi.nlm.nih.gov/articles/PMC8037883/pdf/molecules-26-01845.pdf (last viewed May 28, 2026).

[137] Schultz ST, Gould GG. Acetaminophen Use for Fever in Children Associated with Autism Spectrum Disorder. Autism-open access. 2016;6(2). Epub 2016/10/04. doi: 10.4172/2165-7890.1000170. PubMed PMID: 27695658; PubMed Central PMCID: PMCPMC5044872. https://pmc.ncbi.nlm.nih.gov/articles/PMC5044872/pdf/nihms784085.pdf (last viewed May 28, 2026).

[138] Han VX, Patel S, Jones HF, Dale RC. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nature Reviews Neurology. 2021;17(9):564-79. doi: 10.1038/s41582-021-00530-8. (August 2, 2021) https://pubmed.ncbi.nlm.nih.gov/34341569/ (last viewed May 30, 2026).

B. Conclusion to Statement of Grounds

The call for "more research (and funds)" rather than calls for action is encouraged by perverse incentives within the practice of science today.[139] However, the time for analyses of the acetaminophen/ASD connection considering only epidemiological evidence with substantial limitations and flawed underlying assumptions is in the past. Decisions based on analyses having depth without breadth have led to stagnation and a steady increase in the prevalence of ASD for more than half a century. Although no single line of evidence is conclusive, the weight of the total evidence (Tables 1-5) is now overwhelming, demonstrating that acetaminophen is, in fact, a developmental neurotoxin that is strongly contributory and perhaps causal for many cases of ASD.

Infants' Tylenol and other similar products containing acetaminophen must be taken off the market simply because neonates and infants cannot process the drug. Additionally given the heightened risk of autism when Tylenol and other similar products containing acetaminophen is used by obstetricians and children under six years of age, Boxed Warnings are appropriate.

The FDA's mission is "protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products…."[140] President Roosevelt's signing of the FD&C Act closed many safety and efficacy loopholes and improved the landscape of consumer protection forever.[141]

Clearly, given the government's own warnings and the evidence presented here, the FDA has an obligation to grant this petition.

III. ENVIRONMENTAL IMPACT

The undersigned hereby state 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.

---

[139] O'Ryan ML, Saxena S, Baum F. Time for a revolution in academic medicine? BMJ. 2024;387:q2508. Epub 2024/11/29. doi: 10.1136/bmj.q2508. PubMed PMID: 39608836. https://www.bmj.com/content/bmj/387/bmj.q2508.full.pdf (last viewed May 28, 2026).
[140] FDA, What We Do (November 21, 2023) https://www.fda.gov/about-fda/what-we-do#mission (last viewed May 31, 2026).
[141] FDA, 80 Years of the Federal Food, Drug, and Cosmetic Act (Nov. 7, 2018), https://www.fda.gov/about-fda/fda-history-exhibits/80-years-federal-food-drug-and-cosmetic-act (last viewed May 31, 2026).

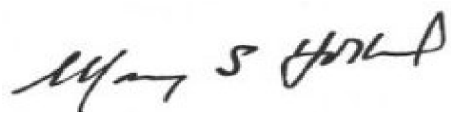
IV. ECONOMIC IMPACT

Economic impact information will be submitted upon request of the Acting Commissioner.

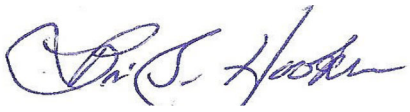
V. CERTIFICATION

The undersigned certify that, to their best knowledge and belief, this Petition includes all information and views on which the Petition relies, and that it includes representative data and/or information known to the Petitioner that are unfavorable to the Petition. Further, the undersigned certify that they have taken reasonable steps to ensure that any representative data and or information which are unfavorable to this petition were disclosed to them. They further certify that the information upon which they have based this action requested herein first became known to the parties on or about the following date: May 2026. The undersigned do not expect to receive payments, including cash and other forms of consideration, to file this information or its contents. We verify under penalty of perjury that the foregoing is true and correct as of the date of this submission of this petition.

Sincerely,



Mary S. Holland, Esq., Chief Executive Officer



Brian S. Hooker, Ph.D., Chief Science Officer

Kim Mack Rosenberg, CHD General Counsel

Ray L. Flores II, Senior Outside Counsel

Enc. Figures 1-3
Tables 1-6

FIGURE 1

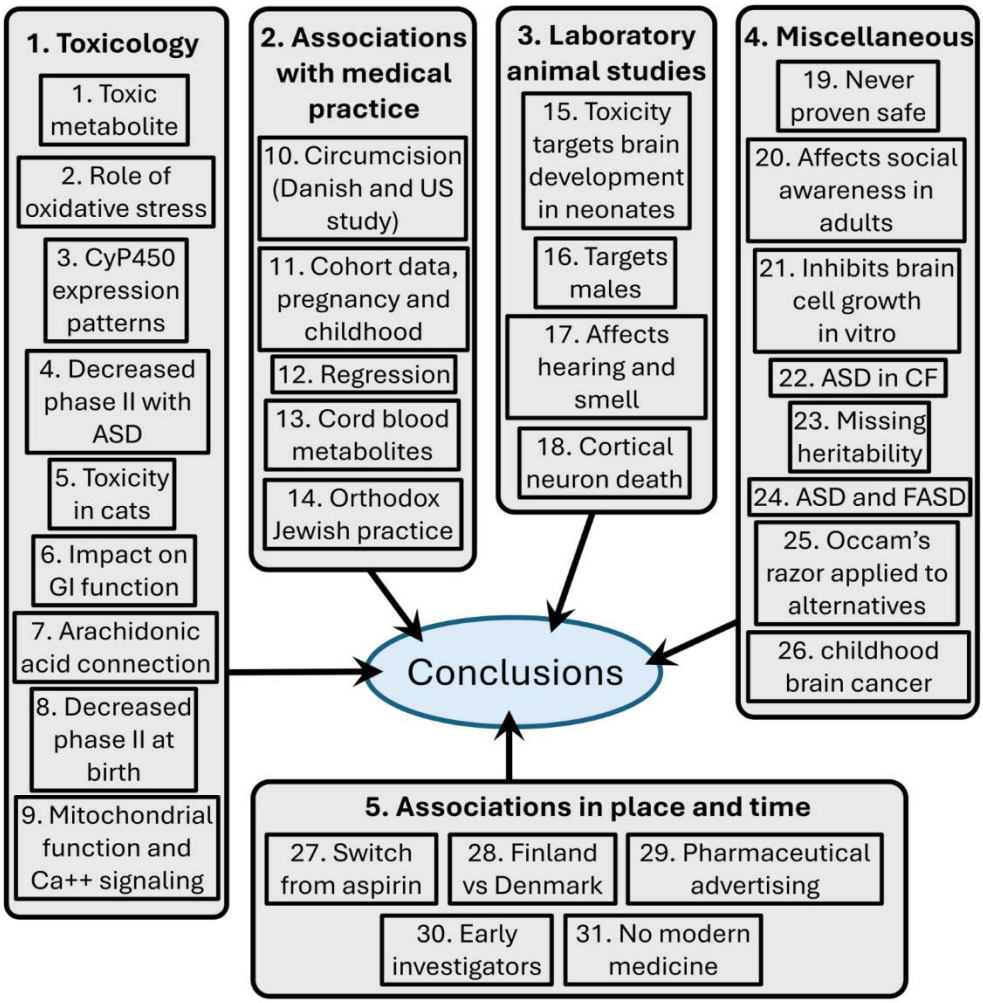


Figure 1. Summary of evidence pointing to the conclusion that exposure of susceptible babies and children to acetaminophen causes many cases of ASD. Information regarding the shorthand notations in the boxes can be found in Tables 1 through 5. In this case, 31 lines of evidence are divided into 5 categories, although the division of evidence into discrete categories is subjective. In this diagram, only one line of evidence is profoundly affected by mistaking interacting variables as confounding factors ("Epidemiology, pregnancy and childhood"; Line of evidence 11 in Table 2).

