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# Therapeutic Acetaminophen Is Not Associated With Liver Injury in Children: A Systematic Review

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# Therapeutic Acetaminophen Is Not Associated With Liver Injury in Children: A Systematic Review

**WHAT'S KNOWN ON THIS SUBJECT:** Although case reports have described liver injury after therapeutic dosing of acetaminophen in children, no previous study has attempted to estimate the risk to a given patient.

**WHAT THIS STUDY ADDS:** A total of 32 414 children in clinical trials and similar reports were recruited to estimate the rate of hepatic adverse events in acetaminophen-treated children. Symptomatic hepatotoxicity occurred in <0.01% of children. This study improves on previous compilations of case reports of this phenomenon.


## abstract

**BACKGROUND:** Concern exists about the potential for liver injury with therapeutic dosing of acetaminophen in children.

**OBJECTIVE:** We systematically reviewed the medical literature to determine the rate at which liver injury has been reported for children prescribed therapeutic doses of acetaminophen (≤75 mg/kg per day orally or intravenously or ≤100 mg/kg per day rectally).

**METHODS:** We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials to locate all studies in which acetaminophen was administered to a defined pediatric population for ≥24 hours and for all case reports of liver injury after therapeutic acetaminophen dosing. Trained reviewers extracted data from each report. Major and minor hepatic adverse events (AEs) were defined prospectively. Causality was assessed by using the Naranjo algorithm.

**RESULTS:** A total of 62 studies that enrolled 32 414 children were included. No child (0% [95% confidence interval: 0.000–0.009]) was reported to have exhibited signs or symptoms of liver disease, to have received an antidote or transplantation, or to have died. Major or minor hepatic AEs were reported for 10 children (0.031% [95% confidence interval: 0.015–0.057]). The highest transaminase value reported was 600 IU/L. Naranjo scores (2–3) suggested "possible" causation. Twenty-two case reports were identified. In 9 cases, the Naranjo score suggested "probable" causation (5–6).

**CONCLUSIONS:** Hepatoxicity after therapeutic dosing of acetaminophen in children is rarely reported in defined-population studies. Case reports suggest that this phenomenon may occur, but few reports contain sufficient data to support a probable causal relationship. *Pediatrics* 2010;126:e1430–e1444



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**KEY WORDS**

acetaminophen, children, drug safety, liver failure, systematic reviews


**ABBREVIATIONS**

FDA—Food and Drug Administration
AE—adverse event
AST—aspartate aminotransferase
ALT—alanine aminotransferase
INR—international normalized ratio
CI—confidence interval


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Acetaminophen is the medication most commonly administered to American children. In an average week, 11% of America's 73.7 million children receive acetaminophen.[1,2]

The toxicity of acetaminophen overdosage is undisputed. In recent hearings by the US Food and Drug Administration (FDA), strategies for preventing unintentional overdosage by caregivers and unsupervised ingestions by children were considered.[3] Some authors[4,5] have proposed that liver injury also may occur with therapeutic acetaminophen dosing.

For most drugs, it is difficult to assess the risk of low-frequency, drug-related adverse events (AEs), because large prospective studies that have assessed safety are not available. However, acetaminophen has been used in a large number of clinical trials. In addition to advantages in data quality, the use of clinical-trial subjects allows calculation of AE rates and formal assessment of AE severity.

We used data from published clinical trials and other studies of defined pediatric patient populations to determine the rate at which liver injury has been reported in children receiving therapeutic doses of acetaminophen for at least 24 hours in the setting of clinical studies. Because rare events may not be observed during clinical trials, we also describe all case reports of liver injury in a child after therapeutic acetaminophen dosing.

## METHODS

### Data Sources

We searched Medline (1966–2006), Old Medline (1950–1965), Embase (1980–2006), the Cochrane Central Register of Controlled Trials (1968–2006), and the reference lists of included studies.

### Literature Search

Our institution maintains a comprehensive, key-worded database of the published medical literature about the therapeutic use and toxicity of acetaminophen. Medline and Embase queries are performed annually. The specific search terms used are listed in Appendix 1. All citations are imported into a database (ProCite 5.0 [Thompson/ISI, Philadelphia, PA]). One of the authors (Dr Dart) reviewed all abstracts and hand-selected articles that contained primary clinical data. Full-text copies of these articles were obtained, and the articles were manually given key words by a single author (Dr Dart). In this database, the term "therapeutic dose" includes all articles that involved pediatric dosing of ≤75 mg/kg per day and adult dosing of ≤4000 mg/d. Articles with the key words "pediatric" and "therapeutic dose" published through 2006 were reviewed for this study. To assess the reliability of the key-wording step, 34 reports were reviewed by a second author (Dr Lavonas).

