Paracetamol (Acetaminophen) use in infants and children was never shown to be safe for neurodevelopment: A systematic review

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Abstract

Although widely believed to be safe for use in infants and children when used as directed, increasing evidence indicates that early life exposure to paracetamol (acetaminophen) may cause long-term neurodevelopmental problems. Further, recent studies in animal models demonstrate that cognitive development is exquisitely sensitive to paracetamol exposure during early development. In this study, evidence for the claim that paracetamol is safe was evaluated using a systematic literature search. Publications on PubMed between 1974 and 2017 that contained the keywords "infant" and either "paracetamol" or "acetaminophen" were considered. Of those initial 3096 papers, 218 were identified that made claims that paracetamol was safe for use with infants or children. Of these, a total of 103 papers were identified as sources of authority for the safety claim, and 36 of those contained actual experiments designed to test safety. The 36 experiments described had a median follow-up time of 24 hours, and none monitored neurodevelopment. Further, no trial considered total exposure to drug since birth, eliminating the possibility that the effects of drug exposure on long-term neurodevelopment could be accurately assessed. On the other hand, abundant and sufficient evidence was found to conclude that paracetamol does not induce acute liver damage in babies or children when used as directed.

Introduction

Hundreds of reports claim emphatically that, when used as directed, paracetamol (acetaminophen) is safe for use in babies and in children. However, mounting evidence points toward the view that paracetamol exposure during early development can have an adverse effect on neurodevelopment, even when used as directed. For example, in a recent review [1], eight studies supporting a link between prenatal paracetamol exposure and neurodevelopmental problems were identified [2-9]. In the three years since that review, five additional studies have confirmed this same relationship, three of which have used data from the Norwegian Mother and Child Cohort Study [10-14]. Although exposure to paracetamol in utero is associated with neurodevelopmental problems, even after consideration of potentially confounding factors, the effects are typically small and the amount of paracetamol required to yield the effect is greater than the amount typically used by average individuals. For example, after adjusting for potential confounders such as parental education level, use of vitamin supplements, parental BMI, smoking, and use of other drugs, Skovlund and colleagues found a weak yet significant association between prenatal exposure to paracetamol and mother-reported communication skills: the chances of being in a lower development category increased with increasing periods of prenatal paracetamol use but not prenatal opioid use [10]. In another example, using propensity score matching, Vlenterie and colleagues found that 28 or more days of paracetamol use during pregnancy was associated with a modestly increased risk of delayed motor milestone attainment (OR: 1.35, 95% CI 1.07–1.70) by children at 18 months [11].

Evidence points toward a higher risk of paracetamol-induced neurodevelopmental disorders when exposure occurs after birth as compared to in utero. Studies using laboratory rodents demonstrate that exposure to near therapeutic doses of paracetamol during the first days of life induces profound, long-term neurological changes [15, 16], whereas somewhat higher doses are required to induce permanent neurological damage during pregnancy [17]. These laboratory studies demonstrate that the target organ for toxicity in neonates is the central nervous system, not the liver, and demonstrate that if paracetamol had been tested using current guidelines, it would never have been approved for use in children. More concerning are observations in children indicating that paracetamol is not safe for neurodevelopment. The 2008 study which first raised a red flag regarding the safety of paracetamol during neurodevelopment found a greater than 20-fold risk of regressive autism with paracetamol use during childhood [18]. Although this relatively small study did not attract enough interest to promote larger studies, other lines of evidence support the view that paracetamol exposure during early life can lead to neurodevelopmental disorders. For example, a startling 2-fold greater incidence of infantile autism in circumcised boys compared to non-circumcised boys [19] can be readily explained by potentially negative impacts of paracetamol exposure during and following the circumcision procedure [1]. Sadly, the widely held and entrenched belief that vaccines induce autism [20, 21] may be yet another result of the impact of paracetamol on neurodevelopment in combination with widespread use of the drug during vaccination [1].

With the above concerns in mind, a systematic evaluation of the peer-reviewed literature was initiated to address the question of why paracetamol is widely believed to be safe for use during early development. All papers published between 1974 and 2017 that contained the keywords "infant" and either "paracetamol" or

"acetaminophen" were considered. All papers which made claims that paracetamol or acetaminophen is safe for use in infants or children were identified, and the justification for this claim was critically evaluated.

Methods

As a first step in understanding why paracetamol is thought to be safe during early development, all titles and abstracts in the PubMed® Database with keywords "infant" and "acetaminophen or paracetamol" published between 1974 and 2017 were identified. The term "infant" rather than "child" was selected because (a) the number of papers with the term "child" was prohibitively large, and (b) the focus of the study was intended to be on drug exposure during early development, from birth to age approximately 6 years, not individuals up to the age of 17 years. In all cases, the terms paracetamol and acetaminophen were taken to be synonymous, and no distinctions were made.

In the second step, two coauthors (JCH and JTS) independently screened all titles and abstracts. In this step, articles that could not be obtained in English and all articles not describing use of paracetamol in humans were eliminated from the study. Based on titles and abstracts (if available), articles were tagged which were deemed likely to make claims regarding the safety of acetaminophen use in infants and children between birth and age 6 years.