FIGURE 2

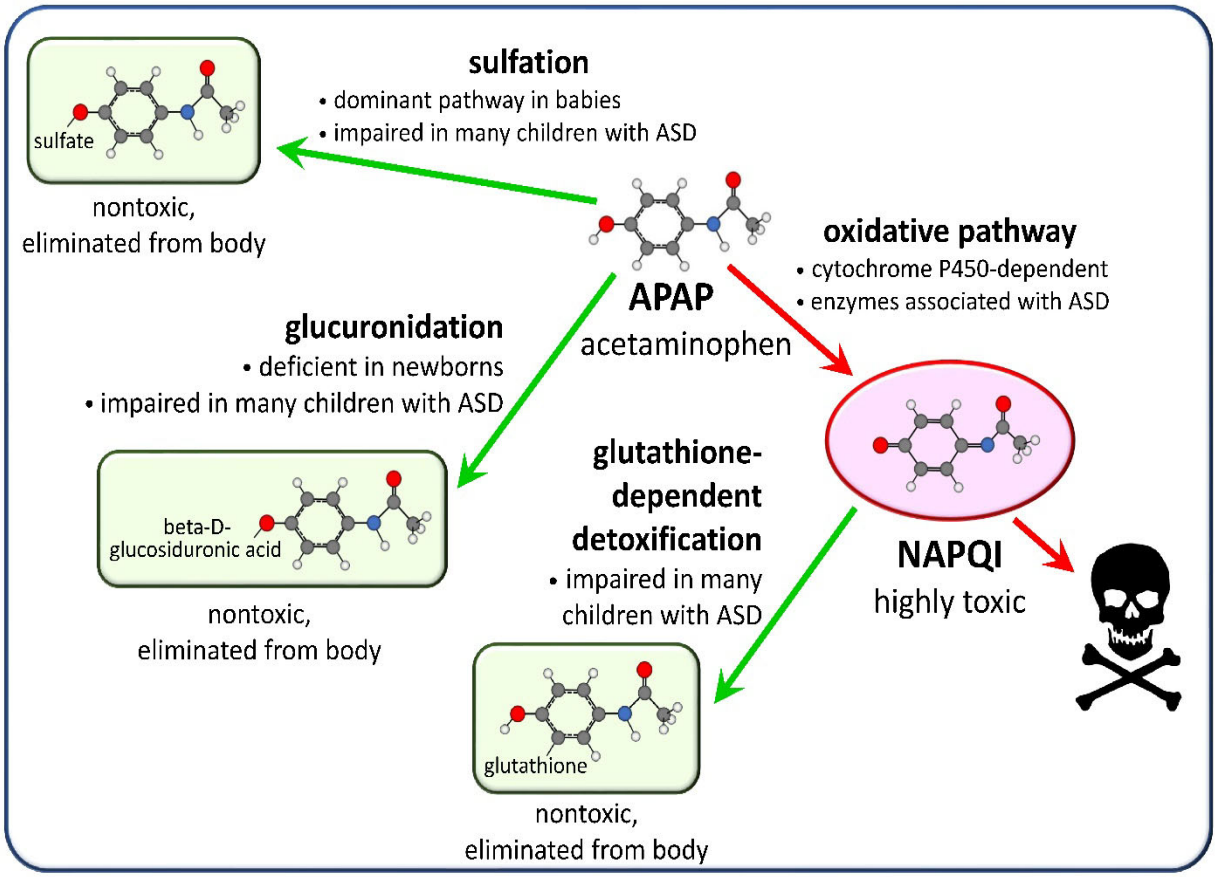


Figure 2. The variable metabolism of acetaminophen in normal adults, in neonates, and in children with autism. The diagram incorporates four lines of evidence (lines of evidence #1, #3, #4, and #8) described in Table 1.

FIGURE 3

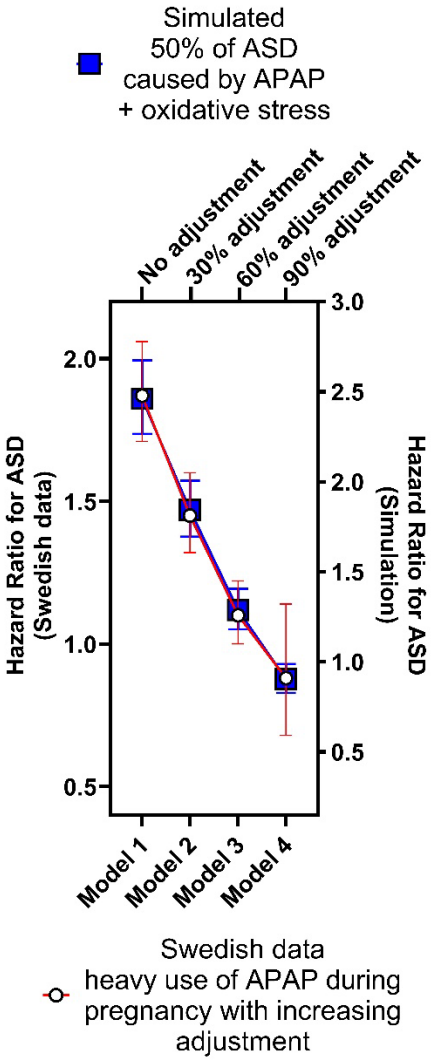


Figure 3. Adjusting for interacting variables obscures associations between acetaminophen and autism. Hazards ratios calculated by Ahlqvist et al.,[142] for heavy use of acetaminophen (APAP) exposure are shown in the white circles. Model 1 adjusted only for time of birth and for sex. Model 2 adjusted for the same factors as Model 1, plus 7 factors associated with inflammation and oxidative stress. Model 3 adjusted for the same factors as Model 2, plus 19 additional factors, including at least a dozen factors associated with inflammation and oxidative stress. Model 4 adjusted for most of the same factors as Model 3, plus "unobserved genetic and environmental confounders shared by full siblings," many of which may be related to inflammation and oxidative stress. These results demonstrate that acetaminophen does not induce

[142] *Id.* at n. 11.

ASD in the absence of factors associated with inflammation and oxidative stress, a fact that has been known for some years.[143] Results calculated according to Jones et al.,[144] using computer simulations in which acetaminophen combined with oxidative stress induces half of all cases of ASD are shown by the blue squares. Jones et al.,[145] previously reported valued at 0%, 30% and 90% adjustment. The value at 60% adjustment (HR 1.288; 95% CI 1.181-1.405) is added for the sake of comparison with the values reported by Ahlqvist et al.,[146]for heavy use of acetaminophen. Error bars indicate 95 % confidence intervals reported by Ahlqvist et al *Id.* [147] and calculated by Jones et al.[148]

[143] *Id.* at n. 77.
[144] *Id.* at n. 12.
[145] *Id.*
[146] *Id*. at n. 11.
[147] *Id.*
[148] *Id.* at n. 12.

Table 1

Pharmacological/toxicological evidence	
Evidence / references	**Background / additional information**
1. Toxic Metabolite: Mechanisms of APAP-mediated injury are plausible. The body converts a fraction of acetaminophen into a toxic metabolite called NAPQI. For review, see Jones et al.[149]	The first study showing that children with ASD are deficient in a metabolic pathway necessary to safely detoxify APAP in babies (sulfation) is now more than a quarter of a century old, [150] and was subsequently corroborated.[151] [152]
2. Oxidative Stress: Genetic, epigenetic, and environmental factors associated with an increased risk of ASD are also associated with oxidative stress, which has an adverse effect on the body's ability to safely metabolize APAP.[153] [154] [155]	The wide array of factors associated with ASD have led to the hypothesis that many things can come together to cause ASD, but ASD is characterized by impairment of social function and other particular behavioral phenotypes, suggesting specificity in the etiology of the condition.
3. One enzyme (CyP450 2E1) which produces the toxic metabolite of APAP (NAPQI) is expressed in the human brain from before birth,[156] is a target of	Polymorphisms in another enzyme (CyP450 1A2) that produces the same toxic metabolite of APAP is associated with ASD.[159] [160]

[149] *Id.* at n. 12.
[150] *Id.* at n. 19.
[151] *Id.* at n. 17.
[152] Pagan C, Benabou M, Leblond C, Cliquet F, Mathieu A, Lemière N, et al. Decreased phenol sulfotransferase activities associated with hyperserotonemia in autism spectrum disorders. Translational Psychiatry. 2021;11(1):23. doi: 10.1038/s41398-020-01125-5. https://www.nature.com/articles/s41398-020-01125-5 (last viewed May 28, 2026).
[153] *Id.* at n. 77.
[154] *Id.* at n. 19.
[155] Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013;18(3):369-81. Epub 01/10. doi: 10.1038/mp.2011.175. PubMed PMID: 22230883. https://pmc.ncbi.nlm.nih.gov/articles/PMC3578948/pdf/mp2011175a.pdf (last viewed May 28, 2026).
[156] Brzezinski MR, Boutelet-Bochan H, Person RE, Fantel AG, Juchau MR. Catalytic activity and quantitation of cytochrome P-450 2E1 in prenatal human brain. J Pharmacol Exp Ther. 1999;289(3):1648-53. Epub 1999/05/21. PubMed PMID: 10336564. (June 1999) https://pubmed.ncbi.nlm.nih.gov/10336564/ (last viewed May 30, 2026).

epigenetic alterations in mothers who have children with ASD [157] and in mothers who took APAP during labor and delivery.[158]	
4. Phase II metabolism is the way the body processes APAP without producing the toxic metabolite. The first study showing that children with ASD are deficient in a phase II metabolic pathway necessary to safely detoxify APAP in babies (sulfation) is now more than a quarter of a century old,[161] and was subsequently corroborated.[162] [163]	Besides sulfation, the human body has one other primary metabolic pathway to metabolize APAP without producing the toxic metabolite, NAPQI. That pathway, glucuronidation, is also apparently deficient in children with ASD.[164]

[159] Santos JX, Rasga C, Marques AR, Martiniano H, Asif M, Vilela J, et al. A Role for Gene-Environment Interactions in Autism Spectrum Disorder Is Supported by Variants in Genes Regulating the Effects of Exposure to Xenobiotics. Frontiers in neuroscience. 2022;16:862315. Epub 2022/06/07. doi: 10.3389/fnins.2022.862315. PubMed PMID: 35663546; PubMed Central PMCID: PMCPMC9161282. https://pmc.ncbi.nlm.nih.gov/articles/PMC9161282/pdf/fnins-16-862315.pdf (last viewed May 28, 2026).

[160] Braam W, Keijzer H, Struijker Boudier H, Didden R, Smits M, Curfs L. CYP1A2 polymorphisms in slow melatonin metabolisers: a possible relationship with autism spectrum disorder? J Intellect Disabil Res. 2013;57(11):993-1000. Epub 2012/07/25. doi: 10.1111/j.1365-2788.2012.01595.x. PubMed PMID: 22823064 (July 23, 2012) https://pubmed.ncbi.nlm.nih.gov/22823064/ (last viewed May 30, 2026).

[157] Zhu Y, Mordaunt CE, Yasui DH, Marathe R, Coulson RL, Dunaway KW, et al. Placental DNA methylation levels at CYP2E1 and IRS2 are associated with child outcome in a prospective autism study. Hum Mol Genet. 2019;28(16):2659-74. Epub 2019/04/23. doi: 10.1093/hmg/ddz084. PubMed PMID: 31009952; PubMed Central PMCID: PMCPMC6687952. https://pmc.ncbi.nlm.nih.gov/articles/PMC6687952/pdf/ddz084.pdf (last viewed May 28, 2026).

[158] Li Y, Hong X, Liang L, Wang X, Ladd-Acosta C. Association between acetaminophen metabolites and CYP2E1 DNA methylation level in neonate cord blood in the Boston Birth Cohort. Clinical epigenetics. 2023;15(1):132. Epub 2023/08/19. doi: 10.1186/s13148-023-01551-4. PubMed PMID: 37596607; PubMed Central PMCID: PMCPMC10439592. https://pmc.ncbi.nlm.nih.gov/articles/PMC10439592/pdf/13148_2023_Article_1551.pdf (last viewed May 28, 2026).