Pediatric formulations of acetaminophen were approved by the FDA for prescription-only marketing in 1955 and for over-the-counter use in 1959. In the United Kingdom, acetaminophen was approved for prescription use in 1956 and sold over-the-counter after 1963. Because these approvals predate the Medline database, we searched the Old Medline database (1950–1965) for relevant articles. The titles and abstracts of identified citations were hand-searched by a single author (Dr Lavonas) for studies that might have contained pediatric data; the full text of all identified articles was reviewed for inclusion.

Neither providing key words nor the process of manually reviewing a long list of articles is foolproof. To reduce the likelihood of a missed article, we searched the Cochrane Central Register of Controlled Trials by using the strategy shown in Appendix 1. One author (Dr Lavonas) reviewed these citations to identify those that might have contained appropriate data. As an additional check, we reviewed the reference list of included studies to identify articles missed by the database searches.

### Study Eligibility

We reviewed 2 types of publications for this report: defined population studies and case reports. Defined population studies, such as clinical trials, were included if they reported repeating therapeutic dosing of acetaminophen to an identifiable group of more than 1 child for at least 24 hours. Case reports, including those embedded in case series and other reports, were included if they reported hepatotoxicity developing in a child after a therapeutic dose of acetaminophen regardless of treatment duration.

### Data Extraction

A single author (Dr Lavonas) abstracted data from each identified article to a structured form. A second reviewer (Ms Reynolds) performed duplicate abstraction on all large trials (≥200 study subjects), all trials in which a hepatic AE was reported, and a random sample of 25% of the remaining articles. Disagreements were resolved by reference to the primary source.

Data abstracted included the number of child subjects; their ages; the indication, dose, and duration for acetaminophen administration; the highest reported levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total serum bilirubin, and international normalized ratio (INR); any reported symptoms or physical findings of hepatotoxicity; use of an acetaminophen antidote; discontinuation of acetaminophen because of a hepatic AE; and the occurrence of liver transplantation or death. For all stud-

ies that reported 1 or more hepatic AE, we analyzed whether sufficient data were available to assign each hepatic AE a severity level (severe, minor, or less than minor, as defined below). If the case-level data were insufficient to assign severity level, we contacted the study's first author for these data. We did not attempt to contact the authors of articles that reported no subjects with hepatic AEs or the authors whose publications contained sufficient data to permit us to determine AE severity for each case. Data were entered into an Excel spreadsheet (Microsoft, Redmond, WA).

The Naranjo scale was used to assess the likelihood of a causal relationship between acetaminophen exposure and hepatic AEs.[6] The Naranjo scale is a validated and widely accepted method for assessing causality in the setting of suspected drug-related AEs. This scale is summarized in Supplemental Appendix 2.

### Definitions

A therapeutic dose of oral acetaminophen was defined as ≤75 mg/kg per 24-hour period, not to exceed 4 g per 24 hours. This dose is concordant with current dosing recommendations from the FDA, the American Academy of Pediatrics, and the label of pediatric acetaminophen formulations sold in the United States.[7–9]

The bioavailability of rectally administered acetaminophen is less than that of the oral form. A kinetic study showed that ratios of the areas under the curve for acetaminophen suppositories, compared with elixir, were 0.79, 0.71, and 0.47 for neonates, infants, and children, respectively.[10] We defined a therapeutic rectal dose of acetaminophen as ≤100 mg/kg per 24-hour period, not to exceed 5 g/day.

Benorylate is an ester of acetaminophen and acetylsalicylate that is rapidly hydrolyzed to these 2 components in vivo. Benorylate is 48% acetaminophen by weight. We included benorylate studies if the dose administered was ≤150 mg/kg per day and ≤8 g/day.

Propacetamol is an acetaminophen prodrug; 1000 mg of propacetamol is hydrolyzed in vivo to 500 mg of acetaminophen. We included propacetamol studies if the dose administered was ≤150 mg/kg per day and ≤8 g/day.

Some studies permitted daily acetaminophen doses that exceeded the thresholds defined above. We included these reports only if the mean or median dose administered was below the thresholds. Similarly, in many studies of postsurgical analgesia, a "loading dose" of 25 to 40 mg/kg acetaminophen was given preoperatively; this strategy has been associated with increased efficacy in pediatric outpatient studies.[11] We included these studies if the sum of loading and postoperative dosing was within the above-listed therapeutic dosing limits.

In the population-based studies, we excluded studies that involved less than 24 hours of acetaminophen therapy, because exposure to therapeutic doses of acetaminophen for less than this restriction was not applied to case reports. A child was defined as aged from birth to 18 years. Some studies from pediatric specialty hospitals included patients older than 18 years. When data from the older subjects could not be separated, we included the study if the mean or median patient age was younger than 19 years.