In the third step, two coauthors (JCH and JTS), continuing to work independently, examined full texts of all tagged titles and abstracts. Texts were examined for the following three assertions:

(a) paracetamol use is "safe" in children or infants
(b) paracetamol is the "drug of choice" in children or infants
(c) paracetamol use is "recommended" for children or infants

In cases where the terms "drug of choice" or "recommended" were used, the context was considered. In some cases, particularly in manuscripts expressing caution regarding the use of paracetamol, these terms were not taken to imply safety, but rather were taken to be an indicator of the common acceptance of the drug. These articles were excluded from the study. Based on this approach, articles were tagged that were considered to have made safely claims regarding the use of paracetamol in infants or children younger than 6 years old.

Still working independently, two coauthors (JCH and JTS) evaluated each manuscript making a claim of safety, determining the source of authority for the stated claim. If no literature was cited to support the claim, this was documented. In cases where the source that was cited contained another citation, that secondary reference was obtained and evaluated. This process continued as needed until an original source or sources describing an actual demonstration of safety was identified. An example of the results of this process is shown in **Figure 1**.
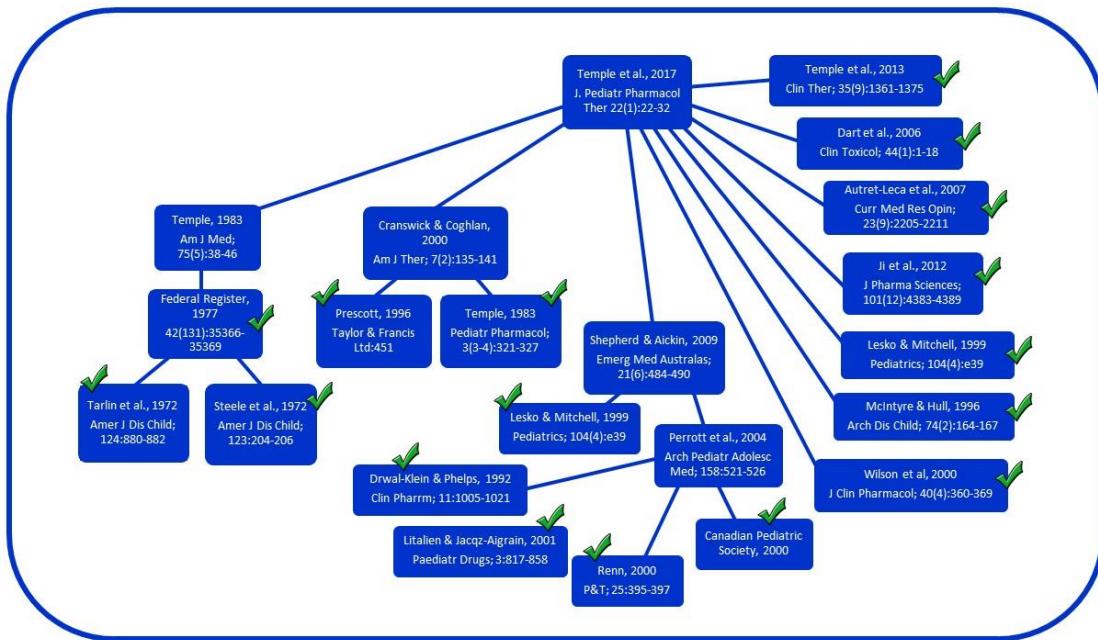
Figure 1. Flow diagram illustrating connections between articles claiming that paracetamol use is safe for infants or children when used as directed. In this example, the citations in a paper by Temple and colleagues in 2017 [25] are assessed. Articles describing new experiments designed to test safety of paracetamol or which contain claims of safety without citation are included in Table 2 and are indicated by a check mark. Articles shown in the diagram which do not describe experiments designed to test safety of paracetamol and which cite other articles as a source for claims of safety [23, 26, 27, 134] are not included in Table 2 and are not indicted by a check in the diagram.

In the fourth step, any discrepancies between the analyses provided by coauthors JCH and JTS were arbitrated by coauthor WP. In the fifth step, articles upon which safety claims were based were compiled. Finally, articles upon which safety claims were based and which contained experiments designed to assess safety were evaluated. For each experiment described, the study group, endpoints measured, and follow-up time were evaluated.

Results

An overview of results from a systematic search for studies demonstrating safety of paracetamol use in infants and children is shown in **Table 1**. The initial Medline search provided 3096 articles that contained the terms infant and either paracetamol or acetaminophen that were published between 1974 and 2017. From these articles, 467 were selected for assessment based on likelihood of safety claims regarding use of paracetamol in infants or children. Of these 467 articles, 218 made safety claims regarding the use of paracetamol in infants or children. During this phase of the study, numerous articles were identified which either claimed or demonstrated that paracetamol use, even at doses beyond the recommended dose, does not generally cause long-term liver damage in infants or children. Any claims of safety for liver function were not evaluated in detail and were not considered in this study. Only general claims of safety were assessed.

Table 1. Number of citations identified in the systematic search during each step of the study. Numbers are provided for both analysts performing the work (JCH and JTS). The overlap is the number of citations that were the same between the two analysts. *Numbers in parentheses indicated the number of citations in which both analysts identified the same citation, but not the same source or sources as the authority for claims of safety.