[161] *Id.* at n. 19.

[162] *Id.* at n. 17.

[163] *Id.* at n. 18.

[164] Stein TP, Schluter MD, Steer RA, Ming X. Autism and phthalate metabolite glucuronidation. J Autism Dev Disord. 2013;43(11):2677-85. Epub 2013/04/12. doi: 10.1007/s10803-013-1822-y. PubMed PMID: 23575644; PubMed Central PMCID: PMCPMC3797149. https://pmc.ncbi.nlm.nih.gov/articles/PMC3797149/pdf/nihms466807.pdf (last viewed May 28, 2026).

5. Toxicity in cats: APAP is not used in domestic cats because they lack of a robust glucuronidation-dependent capacity for metabolism, [165] [166] [167] [168] [169] making them susceptible to APAP-mediated injury. Human neonates also lack a robust glucuronidation-dependent pathway. [170] [171]	Based on liver function in human babies and children, APAP was incorrectly determined to be safe for pediatric use in the 1960s and 1970s (see line of evidence #15 in Table 3), before this evidence became available in the 1980s.

[165] Anvik JO. Acetaminophen toxicosis in a cat. The Canadian veterinary journal = La revue veterinaire canadienne. 1984;25(12):445-7. Epub 1984/12/01. PubMed PMID: 17422485; PubMed Central PMCID: PMCPMC1790690. https://pmc.ncbi.nlm.nih.gov/articles/PMC1790690/pdf/canvetj00265-0017.pdf (1ast viewed May 28, 2026).

[166] Savides MC, Oehme FW, Nash SL, Leipold HW. The toxicity and biotransformation of single doses of acetaminophen in dogs and cats. Toxicol Appl Pharmacol. 1984;74(1):26-34. Epub 1984/06/15. doi: 10.1016/0041-008x(84)90266-7. PubMed PMID: 6729821. (March 1976) https://pubmed.ncbi.nlm.nih.gov/6729821/ (last viewed July 31, 2026).

[167] Court MH. Feline drug metabolism and disposition: pharmacokinetic evidence for species differences and molecular mechanisms. The Veterinary clinics of North America Small animal practice. 2013;43(5):1039-54. Epub 2013/07/31. doi: 10.1016/j.cvsm.2013.05.002. PubMed PMID: 23890237; PubMed Central PMCID: PMCPMC3811070. https://pmc.ncbi.nlm.nih.gov/articles/PMC3811070/pdf/nihms501713.pdf (last viewed May 28, 2026).

[168] Lautz LS, Jeddi MZ, Girolami F, Nebbia C, Dorne J. Metabolism and pharmacokinetics of pharmaceuticals in cats (Felix sylvestris catus) and implications for the risk assessment of feed additives and contaminants. Toxicology letters. 2021;338:114-27. Epub 2020/12/01. doi: 10.1016/j.toxlet.2020.11.014. PubMed PMID: 33253781. https://www.sciencedirect.com/science/article/pii/S037842742030477X?via%3Dihub (last viewed May 28, 2026).

[169] St Omer VV, McKnight ED, 3rd. Acetylcysteine for treatment of acetaminophen toxicosis in the cat. J Am Vet Med Assoc. 1980;176(9):911-3. Epub 1980/05/01. PubMed PMID: 7400022. https://avmajournals.avma.org/view/journals/javma/176/9/javma.1980.176.09.911.xml (last viewed May 28, 2026).

[170] Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children, and adults. Clin Pharmacol Ther. 1976;19(3):284-94. Epub 1976/03/01. doi: 10.1002/cpt1976193284. PubMed PMID: 1261167. (March 1976) https://pubmed.ncbi.nlm.nih.gov/1261167/ (last viewed May 30, 2026).

[171] Cook SF, Stockmann C, Samiee-Zafarghandy S, King AD, Deutsch N, Williams EF, et al. Neonatal Maturation of Paracetamol (Acetaminophen) Glucuronidation, Sulfation, and Oxidation Based on a Parent-Metabolite Population Pharmacokinetic Model. Clin Pharmacokinet. 2016;55(11):1395-411. Epub 2016/10/21. doi: 10.1007/s40262-016-0408-1. PubMed PMID: 27209292; PubMed Central PMCID: PMCPMC5572771.

6. Increasing evidence suggests that the gut/brain axis may play a role in many cases of ASD (Reviewed recently [172] [173]), and APAP is known to adversely affect gut function in laboratory animal models,[174] [175] [176] and possibly in humans.[177]	Aberrant gut function leading to oxidative stress and inflammation is among many factors that would predispose individuals to adverse reactions to APAP leading to ASD,[178] and gut microbial metabolites serve as excellent biomarkers for ASD.[179] [180] However, it remains unknown whether aberrant gut function can be induced by APAP at the time of ASD induction and play a role in that induction.

---

https://pmc.ncbi.nlm.nih.gov/articles/PMC5572771/pdf/nihms893656.pdf (last viewed May 30, 2026).

[172] Fattorusso A, Di Genova L, Dell'Isola GB, Mencaroni E, Esposito S. Autism Spectrum Disorders and the Gut Microbiota. Nutrients. 2019;11(3). Epub 2019/03/03. doi: 10.3390/nu11030521. PubMed PMID: 30823414; PubMed Central PMCID: PMCPMC6471505. https://pmc.ncbi.nlm.nih.gov/articles/PMC6471505/pdf/nutrients-11-00521.pdf (last viewed May 30, 2026).

[173] Peralta-Marzal LN, Prince N, Bajic D, Roussin L, Naudon L, Rabot S, et al. The Impact of Gut Microbiota-Derived Metabolites in Autism Spectrum Disorders. Int J Mol Sci. 2021;22(18). Epub 2021/09/29. doi: 10.3390/ijms221810052. PubMed PMID: 34576216; PubMed Central PMCID: PMCPMC8470471. https://pmc.ncbi.nlm.nih.gov/articles/PMC8470471/pdf/ijms-22-10052.pdf (last viewed May 28, 2026).

[174] Chopyk DM, Stuart JD, Zimmerman MG, Wen J, Gumber S, Suthar MS, et al. Acetaminophen Intoxication Rapidly Induces Apoptosis of Intestinal Crypt Stem Cells and Enhances Intestinal Permeability. Hepatology communications. 2019;3(11):1435-49. Epub 2019/11/09. doi: 10.1002/hep4.1406. PubMed PMID: 31701068; PubMed Central PMCID: PMCPMC6824060. https://pmc.ncbi.nlm.nih.gov/articles/PMC6824060/pdf/HEP4-3-1435.pdf (last viewed May 28, 2026).

[175] Schneider KM, Elfers C, Ghallab A, Schneider CV, Galvez EJC, Mohs A, et al. Intestinal Dysbiosis Amplifies Acetaminophen-Induced Acute Liver Injury. Cellular and Molecular Gastroenterology and Hepatology. 2021;11(4):909-33. doi: https://doi.org/10.1016/j.jcmgh.2020.11.002. https://pmc.ncbi.nlm.nih.gov/articles/PMC7900526/pdf/main.pdf (last viewed May 28, 2026).

[176] Alabbas SY, Giri R, Oancea I, Davies J, Schreibner V, Florin TH, et al. Gut inflammation and adaptive immunity amplify acetaminophen toxicity in bowel and liver. J Gastroenterol Hepatol. 2023;38(4):609-18. doi: https://doi.org/10.1111/jgh.16102. (April 2023) https://pubmed.ncbi.nlm.nih.gov/36598244/ (last viewed May 30, 2026).

[177] McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol - a review. Br J Clin Pharmacol. 2018;84(10):2218-30. Epub 2018/06/05. doi: 10.1111/bcp.13656. PubMed PMID: 29863746; PubMed Central PMCID: PMCPMC6138494. https://pmc.ncbi.nlm.nih.gov/articles/PMC6138494/pdf/BCP-84-2218.pdf (last viewed May 28, 2026).

[178] *Id.* at n. 77.

[179] Flynn CK, Adams JB, Krajmalnik-Brown R, Khoruts A, Sadowsky MJ, Nirmalkar K, et al. Review of Elevated Para-Cresol in Autism and Possible Impact on Symptoms. Int J Mol Sci. 2025;26(4). Epub 2025/02/26. doi: 10.3390/ijms26041513. PubMed PMID: 40003979; PubMed Central PMCID: PMCPMC11855632.

7. APAP binds directly to arachidonic acid [181] and affects arachidonic acid metabolism.[182] Alterations of arachidonic acid[183] and enzymes involved in arachidonic acid metabolism[184] are associated with ASD.	It is unknown what role arachidonic acid plays in ASD, but arachidonic acid plays a role in both the analgesic and antipyretic properties of APAP, and its metabolism is associated with ASD.
8. Decreased phase II metabolism at birth: Human neonates lack a robust glucuronidation-dependent pathway,[185] [186] one of the two main metabolic pathways that avoids the production of NAPQI, the toxic metabolite of APAP.	Although individuals with ASD are particularly deficient in both main pathways used to metabolize APAP without producing the toxic metabolite (sulfation and glucuronidation), all individuals are deficient in glucuronidation at the time of birth. It is during this time period (labor and delivery) when the greatest risks of ASD associated with APAP exposure are found.[187]
9. Mitochondrial function may be impaired in individuals with ASD, [188] and aberrant metabolism of APAP can impair mitochondrial function.[189] Calcium signaling is	Calcium signaling dysfunction can be used as a biomarker for ASD,[192] although it remains unknown whether APAP plays any role in inducing that dysfunction.

https://pmc.ncbi.nlm.nih.gov/articles/PMC11855632/pdf/ijms-26-01513.pdf (last viewed May 28, 2026).