Major and minor hepatic AEs were defined a priori by modifying the Drug-Induced Liver Injury Network criteria,[12] as reported in Table 1.[12–14] Our threshold for a minor hepatic AE was based on recent FDA guidance about drug-induced liver injury, which calls aminotransferase elevations less than 3 times the upper limit of normal "common and nonspecific."[14] The only exception made to our a priori definition during study execution was that we were unable to use an INR of more than 2.0 as a hepatic AE criterion because INR data were rarely reported. No subjects were reported to have an INR of more than 2.0.

**TABLE 1** Major and Minor Study-Outcome Criteria

| |
|---|
| Major hepatic AE |
| Death caused by liver failure |
| Liver transplant |
| Fulfillment of modified Drug-Induced Liver Injury Network criteria[8] |
| Elevation of AST or ALT >5 times the upper limit of normal |
| Elevation of alkaline phosphatase level >2 times the upper limit of normal |
| Jaundice or serum bilirubin level of >2.5 mg/dL (43 mmol/L) combined with ALT, AST, or alkaline phosphatase level >1 time the upper limit of normal |
| Minor hepatic AE |
| Elevation of AST or ALT levels >3 but ≤5 times the upper limit of normal |
| Any sign or symptom attributed by the study investigator to liver injury, in the absence of confirmatory testing |

In studies for which normal ranges of AST, ALT, and alkaline phosphatase were not reported, we used the following standard normal ranges: AST and ALT, up to 40 IU/L; alkaline phosphatase, up to 320 IU/L.[13]

### Statistical Plan

All statistical analyses, including subgroup analyses, were determined a priori and performed by using SAS Enterprise Guide 4.1 (SAS Institute, Inc, Cary, NC). The rates of hepatic AEs were reported with exact Poisson 2-sided 95% confidence intervals (CIs).

## RESULTS

### Literature Review

Our search identified 62 unique clinical trials and other defined population studies. Article flow is presented in Fig 1, and studies are summarized in Table 2.[15–76] Most studies investigated a disease, surgical and/or anesthetic technique, or another medication. In these studies, acetaminophen was given as part of standard therapy, as a

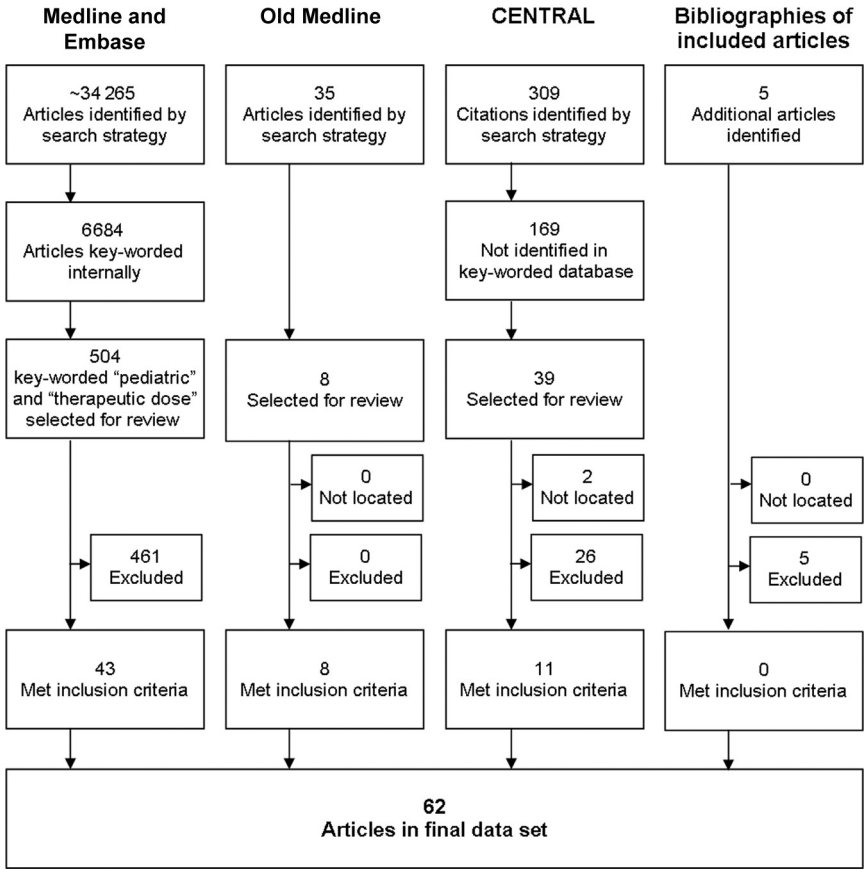


**FIGURE 1**
Article selection.

control intervention, or as rescue medication, and safety surveillance was performed on the study participants.