Step	JCH	Overlap	JTS	Total
1. Medline (APAP + infant)				3096
2. Safety claim, first step	310	193	350	467
3. Safety claim, second step	189	144 (53*)	189	234
4. Safety claim, final	173	128 (37*)	173	218
5. Sources attributed to safety claim				103
6. Sources with experiments attributed to safety claim				36

Of the 218 articles making claims that paracetamol use in infants or children is safe, half (114) provided no citation. The other half (114) of the articles cited additional articles as evidence that paracetamol is safe in infants or children. Cited articles were carefully evaluated as described in the methods. In some cases, those "primary" cited articles did not make original claims of safety, but rather cited additional ("secondary") articles. In cases where a primary article cited another article, the primary article was not considered to have made an original claim of safety, and was not evaluated further. An example of the results of this process is shown in **Figure 1**. Both primary articles and secondary (and tertiary, etc) articles attributed with claims of the safety of paracetamol use in infants or children were compiled and are shown in **Table 2**. In total, 103 articles were identified which were cited as containing original claims that paracetamol use in infants or children is safe when used as directed.

Table 2. Sources cited as stating that acetaminophen is safe for infants or children when used as directed. *This article is cited as "Renn E. The antipyretic use of paracetamol versus ibuprofen in a pediatric care setting. Physical Therapy. 2000;25:395-397." This reference does not apparently exist: The volume number corresponding to the year 2000 for the journal Physical Therapy is 80, not 25. We were unable to determine what actual article it may have originally referred to. **The Canadian Pediatric Society paper from 1998 was mis-cited as being from 2000 in one instance. *** This article, cited as Kehlet and Werner (2003) from the journal Drugs, Volume 63, pp 15-22 (Spec no 2), does not exist on the journal's website for unknown reasons.

Sources cited for safety of paracetamol in children or infants: study number, year, and design	Study subjects	Outcome measures related to safety or safety claims made.	Duration of monitoring	Times cited
1. 1999: Double-blind clinical trial with three treatments, one of paracetamol and two different concentrations of ibuprofen given for fever [22]	9,127 children treated with paracetamol; median age is 14 months	"Serious adverse clinical events" requiring hospitalization: gastrointestinal bleeding, renal failure, anaphylaxis, Reye's syndrome, asthma, bronchiolitis, and vomiting/gastritis	4 weeks	13

2. 1997: Double-blind, randomized, three-way crossover study with three treatments, one each of paracetamol, ibuprofen, and placebo given by parents for headache. Each child with three migraine attacks was treated in random order with single oral doses of the study drugs [34]	80 children were treated with paracetamol, age range approximately 4 to 16 years	Monitoring by parents for "adverse events": nausea, vomiting, and gastric pain	2 hours: all patients received paracetamol at some point, so long-term monitoring was not feasible.	9
3. 1978: Editorial describing current practice with analgesic use in children [35]	NA: Editorial	Claims: "anticipated liver damage is *not* observed" based on personal experience and interactions with other clinicians	NA: Editorial	8
4. 2001: Review describing analgesic use in children [36]	NA: Review	Claims: "40-year safety record in children" without citation	NA: Review	8
5. 1978: Review describing antipyretic therapy in febrile children [37]	NA: Review	Claims: "relatively free of adverse reactions" without citation and 9 citations provided for the statement that hepatotoxicity from paracetamol in children is "very low compared with that seen in adults"	NA: Review	7
6. 2000: Renn, 2000 Erroneous citation*	NA: Erroneous citation	NA: Erroneous citation	NA: Erroneous citation	7
7. 2011: Report describing current recommended practice [38]	NA: Report	Claims: "generally regarded as safe" without citation. Lesko (1999) is cited for equivalent safety between ibuprofen and paracetamol.	NA: Report	7
8. 1983: Review describing pediatric dosing of paracetamol [39]	NA: Review	Claims: "one of the safest" without citation	NA: Review	6
9. 1995: Double-blind clinical trial with three treatments, one of paracetamol and two of different concentrations ibuprofen given for fever [40]	28,130 children treated with paracetamol; median age is 40 months	Serious events defined as hospitalization for acute gastrointestinal bleeding, acute renal failure, or anaphylaxis.	4 weeks	6
10. 1998: Practice guidelines** [41]	NA: Practice guidelines	Claims: "As demonstrated by the numerous	NA: Practice guidelines	5

		prospective clinical studies", paracetamol is "remarkably safe in therapeutic doses", without citation.		
11. 1972: Double-blind study with two treatments, one each of aspirin and paracetamol, given for antipyretic effect [29]	39 children treated with paracetamol, age 6 months to 6 years	Unspecified "complications or side effects"	6 hours	5
12. 1977: Clinical guidelines for use, predominantly focused on aspirin, but also including paracetamol. [28]	NA: Clinical guidelines	Considered to have a "wide range of safety" based on "the large doses of paracetamol required to evoke toxic reactions" in laboratory animals. In addition, considered "safe and effective when used as directed", with two studies cited [29, 30]	NA: Clinical guidelines	4
13. 1978: Commentary on paracetamol use [42]	NA: Commentary	Claims: "safe and effective analgesic and antipyretic in usual therapeutic dosage" without citation.	NA: Commentary	4
14. 1978: Review comparing aspirin's and paracetamol's antipyretic and analgesic activity [43]	NA: Review	Claims: "the choice of agents for antipyresis in clinical practice has been narrowed to aspirin and paracetamol" without citation.	NA: Review	4
15. 1996: Review of paracetamol liver toxicity in children under the age of 6 years [44]	NA: Review	Makes no general safety claim, although extensive references are provided showing that paracetamol does not cause long-term damages to infants' livers.	NA: Review	4
16. 1997: Double-blind clinical trial with three treatments, one of paracetamol and two different concentrations of ibuprofen given for fever [45]	97 children treated with paracetamol; median age is 29 months	Renal function as indicated by blood urea nitrogen (BUN) and creatinine levels.	4 weeks	4