[180] Xiong X, Liu D, Wang Y, Zeng T, Peng Y. Urinary 3-(3-Hydroxyphenyl)-3-hydroxypropionic Acid, 3-Hydroxyphenylacetic Acid, and 3-Hydroxyhippuric Acid Are Elevated in Children with Autism Spectrum Disorders. BioMed research international. 2016;2016:9485412. Epub 2016/04/29. doi: 10.1155/2016/9485412. PubMed PMID: 27123458; PubMed Central PMCID: PMCPMC4829699. https://pmc.ncbi.nlm.nih.gov/articles/PMC4829699/pdf/BMRI2016-9485412.pdf (last viewed May 28, 2026).

[181] *Id.* at n. 37.

[182] *Id.* at n. 36.

[183] *Id.* at n. 39.

[184] *Id.* at n. 38.

[185] *Id.* at n. 170.

[186] *Id.* at n. 171.

[187] *Id.* at n. 92.

[188] Siddiqui MF, Elwell C, Johnson MH. Mitochondrial Dysfunction in Autism Spectrum Disorders. Autism-open access. 2016;6(5). Epub 2016/12/09. doi: 10.4172/2165-7890.1000190. PubMed PMID: 27928515; PubMed Central PMCID: PMCPMC5137782. https://pmc.ncbi.nlm.nih.gov/articles/PMC5137782/pdf/emss-70523.pdf (last viewed May 28, 2026).

[189] Du K, Farhood A, Jaeschke H. Mitochondria-targeted antioxidant Mito-Tempo protects against acetaminophen hepatotoxicity. Arch Toxicol. 2017;91(2):761-73. Epub 2016/03/24. doi: 10.1007/s00204-016-1692-0. PubMed PMID: 27002509; PubMed Central PMCID: PMCPMC5033665. https://pmc.ncbi.nlm.nih.gov/articles/PMC5033665/ (last viewed May 30, 2026).

known to be important in ASD, [190] and APAP adversely affects calcium signaling.[191]	

Table 1. Pharmacology/Toxicology evidence connecting acetaminophen (APAP) use with neurodevelopmental injury and ASD.

[192] Schmunk G, Nguyen RL, Ferguson DL, Kumar K, Parker I, Gargus JJ. High-throughput screen detects calcium signaling dysfunction in typical sporadic autism spectrum disorder. Sci Rep. 2017;7:40740. Epub 2017/02/02. doi: 10.1038/srep40740. PubMed PMID: 28145469; PubMed Central PMCID: PMCPMC5286408. https://pmc.ncbi.nlm.nih.gov/articles/PMC5286408/pdf/srep40740.pdf (last viewed May 28, 2026).

[190] Pourtavakoli A, Ghafouri-Fard S. Calcium signaling in neurodevelopment and pathophysiology of autism spectrum disorders. Mol Biol Rep. 2022;49(11):10811-23. Epub 2022/07/21. doi: 10.1007/s11033-022-07775-6. PubMed PMID: 35857176. (July 20, 2022) https://pubmed.ncbi.nlm.nih.gov/35857176/ (last viewed May 30, 2026).

[191] Salas VM, Corcoran GB. Calcium-dependent DNA damage and adenosine 3',5'-cyclic monophosphate-independent glycogen phosphorylase activation in an in vitro model of acetaminophen-induced liver injury. Hepatology. 1997;25(6):1432-8. Epub 1997/06/01. doi: 10.1002/hep.510250621. PubMed PMID: 9185764. (June 1997) https://pubmed.ncbi.nlm.nih.gov/9185764/ (last viewed May 30, 2026).

Table 2

Associations with Medical Practice/APAP use	
Evidence / references	**Background / additional information**
10. Circumcision of males is associated with a 2-fold increase in the risk for early-onset (infantile) ASD.[193]	Studies in Denmark[194] and the US[195] have identified social problems associated with circumcision. Circumcision is often performed using APAP as an analgesic despite the fact that such use is of highly questionable effectiveness.[196]
11a. Epidemiology (pregnancy): Use of APAP during pregnancy has been associated with adverse long-term effects on the mental health of offspring in numerous studies[197] [198] [199] [200] [201] [202] [203] [204] [205] [206] [207] [208] [209] [210] [211] [212] [213] [214] [215] [216] [217] [218] [219] [220]	This line of evidence has received more attention than any other line of

[193] *Id.* at n. 108.
[194] *Id.*
[195] *Id.* at n. 110.
[196] Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics. 1994;93(4):641-6. Epub 1994/04/01. PubMed PMID: 8134222. (April 1994) https://pubmed.ncbi.nlm.nih.gov/8134222/ (last viewed May 30, 2026).
[197] *Id.* at n. 51.
[198] *Id.* at n. 70.
[199] *Id.* at n. 89.
[200] *Id.* at n. 92.
[201] *Id.* at n. 93.
[202] Tovo-Rodrigues L, Schneider BC, Martins-Silva T, Del-Ponte B, Loret de Mola C, Schuler-Faccini L, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. BMC Psychiatry. 2018;18(1):368. doi: 10.1186/s12888-018-1942-1. https://pmc.ncbi.nlm.nih.gov/articles/PMC6245767/pdf/12888_2018_Article_1942.pdf (last viewed May 28, 2026).
[203] Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MM, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a

propensity score matched cohort study. Int J Epidemiol. 2016;45(6):1998-2008. Epub 2016/09/03. doi: 10.1093/ije/dyw192. PubMed PMID: 27585674; PubMed Central PMCID: PMCPMC5841617. https://pmc.ncbi.nlm.nih.gov/articles/PMC5841617/pdf/dyw192.pdf (last viewed May 28, 2026).

[204] Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study. Epidemiology. 2016;27(6):912-8. Epub 2016/08/02. doi: 10.1097/ede.0000000000000540. PubMed PMID: 27479646. (November 2016) https://pubmed.ncbi.nlm.nih.gov/27479646/ (last viewed May 30, 2026).

[205] Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol. 2016;45(6):2009-17. Epub 2016/12/30. doi: 10.1093/ije/dyw296. PubMed PMID: 28031314. (December 2016) https://pubmed.ncbi.nlm.nih.gov/28031314/ (last viewed May 30, 2026)

[206] Avella-Garcia CB, Julvez J, Fortuny J, Rebordosa C, Garcia-Esteban R, Galan IR, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016;45(6):1987-96. Epub 2016/06/30. doi: 10.1093/ije/dyw115. PubMed PMID: 27353198. (December 2016) https://pubmed.ncbi.nlm.nih.gov/27353198/ (last viewed May 30, 2026)

[207] Skovlund E, Handal M, Selmer R, Brandlistuen RE, Skurtveit S. Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. Pharmacoepidemiol Drug Saf. 2017;26(6):625-34. Epub 2017/02/09. doi: 10.1002/pds.4170. PubMed PMID: 28168770. (June 2017) https://pubmed.ncbi.nlm.nih.gov/28168770/ (last viewed May 30, 2026)

[208] Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA pediatrics. 2014;168(4):313-20. Epub 2014/02/26. doi: 10.1001/jamapediatrics.2013.4914. PubMed PMID: 24566677. (April 2014) https://pubmed.ncbi.nlm.nih.gov/24566677/ (last viewed May 30, 2026).

[209] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism research : official journal of the International Society for Autism Research. 2016;9(9):951-8. Epub 2015/12/22. doi: 10.1002/aur.1591. PubMed PMID: 26688372. (September 2016) https://pubmed.ncbi.nlm.nih.gov/26688372/ (last viewed May 30, 2026).

[210] Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017;140(5). Epub 2017/11/01. doi: 10.1542/peds.2016-3840. PubMed PMID: 29084830; PubMed Central PMCID: PMCPMC5654387 conflicts of interest to disclose. https://pmc.ncbi.nlm.nih.gov/articles/PMC5654387/ (last viewed May 28, 2026).

[211] Thompson JM, Waldie KE, Wall CR, Murphy R, Mitchell EA. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. PLoS One. 2014;9(9):e108210. Epub 2014/09/25. doi: 10.1371/journal.pone.0108210. PubMed PMID: 25251831; PubMed Central PMCID: PMCPMC4177119. https://pmc.ncbi.nlm.nih.gov/articles/PMC4177119/pdf/pone.0108210.pdf (last viewed May 28, 2026).

[212] Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA pediatrics. 2016;170(10):964-70. Epub 2016/08/18. doi: 10.1001/jamapediatrics.2016.1775.

PubMed PMID: 27533796; PubMed Central PMCID: PMCPMC5300094. https://pmc.ncbi.nlm.nih.gov/articles/PMC5300094/pdf/emss-71193.pdf (last viewed May 28, 2026).

[213] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-13. https://pmc.ncbi.nlm.nih.gov/articles/PMC3887567/pdf/dyt183.pdf (last viewed May 28, 2026).

[214] Sznajder KK, Teti DM, Kjerulff KH. Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: A prospective cohort study. PLoS One. 2022;17(9):e0272593. Epub 2022/09/29. doi: 10.1371/journal.pone.0272593. PubMed PMID: 36170224; PubMed Central PMCID: PMCPMC9518858. https://pmc.ncbi.nlm.nih.gov/articles/PMC9518858/pdf/pone.0272593.pdf (last viewed May 28, 2026).

[215] Inoue K, Ritz B, Ernst A, Tseng WL, Yuan Y, Meng Q, et al. Behavioral Problems at Age 11 Years After Prenatal and Postnatal Exposure to Acetaminophen: Parent-Reported and Self-Reported Outcomes. Am J Epidemiol. 2021;190(6):1009-20. Epub 2020/11/25. doi: 10.1093/aje/kwaa257. PubMed PMID: 33230558; PubMed Central PMCID: PMCPMC8248972. https://pmc.ncbi.nlm.nih.gov/articles/PMC8248972/pdf/kwaa257.pdf (last viewed May 28, 2026).