Data abstraction was reliable for most key study outcomes. Interreader agreements were high for the article key-wording step (adult versus pediatric, therapeutic versus supratherapeutic dose, single versus multiple doses) (simple agreement: 97%) and for the major outcome criteria of the number of subjects with hepatic AEs (95%). Agreement was only fair for the number of subjects who received both acetaminophen and follow-up (65%) and for the Naranjo causality score (67%). Therefore, we performed 100% revalidation on the variables of sample size and Naranjo causality score. We successfully contacted the first author of all studies for which additional information was required.

## Results From Clinical Trials and Other Defined Population Studies

Sixty-two unique reports met eligibility criteria. Sixty-one studies involved prospective data collection, whereas 1 report contained prospective and retrospective data. Data were reported from 32 414 children who received acetaminophen for at least 24 hours. Of these 62 publications, 59 studies ($n = 32\,213$ children) reported no major or minor hepatic AEs in any child.

One study examined all inpatients ($n = 100$ children) who received acetaminophen in a pediatric hospital.[41] The most common diagnoses were malignancy, trauma, and infection. Aggregate data were presented, and 8 children developed an AST or ALT value of 100 IU/L or more at some time during hospitalization. In this group, the median peak AST value was 116 IU/L (range: 63–375) and the peak ALT value was 128 IU/L (range: 52–362). No child developed coagulopathy or symptoms of hepatotoxicity, discontinued acetaminophen because of a hepatic AE, or received *N*-acetylcysteine. The highest measured bilirubin level was 1.6 mg/dL (28.3 $\mu$mol/L). Acetaminophen-cysteine protein adducts, a byproduct of the toxic acetaminophen metabolite, *N*-acetyl-*p*-benzo-quinoneimine, were undetectable in all patients. The Naranjo score for these cases was 3, indicating a possible causal relationship between acetaminophen use and transaminase elevations. The author concluded, "It was unlikely that hepatic transaminase elevation in these 8 subjects was related to acetaminophen dosing."[41] The author could not provide case-level information. The data are consistent with 1 to 3 children meeting major hepatic AE criteria, 1 to 6 children meeting criteria for minor hepatic AE, and 1 to 7 children falling below defined hepatic AE thresholds. For the purposes of data analysis, 3 children were assigned to the major hepatic AE classification and 4 to the minor hepatic AE group.

In a prospective observational case series designed to evaluate whether occult hepatotoxicity occurs in children receiving acetaminophen, 2 of 80 children who received $\leq$75 mg/kg per day developed hepatic AEs[58] (R. Shaoul, written communication, 2008). One child met our definition for a major hepatic AE. This child received a single 150-mg dose of acetaminophen daily for 2 days (10.7 mg/kg per day) and developed an AST of 270 IU/L. ALT was not measured, and prothrombin time was normal. One other child experienced a minor hepatic AE after receiving 75 mg/kg acetaminophen per day for 3 days. His peak AST level was 137 IU/L and peak ALT level was 108 IU/L. Both children were shown to have