17. 1972: Clinical study with three treatments, one each of aspirin, paracetamol, and a combination of the two given for fever [30]	80 children treated with paracetamol, age 6 months to 5 years	No outcome measures specified.	6 hours or less	4
18. 2005: Pharmacokinetic study. [46]	NA: Pharmacokinetic study	No safety outcomes reported. No safety claims made.	NA: Pharmacokinetic study	3
19. 2011: Randomized open-label study with two dosing regimens of intravenous paracetamol given for analgesic or antipyretic effect. [47] Intravenous paracetamol contains cysteine, an antidote for paracetamol poisoning. The antidote is not present in the oral medication.	75 patients total were treated with paracetamol, 3 neonates, 25 infants, 25 children, and 22 adolescents	Changes in liver enzymes, changes in vital signs, and reported or observed adverse drug effects, which included the following: anemia, constipation, nausea, vomiting, face edema, pyrexia, hypokalemia, hypomagnesemia, hypophosphatemia, agitation, atelectasis, pleural effusion, pulmonary edema, stridor, wheezing, periorbital edema, and pruritus	48 hours	3
20. 1973: Review describing precautions with paracetamol use [48]	NA: Review	Makes no safety claim with respect to pediatric use.	NA: Review	2
21. 1981: Review comparing efficacy of aspirin and paracetamol in fever reduction in children [49]	NA: Review	Claims: a "high degree of safety" at therapeutic doses without citation.	NA: Review	2
22. 1992: Pharmacokinetic study in adults aged 21-25 years [50]	NA: Pharmacokinetic study	NA: study in adults	NA: Pharmacokinetic study	2
23. 1993: Review [51]	NA: Review	Claims: "Recent data have supported the relative safety (and efficiency) of paracetamol in newborn infants" without citation.	NA: Review	2
24. 1996: Double-blind study with two treatments, one of each ibuprofen and paracetamol, given for fever [52]	47 children were treated with paracetamol, age 0.2 to 9.4 years; median age is 1.6 years	Extensive assessment of adverse events. Claims: "majority of adverse events had a doubtful or	36 hours	2

		no relationship the treatment, and most were considered mild."		
25. 1997: Computer simulation used to predict dosing needed to achieve desired concentration of drug in plasma [53]	NA: Computer simulation	No safety claims made.	NA: Computer simulation	2
26. 1997: Pharmacokinetic study. [54]	NA: Pharmacokinetic study.	No safety outcomes reported. Claims: "Commonly used in children because of its (efficacy and) safety" without citation.	NA: Pharmacokinetic study.	2
27. 1999: Pharmacokinetic study with a single rectal dose of paracetamol [55]	28 preterm neonates, 2 days after birth	No safety outcomes stated. Claimed: "safe"	Up to 12 hours	2
28. 2007: Comparison of efficacy between paracetamol and ibuprofen. First phase was a single dose, double-blind administered in the clinic, followed by an open-label phase administered at home for the second and subsequent doses. [56]	150 patients treated with paracetamol, age range approximately 0.40 to 11 years; average age is 3.71 years	Monitoring for "adverse events," three of which were infections, gastrointestinal disorders, and respiratory disorders.	3 days	2
29. 2008: Retrospective study using data collected in neonates treated with intravenous paracetamol. [57]	149 neonates total, median postmenstrual age 38 weeks and median postnatal age is 5 days	Hepatic enzyme profiles including ALT, AST, and GGT	48 hours	2
30. 2011: Review describing NSAIDs and paracetamol and their roles in reducing side-effects after surgery [58]	NA: Review	Makes no safety claim.	NA: Review	2
31. 2013: Review describing dosing and antipyretic efficacy of paracetamol [59]	NA: Review	Claims: "dosing range is well tolerated in children" without citation.	NA: Review	2
32. 1965. Pharmacology reference book [60]	NA: Review	Pediatric dose stated without citation, and without further discussion of pediatric use. Makes no safety claim.	NA: Review	1
33. 1967: Clinical comparison of a single dose of paracetamol, aspirin, and salicylamide [61]	50 infants treated with paracetamol, up to 48 months old	Unspecified "undesirable effects" not observed	6 hours	1