[216] Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly É J, Ascherio A, Weisskopf MG. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. Am J Epidemiol. 2019;188(4):768-75. Epub 2019/03/30. doi: 10.1093/aje/kwy288. PubMed PMID: 30923825; PubMed Central PMCID: PMCPMC6438812. https://pmc.ncbi.nlm.nih.gov/articles/PMC6438812/pdf/kwy288.pdf (last viewed May 28, 2026).

[217] Parker SE, Collett BR, Werler MM. Maternal acetaminophen use during pregnancy and childhood behavioural problems: Discrepancies between mother- and teacher-reported outcomes. Paediatr Perinat Epidemiol. 2020;34(3):299-308. Epub 2019/11/07. doi: 10.1111/ppe.12601. PubMed PMID: 31693212; PubMed Central PMCID: PMCPMC7192789. https://pmc.ncbi.nlm.nih.gov/articles/PMC7192789/pdf/nihms-1053026.pdf (last viewed May 28, 2026).

[218] Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020;34(3):247-56. Epub 2019/08/27. doi: 10.1111/ppe.12568. PubMed PMID: 31448449; PubMed Central PMCID: PMCPMC8285062. https://pmc.ncbi.nlm.nih.gov/articles/PMC8285062/pdf/nihms-1590632.pdf (last viewed May 28, 2026).

[219] Golding J, Gregory S, Clark R, Ellis G, Iles-Caven Y, Northstone K. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. Paediatr Perinat Epidemiol. 2020;34(3):257-66. Epub 2019/09/17. doi: 10.1111/ppe.12582. PubMed PMID: 31523834; PubMed Central PMCID: PMCPMC7217049. https://pmc.ncbi.nlm.nih.gov/articles/PMC7217049/pdf/PPE-34-257.pdf (last viewed May 28, 2026).

[220] Chen MH, Pan TL, Wang PW, Hsu JW, Huang KL, Su TP, et al. Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study

	evidence, to the point of being the only line of evidence considered by many investigators. However, the numerous studies underpinning this line of evidence are hampered by several factors which can cause errors in estimation of the association between APAP and ASD.[221] For example, a recent study found a dramatic association (odds ratio (OR) for ASD with APAP use = 1.8),[222] but incorrectly and completely cancelled out that association using an error in the assumptions underlying the statistical analysis.[223] [224] [225]
11b. Epidemiology (childhood): Analysis of the Danish National Birth	The study authors

in Taiwan. J Clin Psychiatry. 2019;80(5). Epub 2019/09/12. doi: 10.4088/JCP.18m12612. PubMed PMID: 31509360. (September 2019) https://pubmed.ncbi.nlm.nih.gov/31509360/ (last viewed May 30, 2026).

[221] *Id.* at n. 12.

[222] *Id.* at n. 11.

[223] *Id*. at n. 22.

[224] *Id.* at n. 12.

[225] *Id.* at n. 51.

Cohort (DNBC) revealed an odds ratio (OR) of 1.3 (CI 1.02–1.66) for ASD associated with postnatal APAP exposure,[226] despite the fact that the use of APAP appears to be dramatically underreported in the DNBC.[227]	averaged the results from the DNBC with assessments of autism-like symptoms (not ASD) from smaller data sets, and reported no association between postpartum APAP use and those symptoms (not ASD) in the abstract of the paper.[228] This issue has been addressed in detail by us in the literature[229] [230] but unfortunately may still result in confusion.[231] In addition, the study[232] employed invalid statistical adjustments expected to underestimate the association between APAP and ASD.[233] [234] See text for additional discussion.

[226] *Id.* at n. 70.
[227] *Id.* at n. 20.
[228] *Id.* at n. 70.
[229] *Id.* at n. 20.
[230] *Id.* at n. 22.
[231] *Id.* at n. 34.
[232] *Id.* at n. 70.
[233] *Id.* at n. 22.
[234] *Id.* at n. 12.

12. Regression: APAP use during early childhood is associated with a 20-fold greater risk of regressive ASD.[235] APAP is routinely used after vaccination, both of which cause overwhelming oxidative stress, leading to impaired detoxification.	This case-controlled study, now more than 16 years old, has been widely criticized, but careful analysis does not reveal any credible objections.[236] This study was the first study to separate the impact of vaccines from APAP on neurodevelopment, and the first to implicate APAP with the etiology of ASD. Other studies implicate vaccines, which contain toxicants (aluminum, mercury, formaldehyde, etc.) that cause an increase in oxidative stress and hinder detoxification.[237]
13. Higher levels of APAP in cord blood are associated with ASD.[238]	For the analysis, the authors divided the women into three groups based on cord blood APAP levels. The third with the highest

[235] *Id.* at n. 4.
[236] *Id.* at n. 20.
[237] Hooker and Miller, Health effects in vaccinated versus unvaccinated children, with covariates for breastfeeding status and type of birth. 2021; DOI: 10.15761/JTS.1000459, www.oatext.com/pdf/JTS-7-459.pdf (last viewed July 28, 2026).
[238] *Id.* at n. 92.

	levels had 3.6 times more likelihood of having a child with ASD than the third with the lowest levels of APAP.
14. Ultra-Orthodox Jews[239] in Israel have a reported prevalence of ASD less than half of that of reform Jews. Traditional circumcision practices employed by Ultra-Orthodox Jews do not utilize APAP. Further, Orthodox Jews may use less pain medications during childbirth than others.[240]	Circumcision is often performed using APAP as an analgesic despite the fact that such use is of highly questionable effectiveness. [241] Almost all Israeli Jews are circumcised.[242] Further, decreased use of pain medications during labor and delivery, which may be associated with Orthodox Judaism,[243] would likely lower exposure to APAP

[239] Raz R, Weisskopf MG, Davidovitch M, Pinto O, Levine H. Differences in autism spectrum disorders incidence by sub-populations in Israel 1992-2009: a total population study. J Autism Dev Disord. 2015;45(4):1062-9. doi: 10.1007/s10803-014-2262-z. PubMed PMID: 25287899. https://pmc.ncbi.nlm.nih.gov/articles/PMC4369159/pdf/nihms-633652.pdf (last viewed May 28, 2026).

[240] Zauderer C. Maternity care for Orthodox Jewish couples: implications for nurses in the obstetric setting. Nursing for women's health. 2009;13(2):112-20. Epub 2009/04/17. doi: 10.1111/j.1751-486X.2009.01402.x. PubMed PMID: 19368677. (April 2009) https://pubmed.ncbi.nlm.nih.gov/19368677/ (last viewed May 30, 2026).

[241] *Id.* at n. 196.

[242] Kacker S, Tobian AA. Male circumcision: integrating tradition and medical evidence. The Israel Medical Association journal : IMAJ. 2013;15(1):37-8. Epub 2013/03/15. PubMed PMID: 23484238; PubMed Central PMCID: PMCPMC3638798. https://pmc.ncbi.nlm.nih.gov/articles/PMC3638798/pdf/nihms458035.pdf (last viewed May 28, 2026).

[243] *Id.* at n. 240.

	at the time of life when individuals are the most sensitive to APAP-mediated neurodevelopmental injury.[244]

Table 2. Associations between acetaminophen (APAP) exposure and ASD. Associations in this table reflect associations between acetaminophen use during pregnancy, circumcision, labor and delivery, and early childhood with ASD. The numbering of evidence is continued from Table 1.

[244] *Id.* at n. 3.

Table 3

Laboratory animal studies	
Evidence / references	**Background / additional information**
15. Numerous studies in laboratory animals from multiple laboratories indicate that early life exposure to APAP causes long term changes in brain function. [245] [246] [247] [248] [249] [250] [251] [252] [253] [254] [255] [256] [257] [258]	After adjusting for weight, the amount of APAP that causes profound changes in laboratory animals in some studies is very close to[260] or even less than [261] the amount administered to human babies and children. Thus, APAP could never be used in babies or children if current guidelines for drug safety were applied.

[245] *Id.* at n. 34.
[246] *Id.* at n. 107.
[247] Hussin S, Al-Allaf L. Histological changes of CA and DG regions of hippocampus of rats' brain after exposure to Acetaminophen in postnatal period. Iraqi Journal of Veterinary Sciences. 2022;36(1):151-8. (February 20, 2021) https://www.cabidigitallibrary.org/doi/pdf/10.5555/20220111475#:~:text=The%20current%20study%20tried%20to,microscope%20and%20it%20showed%20that (last viewed May 30, 2026).
[248] Harshaw C, Warner AG. Interleukin-1β-induced inflammation and acetaminophen during infancy: Distinct and interactive effects on social-emotional and repetitive behavior in C57BL/6J mice. Pharmacol Biochem Behav. 2022;220:173463. doi: https://doi.org/10.1016/j.pbb.2022.173463. (September 11, 2022) https://pubmed.ncbi.nlm.nih.gov/36100070/ (last viewed May 30, 2026).
[249] Herrington JA, Guss Darwich J, Harshaw C, Brigande AM, Leif EB, Currie PJ. Elevated ghrelin alters the behavioral effects of perinatal acetaminophen exposure in rats. Dev Psychobiol. 2022;64(3):e22252. Epub 2022/03/22. doi: 10.1002/dev.22252. PubMed PMID: 35312061. (March 2022) https://pubmed.ncbi.nlm.nih.gov/35312061/ (last viewed May 30, 2026).
[250] Blecharz-Klin K, Wawer A, Jawna-Zboińska K, Pyrzanowska J, Piechal A, Mirowska-Guzel D, et al. Early paracetamol exposure decreases brain-derived neurotrophic factor (BDNF) in striatum and affects social behaviour and exploration in rats. Pharmacol Biochem Behav. 2018;168:25-32. Epub 2018/03/17. doi: 10.1016/j.pbb.2018.03.004. PubMed PMID: 29545027. (May 2018) https://pubmed.ncbi.nlm.nih.gov/29545027/ (last viewed May 30, 2026).
[251] Hay-Schmidt A, Finkielman OTE, Jensen BAH, Hogsbro CF, Bak Holm J, Johansen KH, et al. Prenatal exposure to paracetamol/acetaminophen and precursor aniline impairs masculinisation of male brain and behaviour. Reproduction (Cambridge, England). 2017;154(2):145-52. Epub 2017/06/01. doi: 10.1530/rep-17-0165. PubMed PMID: 28559473. (August 2017) https://pubmed.ncbi.nlm.nih.gov/28559473/ (last viewed May 30, 2026).
[252] Baker BH, Rafikian EE, Hamblin PB, Strait MD, Yang M, Pearson BL. Sex-specific neurobehavioral and prefrontal cortex gene expression alterations following developmental acetaminophen exposure in mice. Neurobiol Dis. 2023;177:105970. Epub 2022/12/23. doi: 10.1016/j.nbd.2022.105970. PubMed PMID: 36549432; PubMed Central PMCID: PMCPMC9940030. https://pmc.ncbi.nlm.nih.gov/articles/PMC9940030/pdf/nihms-1869018.pdf (last viewed May 28, 2026).
[253] Saad A, Hegde S, Kechichian T, Gamble P, Rahman M, Stutz SJ, et al. Is There a Causal Relation between Maternal Acetaminophen Administration and ADHD? PLoS One.