**TABLE 2** Included Defined Population Studies

| Study | Reason for Acetaminophen | Age of Subjects[a] | Acetaminophen Dose[a] | Acetaminophen Duration, d[a] | Children Who Received Acetaminophen, *n* | Children With Major AEs, *n* | Children With Minor AEs, *n* | Notes |
|---|---|---|---|---|---|---|---|---|
| Akbas et al[15] (2004) | Pain, tonsillectomy | 4–14 y | 60 mg/kg per d | 7 | 60 | 0 | 0 | — |
| Allegaert et al[16] (2004) | Pain, minor surgical procedures, fever, respiratory infections | 1–76 d | 25–45 mg/kg per d | 2 | 18 | 0 | 0 | Intravenous propacetamol 50–90 mg/kg per d |
| Allegaert et al[17] (2005) | Pain, minor surgical procedures | 0 d–4 mo | 35–45 mg/kg per d | 1.2 | 28 | 0 | 0 | — |
| Anderson et al[18] (2000) | Healthy subjects | 1 d–3 mo | 30–40 mg/kg per d | 2 | 30 | 0 | 0 | — |
| Anderson[19] et al (2005) | Pain, postoperative | 8–14 y | 30 mg/kg per d | ≥1 | 14 | 0 | 0 | Reported patients from study 5 only |
| Bean-Lijewski et al[20] (2007) | Pain, tonsillectomy | 10.2 y | 53 mg/kg per d | 3 | 20 | 0 | 0 | — |
| Berclaz et al[21] (1996) | Pain and fever, malaria | 6–14 y | 45 mg/kg per d | 3 | 23 | 0 | 0 | — |
| Bergendahl et al[22] (2004) | Pain, tonsillectomy | 1–11 y | 60 mg/kg per d | ≥1 | 100 | 0 | 0 | — |
| Bertin et al[23] (1991) | Pain and fever, pharyngitis | 6–12 y | 30 mg/kg per d | 2 | 78 | 0 | 0 | — |
| Bertin et al[24] (1996) | Pain and fever, otitis media | 1–7 y | 30 mg/kg per d | 2 | 73 | 0 | 0 | — |
| Bonnard et al[25] (2005) | Pain, pyeloplasty | 2–16 y | 15–60 mg/kg per d | 1–4 | 22 | 0 | 0 | — |
| Breese Hall et al[26] (1987) | Pain and fever, influenza A | 1–15 y | 40 mg/kg per d | 5 | 32 | 0 | 0 | — |
| Caretti[27] (1986) | Pain and fever, pharyngitis | 5–15 y | 300–600 mg/d | 5 | 21 | 0 | 0 | — |
| Carter[28] (1965) | Pain and fever, respiratory infections | 2–15 y | 600–2400 mg/d | ≥1 | 100 | 0 | 0 | — |
| Catti and Monti[29] (1990) | Pain and fever, influenza | 6 m–1 y | 33–62 mg/kg per d | 5 | 30 | 0 | 0 | — |
| Doran et al[30] (1989) | Pain and fever, varicella | 1–13 y | 40 mg/kg per d | 4 | 37 | 0 | 0 | — |
| Ericsson et al[31] (2006) | Pain, tonsillectomy | 5–15 y | 64 mg/kg per d | 7 | 92 | 0 | 0 | — |
| Falanga et al[32] (2006) | Pain, mostly postoperative | 5–17 y | 21 or 60 mg/kg per d | 2 | 112 | 0 | 0 | — |
| Fosel et al[33] (2005) | Pain, tonsillectomy | 6–14 y | 80–90 mg/kg per d (rectal) | ≥1 | 100 | 0 | 0 | — |
| Gianiorio et al[34] (1993) | Pain and fever, respiratory infection | 3–12 y | 360–864 mg/d | 3–7 | 20 | 0 | 0 | — |
| Gupta et al[35] (2007) | Pain and fever, respiratory infection | 6 m–16 y | 15–60 mg/kg per d | 1.5 | 85 | 0 | 0 | — |
| Howard et al[36] (1994) | Pain, circumcision | 1–3 d | 60 mg/kg per d | 1 | 23 | 0 | 0 | — |
| Hugosson et al[37] (2003) | Pain and fever, malaria | 1–4 y | 45 mg/kg per d | 3 | 38 | 0 | 0 | — |
| Hultcrantz and Ericsson[38] (2004) | Pain, tonsillectomy | 5–15 y | 48 or 55 mg/kg per d | 4.2 or 7.3 | 92 | 0 | 0 | — |
| Huth et al[39] (2004) | Pain, tonsillectomy | 7–12 y | 36 mg/kg per d | 1 | 38 | 0 | 0 | — |
| Jaffe and Grimshaw[40] (1983) | Pain and fever, respiratory infection | 6–12 y | 600 mg/d | 3 | 105 | 0 | 0 | — |