34. 1978: Review describing the pathophysiology of aspirin overdosage [62]	NA: Review	Does not discuss paracetamol. Makes no safety claims	NA: Review	1
35: 1982. Monitoring of drug use by the Pediatric Drug Surveillance Program [63]	1,158 children, up to age 16, received paracetamol	Adverse events not reported. Makes no safety claim	NA: No follow-up conducted	1
36. 1982: An abstract [64] cited by Ragg, 1997 [65]	Not determined	Not determined	Not determined	1
37. 1984: Prospective study observing adverse drug reactions in pediatric inpatients. [66]	132 children, age not specified, received an antipyretic or analgesics while hospitalized (paracetamol not mentioned)	No side effects observed. No safety claims made.	During inpatient stay: time not specified.	1
38. 1989: Editorial comparing ibuprofen and paracetamol [67]	NA: Editorial	Claims: "therapeutic doses of either drug [ibuprofen and paracetamol] cause no discernable adverse effects" without citation.	NA: Editorial	1
39. 1989: Review assessing pain in neonates and the approaches to postoperative analgesia [68]	NA: Review	Claims: "Recent data have supported the relative safety and analgesic efficacy of paracetamol in newborn infants" without citation.	NA: Review	1
40. 1990: Pharmacology reference book [69]	NA: Review	Claims: "usually well tolerated" without citation, but use in pediatric populations is not discussed.	NA: Review	1
41. 1991: Review describing paracetamol hepatotoxicity and poisoning in children [70]	NA: Review	Makes no safety claim	NA: Review	1
42. 1992: Review describing the hepatotoxicity of non-steroidal anti-inflammatory drugs [71]	NA: Review	Claims: Paracetamol is "normally very safe when used properly" although this statement does not necessarily refer to pediatric use	NA: Review	1
43. 1992: Randomized, double-blind, multidose, parallel-group, variable	16 children treated with	Adverse events included headache,	24 to 48 hours	1

duration clinical trial with three different concentrations of ibuprofen and one of paracetamol given for pediatric fever [72]	paracetamol; average age is 5.2 years	gastrointestinal effects, sweating, hypothermia, abdominal pain, agitation, nervousness, and adverse experiences related to the respiratory system.		
44. 1994: Textbook [73] cited by Wilson, 1995. [74]	NA: Textbook	Not determined	NA: Textbook	1
45. 1996: Double-blind study with two treatments, paracetamol and placebo given for postoperative pain [75]	100 children were treated with paracetamol, age 3 to 14 years	Liver enzymes determined by blood samples.	24 hours	1
46. 1996: Randomized study with two treatment groups, one of which received paracetamol preoperatively and the other postoperatively [76]	28 children, age 2 to 8 years	Outcome measures included pain scores and the need for rescue analgesics	240 minutes	1
47. 1997: Double-blind, multicenter study with two treatments, one each of ibuprofen and paracetamol, given for fever [77]	56 children treated with paracetamol, age 8 months to 11 years; average age is 4.2 years	Changes in temperature. Only side effect reported was vomiting.	6 hours	1
48. 1999: Randomized, double-blind, placebo-controlled study with four different concentrations of paracetamol given after induction of anesthesia [78]	90 children treated with paracetamol, age 1 to 7 years	Postoperative pain was evaluated by behavioral assessment and physiologic measurement. Only side effects reported were postoperative nausea and vomiting	24 hours	1
49. 1999: Clinical trial examining the efficacy and pharmacokinetics of paracetamol in term infants (multiple-dose) [79]	10 infants, up to the age of 2 days	Adverse events not reported. Claims: "paracetamol can be administered safely to neonates on the first day of life"	First 2 days after birth	1
50. 2000: Review describing non-opioid drugs for treatment of postoperative pain [80]	NA: Review	Claims: rectal paracetamol "seems safe in children" without citation.	NA: Review	1

51. 2000: Pharmacokinetic study of postoperative, repeated dosing of rectal paracetamol [81]	21 children, age 9 weeks to 11 years	No sign of adverse effects observed. Claims: Paracetamol has gained wide acceptance as a simple and safe antipyretic and analgesic in children", without citation.	Variable, from 1 to 5 days	1
52. 2000: Observational study of calls to a poison center to evaluate pediatric paracetamol exposures [82]	1,019 children up to the age of 7 years	Parent's report of signs of hepatotoxicity.	72 hours	1
53. 2000: Review of paracetamol's history, present and future [83]	NA: Review	Claims: paracetamol is an "effective and remarkably safe drug when used properly" without citation	NA: Review	1
54. 2000: Randomized, double-blind study with two treatments, one each of diclofenac and paracetamol for postoperative analgesia [84]	24 children treated with paracetamol, age 5 to 15 years; median age is 10 years	Outcome measures used were pain scores and relief of pain or dysphagia. Only side effects reported were nausea and vomiting.	3 days	1
55. 2000: Integrated Management of Childhood Illness handbook by the World Health Organization [85]	NA: Review	Makes no safety claims	NA: Review	1
56. 2000: Randomized, double-blind, multicenter study comparing paracetamol controlled-release sprinkles and paracetamol immediate-release elixir in febrile children [86]	120 patients, age 2 to 11 years	Disorientation, extreme irritability, and confusion were the only adverse events recorded.	8 to 10 hours	1
57. 2000: Guide to pediatric medication and nutrition [87]	NA: Review	Claims: "Usually well tolerated when used as directed", without citation.	NA: Review	1
58. 2001: Review describing treatment with paracetamol in infants [88]	NA: Review	Claims: "generally considered a safe drug" without citation but warns of potential toxicity with glutathione depletion.	NA: Review	1
59. 2001Literature review describing perioperative use of high-dose of rectal paracetamol [89]	NA: Review	Claims: "administration of high-dose rectal paracetamol in the	NA: Review	1