[259]	
16. Early life exposure to APAP has a greater long-term impact on male laboratory animals than female laboratory animals.[262] [263] [264] [265] ASD is more common in males than in females.	The reason or reasons why males are more susceptible to APAP-mediated injury has been considered in some detail, and several plausible mechanisms have been proposed[266] [267]

2016;11(6):e0157380. Epub 2016/06/15. doi: 10.1371/journal.pone.0157380. PubMed PMID: 27295086; PubMed Central PMCID: PMCPMC4905664. https://scispace.com/pdf/is-there-a-causal-relation-between-maternal-acetaminophen-8jfsij8kjd.pdf (last viewed May 28, 2026).

[254] Klein RM, Motomura VN, Debiasi JD, Moreira EG. Gestational paracetamol exposure induces core behaviors of neurodevelopmental disorders in infant rats and modifies response to a cannabinoid agonist in females. Neurotoxicol Teratol. 2023;99:107279. Epub 2023/07/01. doi: 10.1016/j.ntt.2023.107279. PubMed PMID: 37391024. (September 2023) https://pubmed.ncbi.nlm.nih.gov/37391024/ (last viewed May 30, 2026).

[255] Klein RM, Rigobello C, Vidigal CB, Moura KF, Barbosa DS, Gerardin DCC, et al. Gestational exposure to paracetamol in rats induces neurofunctional alterations in the progeny. Neurotoxicol Teratol. 2020;77:106838. Epub 2019/10/24. doi: 10.1016/j.ntt.2019.106838. PubMed PMID: 31644948. (January-February 2020) https://pubmed.ncbi.nlm.nih.gov/31644948/ (last viewed May 30, 2026).

[256] Suda N, Hernandez JC, Poulton J, Jones JP, Konsoula Z, Smith C, et al. Therapeutic doses of paracetamol with co-administration of cysteine and mannitol during early development result in long term behavioral changes in laboratory rats. PLoS One. 2020;16(6):e0253543. doi: https://doi.org/10.1371/journal.pone.0253543. https://pmc.ncbi.nlm.nih.gov/articles/PMC8232535/pdf/pone.0253543.pdf (last viewed May 28, 2026).

[257] Philippot G, Gordh T, Fredriksson A, Viberg H. Adult neurobehavioral alterations in male and female mice following developmental exposure to paracetamol (acetaminophen): characterization of a critical period. J Appl Toxicol. 2017;37(10):1174-81. Epub 2017/04/28. doi: 10.1002/jat.3473. PubMed PMID: 28448685. (October 2017) https://pubmed.ncbi.nlm.nih.gov/28448685/ (last viewed May 30, 2026).

[258] Dean SL, Knutson JF, Krebs-Kraft DL, McCarthy MM. Prostaglandin E2 is an endogenous modulator of cerebellar development and complex behavior during a sensitive postnatal period. Eur J Neurosci. 2012;35(8):1218-29. Epub 2012/04/20. doi: 10.1111/j.1460-9568.2012.08032.x. PubMed PMID: 22512254; PubMed Central PMCID: PMCPmc3534986. https://pmc.ncbi.nlm.nih.gov/articles/PMC3534986/pdf/nihms428627.pdf (last viewed May 28, 2026).

[260] *Id.* at n. 107.

[261] *Id.* at n. 256.

[259] Philippot G, Hosseini K, Yakub A, Mhajar Y, Hamid M, Buratovic S, et al. Paracetamol (Acetaminophen) and its Effect on the Developing Mouse Brain. Frontiers in toxicology. 2022;4:867748. Epub 2022/04/09. doi: 10.3389/ftox.2022.867748. PubMed PMID: 35391823; PubMed Central PMCID: PMCPMC8981466. (March 2022) https://pubmed.ncbi.nlm.nih.gov/35391823/ (Last viewed May 30, 2026)

[262] *Id.* at n. 252.

17. Prenatal exposure of laboratory rats to APAP causes problems with the processing of sound[268] and with olfactory function.[269] Impairment of olfactory function [270] and some degree of auditory dysfunction (reviewed by Graeca and Kulesza [271]) are associated with ASD.	It is unknown whether these effects of APAP on laboratory animals are related to altered processing of smell and hearing in some individuals with ASD.
18. APAP causes apoptosis-mediated death of cortical neurons in laboratory rats,[272] and cortical neurons may be involved in the pathology of ASD.[273] [274]	Increased levels of biomarkers for neuronal apoptosis[275] [276] [277] and impaired autophagy[278] are associated with ASD. Autophagy is necessary to clearing damaged organelles such as mitochondria,[279] which are created by aberrant metabolism of APAP.[280]

---

[263] *Id.* at n. 258.

[264] Kanno SI, Tomizawa A, Yomogida S, Hara A. Glutathione peroxidase 3 is a protective factor against acetaminophen-induced hepatotoxicity in vivo and in vitro. Int J Mol Med. 2017;40(3):748-54. Epub 2017/07/06. doi: 10.3892/ijmm.2017.3049. PubMed PMID: 28677736; PubMed Central PMCID: PMCPMC5547967. (September 2017) https://pubmed.ncbi.nlm.nih.gov/28677736/ (last viewed May 30, 2026)

[265] Rigobello C, Klein RM, Debiasi JD, Ursini LG, Michelin AP, Matsumoto AK, et al. Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. Behav Brain Res. 2021;408:113294. Epub 2021/04/10. doi: 10.1016/j.bbr.2021.113294. PubMed PMID: 33836167. (June 25, 2021) https://pubmed.ncbi.nlm.nih.gov/33836167/ (last viewed May 30, 2026).

[266] *Id.* at n. 258.

[267] *Id.* at n. 264.

[268] *Id.* at n. 34.

[269] *Id.* at n. 255.

[270] Xu M, Minagawa Y, Kumazaki H, Okada KI, Naoi N. Prefrontal Responses to Odors in Individuals With Autism Spectrum Disorders: Functional NIRS Measurement Combined With a Fragrance Pulse Ejection System. Front Hum Neurosci. 2020;14:523456. Epub 2020/11/03. doi: 10.3389/fnhum.2020.523456. PubMed PMID: 33132871; PubMed Central PMCID: PMCPMC7579723. https://pmc.ncbi.nlm.nih.gov/articles/PMC7579723/pdf/fnhum-14-523456.pdf (last viewed May 28, 2026).

[271] *Id.* at n. 34.

[272] *Id.* at n. 84.

[273] Donovan AP, Basson MA. The neuroanatomy of autism - a developmental perspective. J Anat. 2017;230(1):4-15. Epub 2016/09/14. doi: 10.1111/joa.12542. PubMed PMID: 27620360; PubMed Central PMCID: PMCPMC5192959. https://pmc.ncbi.nlm.nih.gov/articles/PMC5192959/pdf/JOA-230-4.pdf (last viewed May 28, 2026).

[274] Casanova MF, Sokhadze EM, Casanova EL, Opris I, Abujadi C, Marcolin MA, et al. Translational Neuroscience in Autism: From Neuropathology to Transcranial Magnetic

Table 3. Laboratory animal studies indicating that acetaminophen (APAP) is a neurodevelopmental toxin and pointing toward a connection between acetaminophen use and ASD. The numbering of evidence is continued from Table 2.

Stimulation Therapies. The Psychiatric clinics of North America. 2020;43(2):229-48. Epub 2020/05/23. doi: 10.1016/j.psc.2020.02.004. PubMed PMID: 32439019; PubMed Central PMCID: PMCPMC7245584. https://pmc.ncbi.nlm.nih.gov/articles/PMC7245584/pdf/nihms-1583272.pdf (last viewed May 28, 2026).

[275] Dong D, Zielke HR, Yeh D, Yang P. Cellular stress and apoptosis contribute to the pathogenesis of autism spectrum disorder. Autism research : official journal of the International Society for Autism Research. 2018;11(7):1076-90. Epub 2018/05/16. doi: 10.1002/aur.1966. PubMed PMID: 29761862; PubMed Central PMCID: PMCPMC6107407. https://pmc.ncbi.nlm.nih.gov/articles/PMC6107407/pdf/nihms962024.pdf (last viewed May 28, 2026).

[276] Lv MN, Zhang H, Shu Y, Chen S, Hu YY, Zhou M. The neonatal levels of TSB, NSE and CK-BB in autism spectrum disorder from Southern China. Translational neuroscience. 2016;7(1):6-11. Epub 2017/01/27. doi: 10.1515/tnsci-2016-0002. PubMed PMID: 28123815; PubMed Central PMCID: PMCPMC5017591. https://pmc.ncbi.nlm.nih.gov/articles/PMC5017591/pdf/tnsci-2016-0002.pdf (last viewed May 28, 2026).