**TABLE 2** Continued

| Study | Reason for Acetaminophen | Age of Subjects[a] | Acetaminophen Dose[a] | Acetaminophen Duration, d[a] | Children Who Received Acetaminophen, *n* | Children With Major AEs, *n* | Children With Minor AEs, *n* | Notes |
|---|---|---|---|---|---|---|---|---|
| James et al[41] (2001) | Pain and/or fever, malignancy, trauma, infection | 0–21 y | 48 mg/kg per d | 2 | 100 | 3 | 4 | See text |
| Kaye et al[42] (1966) | Fever, various infections | 8–15 y | 14–30 mg/kg per d | 3 | 12 | 0 | 0 | — |
| Kearns et al[43] (1985) | Fever, meningitis, pneumonia, other infections | 3–6 y | 60 mg/kg per d | 4 | 18 | 0 | 0 | — |
| Lal et al[44] (2000) | Pain and fever, respiratory infection | 1–4 y | 10 mg/kg per d | 5 | 51 | 0 | 0 | — |
| Lesko and Mitchell[45] (1995) | Pain and fever, upper respiratory infections, otitis media, and pharyngitis | 6 m–12 y | 32 mg/kg per d | 6–10 doses | 28 130 | 0 | 0 | — |
| McIntyre and Hull[46] (1996) | Pain, tonsillectomy | 2 m–12 y | 50 mg/kg per d | 1–3 | 13 | 0 | 0 | — |
| Moir et al[47] (2000) | Fever | 3–12 y | 15–60 mg/kg per d | 1–10 | 51 | 0 | 0 | — |
| Molliex et al[48] (1996) | Pain, tonsillectomy | 8–15 y | 300–600 mg/d rectally | 1 | 24 | 0 | 0 | — |
| Nwanyanwu et al[49] (1999) | Pain and fever, malaria | 0–4 y | 50 mg/kg per d | 3 | 28 | 0 | 0 | — |
| Owczarak and Haddad[50] (2006) | Pain, tonsillectomy | 1–5 y | 60 mg/kg per d | 10 | 56 | 0 | 0 | — |
| Ozlugedik et al[51] (2006) | Pain, tonsillectomy | 6.4 y | ≤75 mg/kg per d | 7 | 60 | 0 | 0 | — |
| Pendeville et al[52] (2000) | Pain, tonsillectomy | 2–9 y | 45 mg/kg per d | 3 | 25 | 0 | 0 | — |
| Phadke et al[53] (1985) | Pain and fever, upper respiratory infections, measles | 2–12 y | ~15–30 mg/kg per d | 5 | 23 | 0 | 0 | — |
| Powell and Ansell[54] (1974) | Pain, Still's disease (juvenile rheumatoid arthritis) | 6–15 y | 36–72 mg/kg per d | 14 | 18 | 0 | 0 | Pilot-phase subjects only |
| Reuter and Montgomery[55] (1964) | Pain, tonsillectomy | 4–13 y | 130–260 mg per dose | 7 | 100 | 0 | 0 | — |
| Salvioli et al[56] (1995) | Pain, upper respiratory and urinary tract infections | 6 m–16 y | 375–1500 mg/d | 5.4 | 168 | 0 | 0 | — |
| Sarrell et al[57] (2006) | Fever | 6 m–2 y | 50–75 mg/kg per d | 3 | 309 | 0 | 0 | Groups A and C only |
| Shaoul et al[58] (2004) | Fever | 1 m–16 y | ≤80 mg/kg per d | 2–3 | 80 | 1 | 1 | Excluded 27 patients with dose of >80 mg/kg per d |
| Smyth et al[59] (2004) | Pain, craniotomy | ≤21 y | 40 mg/kg per d | 2.2 | 25 | 0 | 0 | — |
| Sowunmi et al[60] (2005) | Pain and fever, malaria | ≤12 y | 45 mg/kg per d | 1.1 | 153 | 0 | 0 | — |
| Spika et al[61] (1986) | Pain and fever, epiglottitis and meningitis | 2–5 y | 50 mg/kg per d | 2–3 | 5 | 0 | 0 | — |

**TABLE 2** Continued

| Study | Reason for Acetaminophen | Age of Subjects[a] | Acetaminophen Dose[a] | Acetaminophen Duration, d[a] | Children Who Received Acetaminophen, *n* | Children With Major AEs, *n* | Children With Minor AEs, *n* | Notes |
|---|---|---|---|---|---|---|---|---|
| Steru et al[62] (1983) | Pain and fever, respiratory infection, otitis media | 4 m–10 y | 22–35 mg/kg per d | ≥1 | 21 | 1 | 0 | — |
| Sugimura et al[63] (1994) | Pain and fever, pharyngitis | 6 m–15 y | ≤40 mg/kg per d | 3 | 144 | 0 | 0 | Excluded 64 patients with 0 doses/d |
| Sutrisna et al[64] (1991) | Pain and fever, respiratory infection | 0–5 y | 30 mg/kg per d | 5 | 889 | 0 | 0 | — |
| Sutters et al[65] (2004) | Pain, tonsillectomy | 6–15 y | 48 mg/kg per d | 3 | 52 | 0 | 0 | — |
| Thompson et al[66] (1987) | Pain and fever, Influenza | 1–12 y | 10 mg/kg per d | 5 | 34 | 0 | 0 | — |
| Tobias et al[67] (1997)[b] | Pain, encephalocele repair | 5.7 y | 38.5 mg/kg per d | ≥1 | 12 | 0 | 0 | Group 2 patients only |
| Ugazio et al[68] (1993) | Pain and fever, respiratory infection | 3–6 y | 15–41 mg/kg per d | 3–9 | 50 | 0 | 0 | — |
| Ulukol et al[69] (1999) | Pain and fever, respiratory infection | 2–14 y | 30 mg/kg per d | 5 | 30 | 0 | 0 | — |
| Vallee et al[70] (2007) | Pain, tonsillectomy | 5–17 y | 60 mg/kg per d | ≥3 | 40 | 0 | 0 | — |
| Van Esch et al[71] (1995) | Fever | 10 m–4 y | 40 mg/kg per d | 1–3 | 33 | 0 | 0 | — |
| Vinh et al[72] (2004) | Fever, typhoid | 2–14 y | 48 mg/kg per d | 2–36 | 40 | 0 | 0 | — |
| Walson et al[73] (1992) | Fever | 6 m–11 y | 60 mg/kg per d | 1–2 | 16 | 0 | 0 | — |
| Weippl et al[74] (1985) | Fever | 6 m–12 y | 12–25 mg/kg per d | 2 | 54 | 0 | 0 | — |
| Wilson and Helgadottir[75] (2006) | Pain, tonsillectomy | 3–7 y | 55, then 40 mg/kg per d | 3 | 68 | 0 | 0 | — |
| Zernikow et al[76] (2006) | Pain, cancer | 9 y | 23.1 mg/kg per d | 6.8 | 91 | 0 | 0 | — |
| Total | — | — | — | — | 32 414 | 5 | 5 | — |

[a] Mean, median, or range, as reported in the study.