		perioperative period appears to be safe" without citation.		
60. 2001: Review describing paracetamol toxicity in children [90]	NA: Review	Claims: safety based on NAPQI production and glutathione levels without citation.	NA: Review	1
61. 2001: Review describing the neurobiology of pain [91]	NA: Review	Makes no safety claim	NA: Review	1
62. 2001: Randomized, stratified, placebo-controlled, single-dose, double-blind, triple-dummy, single-center, parallel-group study with four treatments, one each of ibuprofen, ketoprofen, paracetamol, and placebo given for postoperative dental pain [92]	NA: minimum age 16 years, average age 22.2 years	NA: minimum age 16 years, average age 22.2 years	NA: minimum age 16 years, average age 22.2 years	1
63. 2001: Blinded study conducted to observe the analgesic efficacy of rectal and oral paracetamol in two separate groups in children after craniofacial surgery [93]	40 patients, average age is 10.3 years	Paracetamol plasma concentrations and pain scores. Only side effect reported was vomiting. Makes no safety claims.	24 hours	1
64. 2002: Review comparing the effects of paracetamol, NSAIDs or their combination in postoperative pain management [94]	NA: Review	Claims: "low incidence of adverse effects" without citation	NA: Review	1
65. 2002: Literature review describing paracetamol and ibuprofen use for fever treatment in children [95]	NA: Review	Claims: "Both drugs appeared well tolerated and no evidence of difference in short-term adverse effects was observed" without citation	NA: Review	1
66. 2003: Editorial describing use of antipyretics [96]	NA: Editorial	Claims: paracetamol is "traditional(ly) considered to be safe based on (a) large clinical experience over (a) long time" without citation.	NA: Editorial	1
67. 2003: Erroneous or out of print citation*** [97]	NA: Erroneous or out of print citation	NA: Erroneous or out of print citation	NA: Erroneous or out of print citation	1
68. 2003: Review describing anti-inflammatory agents and paracetamol in neonates [98]	NA: Review	Claims: "paracetamol remains the drug of choice for	NA: Review	1

		antipyresis in neonates" and "the adverse effect of paracetamol is more favorable" without citation		
69. 2003: Randomized, double-blind, placebo-controlled study with four treatments groups, ibuprofen, paracetamol, a combination of the two, and placebo. The purpose was to observe the analgesic efficacy of each treatment [99]	80 children treated with paracetamol, age 1 to 6 years; average age is 2.7 years	Adverse events defined as retching, vomiting, abdominal pain, and dizziness	All children were kept in the PACU for 1.5 hours. The parents of the children were asked to record the well-being of their child until 24 hours after anesthesia.	1
70. 2004: Pharmacokinetic study with a single intravenous dose of propacetamol [100]	30 neonates, 24 hours after birth	Liver enzymes determined by blood samples.	10 hours	1
71. 2004: Systematic review assessing the prevalence of aspirin induced asthma in adults and children and other issues related to the syndrome [101]	NA: Review	Makes no safety claim with respect to pediatric use.	NA: Review	1
72. 2005: Review describing paracetamol's tolerability profile [102]	NA: Review	Claims: "Paracetamol is a very well tolerated drug at therapeutic doses" without citation, although this statement does not necessarily refer to pediatric use.	NA: Review	1
73. 2005: Randomized, double-blind study with three treatments, one each of ibuprofen, paracetamol, and placebo given before surgery [103]	25 children treated with paracetamol, age 3 to 12 years	Agitation in recovery measured using Oucher's scale	24 hours	1
74. 2005: Evaluation of pain management guidelines for tonsillectomy [104]	37 children, age 5-11 years.	Evaluation of nausea and vomiting.	16 to 20 hours	1
75. 2006: Practice guidelines [105]	NA: Practice guidelines	Makes no safety claim	NA: Practice guidelines	1
76. 2006: Practice guideline to assist poison center personnel with management of paracetamol poisoning [106]	NA: Guidelines	Makes no safety claim	NA: Guidelines	1
77-79. 2004-2010: Three textbooks [107-109] cited by Karbasi and colleagues [110]	NA: Textbooks	Not determined	NA: Textbooks	1
80. 2007: Review describing paracetamol safety and hepatotoxicity [111]	NA: Review	Claims: "an excellent overall safety record" with infants and	NA: Review	1

		children without citation		
81. 2007. Open-label, single-sequence, multiple-dose study with intravenous paracetamol in adults [112]	NA: study in adults	NA: study in adults	NA: study in adults	1
82. 2007: Randomized double-blind placebo-controlled study with paracetamol given for fever [113]	103 children treated with paracetamol, age 6 months to 6 years; average age is 26.1 months	Outcome measures included fever clearance time, rate of fall of temperature, percent reduction of temperature, proportion of afebrile children, symptomatic improvement and clinical and biochemical adverse effects. Claims: "considered to be a safe drug at therapeutic levels."	6 hours	1
83. 2007: Randomized, double-blind, placebo-controlled study with three treatments, one each of naproxen, paracetamol, and placebo before the induction of anethesia [114]	30 children treated with paracetamol, age 1 to 6 years, average age is 1.3 years	Need for postoperative rescue fentanyl and the incidence of postoperative nausea and vomiting.	Minimum of 2 hours	1
84. 2007: Study with zolmitriptan nasal spray, not paracetamol [115]	NA: study not involving paracetamol	NA: study not involving paracetamol	NA: study not involving paracetamol	1
85. 2007: Guidelines for assessment and initial management of fever in children younger than 5 years [116]	NA: Clinical guidelines	Makes no safety claim	NA: Clinical guidelines	1
86. 2007: Review describing systemic analgesics for children [117]	NA: Review	Claims: "when the maximum daily dose of paracetamol is observed it is well tolerated" without citation	NA: Review	1
87. 2009: Comparative study with three treatments: paracetamol, ketoprofen, and ibuprofen given for fever [118]	112 children were treated with paracetamol, average age about 4 years old.	Children were monitored without observation of drug-related side effects. Makes no safety claim	Up to 48 hours	1
88. Randomized, controlled trial in which patients received either paracetamol or placebo for postoperative pain [119]	29 infants were treated with paracetamol, age 0-2 months	Did not report any adverse events. Measured the efficacy of	48 hours	1