[277] Stancioiu F, Bogdan R, Dumitrescu R. Neuron-Specific Enolase (NSE) as a Biomarker for Autistic Spectrum Disease (ASD). Life (Basel, Switzerland). 2023;13(8). Epub 2023/08/26. doi: 10.3390/life13081736. PubMed PMID: 37629593; PubMed Central PMCID: PMCPMC10455327. https://pmc.ncbi.nlm.nih.gov/articles/PMC10455327/pdf/life-13-01736.pdf (last viewed May 28, 2026).

[278] Ham A, Chang AY, Li H, Bain JM, Goldman JE, Sulzer D, et al. Impaired macroautophagy confers substantial risk for intellectual disability in children with autism spectrum disorders. Mol Psychiatry. 2024. Epub 2024/09/06. doi: 10.1038/s41380-024-02741-z. PubMed PMID: 39237724. https://pmc.ncbi.nlm.nih.gov/articles/PMC12743320/pdf/nihms-2123171.pdf (last viewed May 28, 2026).

[279] Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol. 2010;221(1):3-12. Epub 2010/03/13. doi: 10.1002/path.2697. PubMed PMID: 20225336; PubMed Central PMCID: PMCPMC2990190. https://pubmed.ncbi.nlm.nih.gov/20225336/ (last viewed July 3, 2026).

[280] *Id.* at n. 189.

Table 4

Miscellaneous observations	
Evidence / references	**Background / additional information**
19. APAP was never demonstrated to be safe for neurodevelopment. [281] Over two hundred papers in the medical literature claim that APAP is safe for babies and/or children when used as directed, but all studies were based on the false assumption that adverse reactions in babies would involve easily measured liver injury, the same as in adults.[282]	One study in laboratory animals in the 1980s showed that even lethal doses of APAP do not cause liver failure in neonates,[283] but the first study showing APAP-mediated neurodevelopmental brain injury in laboratory animals was not published until 2013.[284] Like APAP, opioids have also never been shown to be safe for neurodevelopment.[285] However, unlike APAP, opioids are not generally assumed to be safe for neurodevelopment when used as directed. Further, one study probing the safety of prenatal opioid exposure found reductions in communication skills in children associated with prenatal APAP exposure, but not with prenatal opioid exposure.[286]
20. APAP temporarily blunts social trust[287] and awareness,[288]	Although the mechanisms are unknown, these studies show that APAP affects aspects of mental function that

[281] *Id.* at n. 44.
[282] *Id.* at n. 44.
[283] Green MD, Shires TK, Fischer LJ. Hepatotoxicity of acetaminophen in neonatal and young rats. I. Age-related changes in susceptibility. Toxicol Appl Pharmacol. 1984;74(1):116-24. Epub 1984/06/15. doi: 10.1016/0041-008x(84)90277-1. PubMed PMID: 6729816. (June 15, 2984) https://pubmed.ncbi.nlm.nih.gov/6729816/ (last viewed May 30, 2026).
[284] *Id.* at n. 107.
[285] Kinoshita M, Stempel KS, Borges do Nascimento IJ, Bruschettini M. Systemic opioids versus other analgesics and sedatives for postoperative pain in neonates. Cochrane Database Syst Rev. 2023;3(3):Cd014876. Epub 2023/03/05. doi: 10.1002/14651858.CD014876.pub2. PubMed PMID: 36870076; PubMed Central PMCID: PMCPMC9983301. https://pmc.ncbi.nlm.nih.gov/articles/PMC8404962/pdf/CD014876.pdf (last viewed May 28, 2026).
[286] Skovlund E, Handal M, Selmer R, Brandlistuen RE, Skurtveit S. Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. Pharmacoepidemiol Drug Saf. 2017;26(6):625-34. Epub 2017/02/09. doi: 10.1002/pds.4170. PubMed PMID: 28168770. https://pubmed.ncbi.nlm.nih.gov/28168770/ (last viewed July 2, 2026).
[287] Roberts ID, Krajbich I, Way BM. Acetaminophen influences social and economic trust. Scientific Reports. 2019;9(1):4060. doi: 10.1038/s41598-019-40093-9. https://pmc.ncbi.nlm.nih.gov/articles/PMC6412049/pdf/41598_2019_Article_40093.pdf (last viewed May 28, 2026).
[288] Dewall CN, Macdonald G, Webster GD, Masten CL, Baumeister RF, Powell C, et al. Acetaminophen reduces social pain: behavioral and neural evidence. Psychol Sci.

emotional responses to external stimuli,[289] and the ability to identify errors[290] in adults.	are impaired in individuals with ASD.
21. APAP inhibits neuronal cell growth in tissue culture experiments, altering "arborization," the process by which neurons branch out to make connections with other neurons. [291] APAP[292] [293] and a metabolite of APAP[294] also cause death of brain cells in culture.	Adverse effects of APAP on neuronal cell growth in culture (*in vitro*) are dose dependent, and observable at concentrations near those achieved in clinical therapy. [295] These effects *in vitro* would discourage use of APAP in humans if current guidelines for drug safety were applied.
22. Cystic fibrosis (CF) is associated with unusually efficient	The mental health of patients with cystic fibrosis has been characterized extensively, but no association between

2010;21(7):931-7. Epub 2010/06/16. doi: 10.1177/0956797610374741. PubMed PMID: 20548058. (July 2010) https://pubmed.ncbi.nlm.nih.gov/20548058/ (last viewed May 30, 2026).

[289] Durso GRO, Luttrell A, Way BM. Over-the-Counter Relief From Pains and Pleasures Alike: Acetaminophen Blunts Evaluation Sensitivity to Both Negative and Positive Stimuli. Psychol Sci. 2015;26(6):750-8. Epub 04/10. doi: 10.1177/0956797615570366. PubMed PMID: 25862546. https://pmc.ncbi.nlm.nih.gov/articles/PMC4515109/pdf/nihms703262.pdf (last viewed May 28, 2026).

[290] Randles D, Kam JWY, Heine SJ, Inzlicht M, Handy TC. Acetaminophen attenuates error evaluation in cortex. Social Cognitive and Affective Neuroscience. 2016;11(6):899-906. doi: 10.1093/scan/nsw023. https://pmc.ncbi.nlm.nih.gov/articles/PMC4884318/pdf/nsw023.pdf (last viewed May 28, 2026).

[291] Labba N-A, Wæhler HA, Houdaifi N, Zosen D, Haugen F, Paulsen RE, et al. Paracetamol perturbs neuronal arborization and disrupts the cytoskeletal proteins SPTBN1 and TUBB3 in both human and chicken in vitro models. Toxicol Appl Pharmacol. 2022;449:116130. doi: https://doi.org/10.1016/j.taap.2022.116130. https://www.sciencedirect.com/science/article/pii/S0041008X22002757?via%3Dihub (last viewed May 28, 2026).

[292] *Id.* at n. 84.

[293] Vigo MB, Pérez MJ, De Fino F, Gómez G, Martínez SA, Bisagno V, et al. Acute acetaminophen intoxication induces direct neurotoxicity in rats manifested as astrogliosis and decreased dopaminergic markers in brain areas associated with locomotor regulation. Biochem Pharmacol. 2019;170:113662. doi: https://doi.org/10.1016/j.bcp.2019.113662. (December 2019) https://pubmed.ncbi.nlm.nih.gov/31606411/ (last viewed May 30, 2026).

[294] Schultz S, DeSilva M, Gu TT, Qiang M, Whang K. Effects of the analgesic acetaminophen (Paracetamol) and its para-aminophenol metabolite on viability of mouse-cultured cortical neurons. Basic Clin Pharmacol Toxicol. 2012;110(2):141-4. Epub 2011/07/21. doi: 10.1111/j.1742-7843.2011.00767.x. PubMed PMID: 21771276. (July 20, 2011) https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1742-7843.2011.00767.x (last viewed May 30, 2026).

[295] *Id.* at n. 291.

(effective) metabolism of APAP, [296] [297] and the prevalence of ASD is apparently very low in patients with cystic fibrosis.[298]	ASD and cystic fibrosis has been reported.
23. The "missing heritability" paradox of ASD suggests that epigenetic factors or very early exposure to environmental factors might influence the onset of ASD. [299]	The role of APAP in the induction of ASD nicely resolves the missing heritability paradox connected with ASD, in which sibling studies indicate a high contribution of genetics, but genome wide studies fail to identify the genes involved. [300] The observation that abuse of a mother when she was a child is associated with ASD in the offspring[301] is one example of evidence that supports this view.
24. ASD and fetal alcohol spectrum disorder (FASD) are similar in many regards. Reviewed by Jones et al.[302] A spectrum disorder can also be triggered by the drug valproate.[303]	These observations demonstrate that a complex spectrum disorder (FASD) sharing many similarities with ASD can (a) be induced by a single chemical and (b) be influenced by a variety of genetic and environmental factors.
25. Theories regarding genetic causation of autism are not consistent with known observations and/or require elaborate/complex scenarios to be true.	Some alternative explanations depend on the view that the incidence of ASD has not increased dramatically over time, a view that is contradicted by numerous lines of evidence showing that ASD is an effect of industrialized culture.[304] [305]

[296] Hutabarat RM, Unadkat JD, Kushmerick P, Aitken ML, Slattery JT, Smith AL. Disposition of drugs in cystic fibrosis. III. Acetaminophen. Clin Pharmacol Ther. 1991;50(6):695-701. Epub 1991/12/01. PubMed PMID: 1752114. (December 1991) https://pubmed.ncbi.nlm.nih.gov/1752114/ (last viewed May 30, 2026).
[297] Kearns GL. Hepatic drug metabolism in cystic fibrosis: recent developments and future directions. Ann Pharmacother. 1993;27(1):74-9. Epub 1993/01/01. PubMed PMID: 8431626. (January 1993) https://pubmed.ncbi.nlm.nih.gov/8431626/ (last viewed May 30, 2026).
[298] *Id.* at n. 77.
[299] Maher B. Personal genomes: The case of the missing heritability. Nature. 2008;456(7218):18-21. doi: 10.1038/456018a. (November 6, 2008) https://pubmed.ncbi.nlm.nih.gov/18987709/ (last viewed May 30, 2026).
[300] *Id.*
[301] Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG. Maternal exposure to childhood abuse is associated with elevated risk of autism. JAMA psychiatry. 2013;70(5):508-15. doi: 10.1001/jamapsychiatry.2013.447. PubMed PMID: PMC4069029. https://pmc.ncbi.nlm.nih.gov/articles/PMC4069029/pdf/nihms588841.pdf (last viewed May 28, 2026).
[302] *Id.* at n. 12.
[303] *Id.* at n. 28.
[304] *Id.* at n. 20.
[305] *Id.* at n. 12.