[b] Studies did not involve prospective data collection (combined prospective and retrospective data collection).

acute Epstein-Barr virus infections. The Naranjo causality scores were 2 ("possibly related") in each case.

In a randomized trial designed to compare the efficacy of 2 doses of acetaminophen (22 vs 35 mg/kg per day) for the treatment of fever, 1 of the 21 child subjects had a "rapid, very elevated increase" of unspecified transaminase levels to 600 IU/L.[62] This child, and a second child whose peak transaminase level of 42 IU/L did not fulfill hepatic AE criteria, discontinued acetaminophen because of transaminase changes. Both patients were found to have acute viral hepatitis. Clinical signs and symptoms were not reported; recovery was implied but not explicitly stated. The Naranjo causality score was 2 ("possibly related").

One additional study reported transaminase elevations below our hepatic AE threshold definitions. In a randomized clinical trial designed to evaluate the safety and effectiveness of acetaminophen (50–75 mg/kg per day), ibuprofen, or both for the treatment of fever, transaminase levels were measured for all patients on days 3, 5, and 14 after initiation of therapy.[57] Although 8 of 464 study subjects manifested some AST elevation, the highest AST measured in any patient in this study was 28 IU/L (E. Michael Sarrell, written communication, 2008). No child had prothrombin time or bilirubin elevations or signs or symptoms of hepatotoxicity, and all transaminase elevations resolved spontaneously.

Among 32 414 children reported in these 62 studies, no child (0% [95% CI: 0.000–0.009]) was reported to exhibit

signs or symptoms of liver disease, to have received an antidote or liver transplantation, or to have died. Hepatic AEs of at least mild severity were reported for up to 10 children (0.031% [95% CI: 0.015–0.057]), of whom up to 5 children (0.015% [95% CI: 0.005–0.036]) had reported abnormalities that fulfilled our major hepatic AE criteria. In all 10 cases, the Naranjo scores (2–3) suggested a possible causal relationship between acetaminophen exposure and hepatic AEs. Although 2 children were reported to discontinue acetaminophen use because of transaminase elevations, both were found to have acute viral hepatitis.

### Results From Case Reports

Because rare AEs may not be observed during clinical trials, we also identified all case reports of hepatic AEs after therapeutic acetaminophen dosing. Including the studies described above, 17 publications provided case-level data for 26 children (Table 3).[4,5,59,62,77–89] Four of these reports seemed to be duplicates, which left a total of 22 children described. The population of exposed children from which these reports are derived is unknown. Four patients died, 1 survived with neurologic sequelae, and 17 recovered fully. Ages ranged from 4 weeks to 18 years. In 13 cases for which weight-based acetaminophen dosing was reported, the median reported dose was 39 mg/kg per day (range: 10.7–75 mg/kg per day). An additional 6 cases included only absolute dosing information (range: 120–3200 mg/day),[77,80–82,87,89] whereas 3 reports did not include total daily dosage.[4,84] The median duration of acetaminophen administration was 3 days (range: 1 day to 8 years). Serologic evidence of acute viral hepatitis was positive in 4 cases,[58,62,88] negative in 13 cases,[4,5,80,83,84,86,87,89] and not reported in 5 cases.[77,81,82,85] Although no patient had reported evidence of autoimmune disease, information about testing was only provided in reports for 11 patients.[4,84–87,89] Histologic features of centrilobular necrosis were present in 8 cases,[4,81,84,86–88] whereas 1 patient had a histologic pattern not generally associated with acetaminophen injury.[89] Liver biopsies were either not performed or not reported in 13 cases.*

Few patients had putative risk factors for acetaminophen toxicity. Although not described as malnourished, 2 patients had reported weights that fell below the fifth percentile for age.[13,83,88] One patient was taking phenobarbital, a cytochrome P450–inducing medication.[83] An acute febrile illness preceded recognition of hepatic injury in 15 cases.† Although decreased oral intake during acetaminophen dosing was only described for 5 patients,[4] this information was missing from many reports, probably because anorexia normally accompanies fever.