		paracetamol, not safety.		
89. 2009: Review describing the Italian Pediatric Society guidelines on the management of fever in children [120]	NA: Review	Claims: paracetamol is "generally well tolerated" without citation.	NA: Review	1
90. 2009: Review describing drugs of choice for sedation and analgesia in the NICU [121]	NA: Review	Makes no safety claims	NA: Review	1
91. 2009: Review describing the peri-operative use of paracetamol [122]	NA: Review	Claims: paracetamol is a "safe, well-tolerated drug with proven efficacy" without citation.	NA: Review	1
92. 2009: Systematic review of the clinical safety and tolerability of ibuprofen compared with paracetamol in pediatric pain and fever [123]	NA: Review	Makes no safety claims	NA: Review	1
93. 2009: Online survey of anesthetists and the current prescribing practice of i.v. paracetamol [124]	NA: Survey	Makes no safety claims	NA: Survey	1
94: 2010: Hemodynamic study with intravenous paracetamol in neonates [125]	72 neonates, age 1 to 27 days; average age is 3 days	Assessment of hemodynamics. No safety claims made.	6 hours	1
95: 2010: Review describing post-operative pain management [126]	NA: Review	Makes no safety claim	NA: Review	1
96: 2010: Meta-analysis of efficacy and safety of ibuprofen and paracetamol in children and adults [127]	NA: Review	Claims similar safety profiles between paracetamol and ibuprofen, but makes no absolute safety claim	NA: Review	1
97: 2011: Study of efficacy and safety in adults [128]	NA: study in adults	NA: study in adults	NA: study in adults	1
98: 2011: Literature review of clinical trials of intravenous paracetamol for postoperative pain [129]	NA: Review	Claims: it "has been well known as a safe and effective" without citation	NA: Review	1
99: 2012: Review of efficacy and pharmacokinetics of paracetamol in pediatric patients [130]	NA: Review	Makes no safety claims	NA: Review	1
100: 2012: Retrospective study using data collected on pediatric surgery patients to identify the status and risk factors of major infections [24]	230 patients, age 0 to 15 years, average age is 4.28 years	Postoperative fever and its etiologies, mortality discharge, and rates of re-open sternotomy reintubation	1 year	1

101. 2013: Case series evaluating the efficacy of intravenous paracetamol in preterm infants with hemodynamically significant patent ductus arteriosus (hsPDA) [131]	10 preterm infants, age 2 to 15 days	Pre- and posttreatment levels of liver enzymes	3 days	1
102. 2013: Mechanistic study in laboratory animals [132]	NA: Study in laboratory animals	Makes no safety claim	NA: Study in laboratory animals	1
103. 2014. Literature review assessing liver toxicity due to paracetamol in children [133]	NA: Review	Claims: "doses of less than 75 mg/kg/day of paracetamol are safe for children younger than 6 years of age" without citation	NA: Review	1

Several studies emerged as popular citations for the claim that paracetamol use in infants or children is safe when used as directed. Only 19 articles were cited more than twice, and the most popular article [22] was cited a total of 13 times (Table 2) by the 218 articles we identified. However, in some cases, well cited articles did not make original claims of safety, and are therefore not included in Table 2. For example, an article by Perrott and colleagues in 2004 [23] was cited a total of 7 total times by the 218 articles we identified. However, Perrott's article, being a review, does not make original claims of safety, but rather cites additional articles as the authority for assurance of safety (Figure 1). Thus, Perrott's article is not included in Table 2 as an original source for the claim that use of paracetamol is safe for infants and children when used as directed.