26. APAP exposure in utero is associated with increases in childhood brain cancer. This connection was first noted in 2010 in Sweden using a case-controlled method,[306] although the association was not statistically significant (OR 1.7; CI 0.6–5.4). A more recent study from Taiwan [307] supported the association and was statistically significant (HR 2.4; CI 1.10–5.39).	In the study from Taiwan, which evaluated cancer in about 2.27 million mother-child pairs,[308] medulloblastoma, a type of brain cancer, was the *only* type of cancer in children significantly associated with prenatal use of APAP. An increased risk of cancer might potentially result of cellular injury and subsequent repair of that injury,[309] although it remains unknown if APAP-associated brain cancer risks are related to processes involved in the etiology of ASD.

Table 4. Miscellaneous observations connecting acetaminophen (APAP) with ASD. The numbering of evidence is continued from Table 3. CI = 95% confidence interval; HR = hazard ratio; OR = odds ratio.

[306] Stålberg K, Haglund B, Strömberg B, Kieler H. Prenatal exposure to medicines and the risk of childhood brain tumor. Cancer epidemiology. 2010;34(4):400-4. Epub 2010/06/01. doi: 10.1016/j.canep.2010.04.018. PubMed PMID: 20510665. (May 26, 2010) https://pubmed.ncbi.nlm.nih.gov/20510665/ (last viewed May 30, 2026).

[307] Sirirungreung A, Lee PC, Hu YH, Liew Z, Federman N, Ritz B, et al. Exposure to Acetaminophen (Paracetamol) during Pregnancy and Childhood Cancer: A Population-Based Cohort Study in Taiwan. Cancer Epidemiol Biomarkers Prev. 2026;35(2):330-40. Epub 2025/12/04. doi: 10.1158/1055-9965.epi-25-1034. PubMed PMID: 41342591; PubMed Central PMCID: PMCPMC12782464. https://pmc.ncbi.nlm.nih.gov/articles/PMC12782464/pdf/nihms-2129429.pdf (last viewed May 28, 2026).

[308] *Id.*

[309] Kuraishy A, Karin M, Grivennikov SI. Tumor promotion via injury- and death-induced inflammation. Immunity. 2011;35(4):467-77. Epub 2011/11/01. doi: 10.1016/j.immuni.2011.09.006. PubMed PMID: 22035839; PubMed Central PMCID: PMCPMC3587290. https://pmc.ncbi.nlm.nih.gov/articles/PMC3587290/pdf/nihms331675.pdf (last viewed May 28, 2026).

Table 5

Associations in place and time	
Evidence / references	**Background / additional information**
27. The incidence of ASD began to increase in the early 1980s, coinciding with the increase in APAP use after aspirin was associated with Reye's syndrome. [310] The ratio of regressive to infantile ASD also rose at the same time.[311]	Temporal associations do not prove causality, but are a necessary prerequisite for causality to exist. The increased ratio of regressive to infantile ASD, noted in 2000,[312] would suggest that something was introduced into the environment that could induce ASD after months or even years of neurodevelopment.
28. The popularity of APAP use and the prevalence of ASD was substantially higher in Denmark than in Finland in the mid-2000s. [313]	Geographic-dependent associations do not prove causality, but do contribute to the total body of evidence. Particularly in the absence of alternative explanations, these associations can be compelling.
29. The incidence of ASD has steadily increased [314] as direct-to-consumer advertising,[315] marketing of over-the-counter medications, and perhaps other factors such as mandated use of APAP with the MenB vaccine (see discussion) have led to increased APAP exposure early in life.	Temporal associations do not prove causality, but are a necessary prerequisite for causality to exist. Alternative explanations for the rise in prevalence of ASD face several insurmountable problems, previously reviewed. [316] [317] One possible explanation for the persistence of unrealistic alternative explanations may be that many investigators are unaware of a satisfactory explanation consistent with available evidence.
30. Numerous investigators noted a very low prevalence of ASD prior to 1970 or noted increases in the prevalence of ASD that could not be attributed to factors other	Grunya Sukhareva [319] [320] and Leo Kanner[321] [322] were both renowned for their breadth of knowledge and grasp of pediatric psychology, and both described autism essentially the same as it is described today. Yet neither recognized a high prevalence of the disorder in the 1920s

[310] *Id.* at n. 77.
[311] Rimland, B. The autism increase: research needed on the vaccine connection. Autism Research Review International. Autism Research Review International Vol. 14, No. 1, 2000 https://www.researchgate.net/publication/282530363_Leo_Kanner_Hans_Asperger_and_the_discovery_of_autism (last viewed May 31, 2026).
[312] *Id.*
[313] *Id.* at n. 3.
[314] *Id.* at n. 77.
[315] Donohue J. A history of drug advertising: the evolving roles of consumers and consumer protection. Milbank Q. 2006;84(4):659-99. doi: 10.1111/j.1468-0009.2006.00464.x. PubMed PMID: 17096638. https://pmc.ncbi.nlm.nih.gov/articles/PMC2690298/pdf/milq0084-0659.pdf (last viewed May 28, 2026).
[316] *Id.* at n. 20.
[317] *Id.* at n. 12.

than a real increase. Reviewed by Jones et al. [318]	and 1940s, respectively. Further, neither was ridiculed by contemporaries for describing a common, previously well-known condition.
31. Studies in several countries with chronic shortages of medication found dramatically lower-than-expected levels of ASD relative to other developmental issues, including Down syndrome. Reviewed by Jones et al.[323]	In addition to evidence presented in the previous review of this issue, [324] apparently low levels of ASD in Cuba have been identified, where 241 cases of ASD in the entire nation (1 in 25,000 children) were identified in a 2016 report. [325] APAP is available in Cuba by prescription only,[326] and multiple travel advisors cite APAP in particular as being in short supply in Cuba.[327] In addition, individuals with pervasive developmental disorders, about 50% of which typically have ASD, were found among second generation Israeli immigrants from Ethiopia, but not among first generation Israeli immigrants from Ethiopia ($p = 0.0022$). [328]

Table 5. Associations in place and time connecting acetaminophen (APAP) use with ASD. The numbering of evidence is continued from Table 4.

---

[319] *Id.* at n. 101.
[320] *Id.* at n. 102.
[321] *Id.* at n. 95.
[322] Baron-Cohen S. Leo Kanner, Hans Asperger, and the discovery of autism. The Lancet. 2015;386(10001):1329-30. doi: 10.1016/S0140-6736(15)00337-2. https://docs.autismresearchcentre.com/papers/2015_sbc_lancet-review-of-silberman.pdf (last viewed July 3, 2026).
[318] *Id.* at n. 12.
[323] *Id.* at n. 12.
[324] *Id*. at n. 12.
[325] IN SPANISH Aguiar AG, Mainegra FD, García RO, Hernandez FY. Diagnosis in children with autism spectrum disorders in their development in textual comprehension. Rev Medical Sciences. 2016;20(6):729-37. (2016) https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=69835 (last viewed May 30, 2026).
[326] Kosteva D. A Peek at Pharmacy Practice in Cuba: Pharmacy Times; 2016. Available from: https://www.pharmacytimes.com/view/a-peek-at-pharmacy-practice-in-cuba (last viewed May 28, 2026).
[327] Sainsbury B. 20 things to know before visiting Cuba: Lonely Planet; 2024 [cited 2024 December 18]. https://www.lonelyplanet.com/articles/things-to-know-before-traveling-to-cuba (last viewed May 30, 2026).
[328] Kamer A, Zohar AH, Youngmann R, Diamond GW, Inbar D, Senecky Y. A prevalence estimate of pervasive developmental disorder among immigrants to Israel and Israeli natives- a file review study. Social psychiatry and psychiatric epidemiology. 2004;39(2):141-5. Epub 2004/03/31. doi: 10.1007/s00127-004-0696-x. PubMed PMID: 15052396. https://pubmed.ncbi.nlm.nih.gov/15052396/ (last viewed May 30, 2026).

Table 6

Variable	HR (CI)	p
APAP, actual risk built into virtual construct	2.667 (NA)	NA
APAP, result of regression analysis	2.55 (2.41-2.71)	2×10^{-16}
APAP, adjusted for all contributing cofactors	0.85 (0.80-0.90)	2×10^{-7}
OS factor 1, all individuals	1.24 (1.23-1.26)	2×10^{-16}
OS factor 1, virtual individuals with APAP use only	1.32 (1.30-1.34)	2×10^{-16}
OS factor 1, virtual individuals with no APAP use only	1.00 (0.97-1.03)	0.90

Table 6: Consequences of assumptions underlying multivariate analysis of observational data in a virtual computer construct. Acetaminophen (APAP) is "shown" to be protective against ASD (HR < 1.0), even though it induced 50 % of all cases of ASD in the virtual construct. The virtual data set was constructed and analyzed as previously described[329] using a Cox regression analysis, with 240,000 individuals, 60 % exposure to APAP and one in 36 individuals with ASD. In this virtual data set, 50 % of ASD was induced by exposure to acetaminophen combined with the sum of 10 cofactors, modeling the contribution of oxidative stress (OS) related factors in the induction of ASD. The other 50 % of ASD cases were randomly assigned. The propensity for acetaminophen exposure was dependent on levels of oxidative stress, as previously described.[330] n = 96,000 virtual individuals without APAP use, and n = 144,000 virtual individuals with APAP use. CI = confidence interval. NA = not applicable.

[329] *Id.* at n. 12.
[330] *Id.* at n. 12.