Of the 103 articles cited as authority for the safety of paracetamol use in infants or children, 27 did not make claims of safety and did not address safety experimentally (Table 2). Thus, 76 of the 103 articles did address safety, and 48 of these (63%) had already been identified in the original 218 articles culled from the Medline search. Of the 103 articles, 36 articles described experimental studies which involved paracetamol use in infants or children. Although several of these studies provided measures of liver function (Table 2), none of these 36 studies provided any assessment of neuropsychiatric function. Further, the median follow-up time of all 36 studies was 24 hours (**Figure 2**), far too short to identify any long-term effects of drug exposure on neuropsychiatric function. Four studies had a follow-up time of longer than 10 days, with one study in particular [24] evaluating patients out to one year. However, these studies were blind to any potential effects of drug exposure on long-term neuropsychiatric function. For example, although patients were followed for a full year in one study [24], the only endpoint measured was re-admission for surgery.
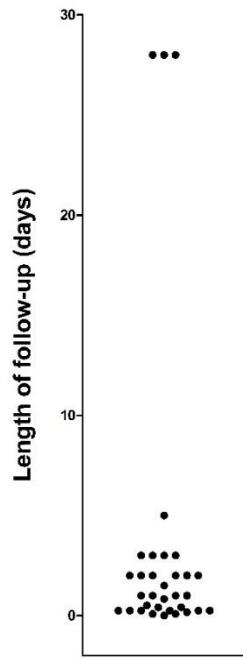
Figure 2. Maximum follow-up times for 34 of the 36 studies describing experiments designed to test the safety of acetaminophen in infants or children. One study [24] monitoring readmission for surgery for one year is omitted from the graph. Another study [66] observing patients during their inpatient visit did not specify duration of monitoring, and therefore could not be included in the graph. The three studies monitoring outcomes for 4 weeks (shown on the graph) did not monitor neuropsychiatric function.

The path from more recent papers to the original research addressing the safety of paracetamol in infants and children was sometimes convoluted. In one notable case, a popular citation did not did appear the literature (Table 2). Not only did the volume and journal number not match, but the title could not be found elsewhere. As another example, the citations reporting safety of paracetamol use in children reported by Temple and colleagues in 2017 [25] are illustrated in **Figure 1**. This article provides a detailed description of three prior reports to the European Medicines Agency (reports 24570, 24571, and 47402) which, together, according to the authors, "confirm that the recommended standard paracetamol dose of 10 to 15 mg/kg is a safe and effective dose for use in pediatric patients when administered as a single dose or as multiple doses for up to 72 hours." However, the only safety measure used in the three studies was ALT levels as a marker for liver function, assessed for a maximum of 72 hours. In addition to the three reports described in their publication, Temple and colleagues cite 10 additional articles as sources for safety, including the claim that paracetamol has a "well-established efficacy and favorable safety profile" (Figure 1). Among these 10 papers is a clinical trial [26] that addresses efficacy but not safety, and refers to two other papers that address safety, one by Lesko [22]. The paper by Lesko contradicts the view that paracetamol is safe, finding that paracetamol is significantly worse than ibuprofen in terms of risk for outpatient visits following treatment of children with asthma. Another of the articles cited by Temple in 2017, a review written by Temple more than 30 years before [27], cites a paper in the Federal Register [28] as the source for the statement

that "Paracetamol is relatively free of side effects and has a wide margin of safety between therapeutic doses and toxic doses." The document in the Federal Register [28], a lengthy treatise primarily focused on determination of the appropriate dose for adults of salicylates in general and aspirin in particular, in turn cites two papers involving safety studies of paracetamol in the human pediatric population. One of those studies [29] evaluated 98 children using a blinded approach comparing aspirin and paracetamol, and monitored the children for only 6 hours. The other study [30] monitored 20 children following administration of both aspirin and paracetamol. In that study, monitoring occurred for 6 hours or less and no information was provided regarding particular side effects that were being assessed. Importantly, the Federal Register [28] attributed their view that paracetamol has "a wide range of safety" to laboratory animal studies showing that the lethal dose of paracetamol is significantly greater than the dose administered to humans. Unfortunately, studies had not been conducted at that time showing that paracetamol induces permanent neurodevelopmental injury in laboratory animals at far lower doses than the lethal dose [15, 16], similar to doses administered to infants and children.

Discussion:

Our initial search of the PubMed® Database and review of more than 3000 titles and abstracts yielded 218 papers making claims that paracetamol is safe for infants and children when used as directed. Claims of safety in those 218 papers were traced back to 103 articles shown in Table 2, but less than 20 of those were cited more than twice, indicating that a limited number of studies are considered key or cornerstone to the view that paracetamol is safe for use in infants or children.

This study confirms the view that paracetamol use in infants and children is widely thought to be safe when used as directed, without reservations or caveats. The fact that 27 out of 103 citations did not, in fact, demonstrate safety or make safety claims might suggest that the safety of paracetamol is taken for granted, and is not carefully considered. This view is supported by the observation that one popular citation for safety does not exist in the literature.

Despite apparently being taken for granted, this study demonstrates that the drug was never shown to be safe for neurodevelopment. This conclusion is consistent with emerging studies showing a connection between paracetamol use during development and long term neuropsychiatric disfunction as described in the Introduction. This conclusion is also consistent with emerging studies in animal models showing exquisite sensitivity of long-term behavior to early life exposure to paracetamol at near-therapeutic doses.

Although not the intended purpose of this systematic review, it demonstrated that paracetamol has been proven safe for liver function in infants and in small children, even at doses higher than those currently recommended. During the course of this review, an assumption was repeatedly encountered: because the target of paracetamol toxicity in adults is the liver, demonstration of safety in infants and children need only be tested in the liver. This assumption was/is held despite the fact that the target tissue for drug function is in the central nervous system, not the liver. A similar assumption has proven tragically fatal in the past, when it was assumed that metabolism of the

antibiotic chloramphenicol was the same in infants as in adults. In that case, administration of the drug in infants led to a number of deaths [31-33] before the problem was identified.

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