Naranjo scores suggested possible causation (scores of 1–4) in 13 cases[58,62,77,80–86,88] and probable causation (scores of 5–6) in 9 cases.[4,5,87,89] One death was associated with a Naranjo score (5) that suggested probable causation.[5]

## DISCUSSION

Our systematic review revealed a large number of clinical trials and observational studies that involved the use of acetaminophen at a therapeutic dosage. Collectively, the 32 000 patients in these studies may represent the largest population of children directly observed for toxicity from a single drug. In this population, no child was reported to have symptomatic liver injury, require an acetaminophen antidote, undergo liver transplantation, or die. Transaminase elevations were reported for 10 children (0.031% [95% CI: 0.015–0.057]), none of whom had other evidence of liver dysfunction. Although discontinuation of acetaminophen because of hepatic AEs was reported for 2 children, both were subsequently shown to have acute viral hepatitis. In fact, each of the 3 authors[41,58,62] who reported hepatic AEs after acetaminophen administration stated their belief that the association was not causal.

Most children in these studies were clinically ill with the conditions for which acetaminophen is typically prescribed: acute infections and postoperative pain. Children received acetaminophen by mouth, feeding tube, rectal suppository, and intravenous infusion. Children were enrolled from all common practice settings (physician offices, hospital-based clinics, surgery centers, NICUs, and hospital inpatient wards) and from both the developed and developing world. Ages ranged from very premature infants (27 weeks' postconceptional and 0 days' postnatal age) to adolescent and young-adult age.

Transaminase elevations, not accompanied by hyperbilirubinemia, coagulopathy, or bile stasis, occur with several medications, including aspirin, statins, tacrine, and heparin, that rarely, if ever, cause severe drug-induced liver injury.[10] Although it is undeniable that acetaminophen overdosage can cause fatal liver injury, the medical significance of transient, isolated transaminase elevations is unclear.

Our results are supported by several other lines of evidence. Between 1958 and 1977, 598 deaths from accidental poisoning in children were recorded in the United Kingdom; only 1 was caused by acetaminophen.[90] The report did not describe whether the acetaminophen dose was appropriate. None of the 51 children treated for acetaminophen-induced hepatotoxicity in the Birming-

*Refs 4, 5, 58, 62, 77, 80, 82, 83, and 85.
†Refs 4, 57, 58, 62, 77, 81–83, 85, 86, and 89.

**TABLE 3** Published Case Reports of Liver Injury Occurring in Children After Reported Therapeutic Dosing of Acetaminophen, 1960–2006

| Report | Age/Gender | Acetaminophen Dose | Duration | Condition Being Treated | Acetaminophen Level; Time After Last Dose | Antidote Administered | Final Outcome | Naranjo Causality Score | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Individual patients in defined-population studies | | | | | | | | | |
| Steru et al[62] (1983) (patient 3) | 4 mo/male | 22 mg/kg per d | 2 d | Fever, viral hepatitis | NR | No | Recovered | 2 | Viral hepatitis |
| Shaoul et al[58] (2004) | 15 mo/NR | 75 mg/kg per d | 3 d | Fever, Epstein-Barr virus infection | 4.2 μg/mL, time NR | No | Recovered | 2 | Positive EBV serology |
| Shaoul et al[58] (2004) | 3 y/NR | 10.7 mg/kg per d | 2 d | Fever, Epstein-Barr virus infection | None detected, time NR | No | Recovered | 2 | Positive EBV serology |
| Patients reported in case reports other studies from which the source population is not defined | | | | | | | | | |
| Greene et al[77] (1983) (case 1) | 7 wk/female | 30 mg every 4–5 h (~40 mg/kg per d) | 6–8 d | Persistent fever | 10.7 μg/mL; 54 h | No | Recovered | 4 | Etiology of persistent fever never established; level suggests supratherapeutic dosing; also reported as case No. 11 by Heubi et al[78] (1988) and Table 3, case 2 by Penna and Buchanan (1991)[79] |
| Bell et al[80] (1987) (case 1) | 18 y/female | 3200 mg/d | 8 y | Chronic headache | None detected | No | Recovered | 4 | |
| Litovitz et al[81] (1988) (case 111) | 4 y/male | 1000 mg (weight NR) | 1 d | Fever, vomiting, and abdominal pain for 1 wk | 250 μg/mL, time NR | Yes | Death | 4 | Reported level is not consistent with therapeutic dosing. Also reported as case 42 by Heubi et al[78] (1988) |
| Fudin et al[82] (1989) | 7 y/male | 2.5 g/d | 2 d | Fever, pneumonia with *Klebsiella* sepsis | "Trace," time NR | No | Recovered | 3 | |
| Chiossi et al[83] (1991) | 4 y/female | 60 mg/kg per d | 3 d | Fever | NR | No | Recovered | 3 | Chronic spastic cerebral palsy and malnutrition (8.3 kg); prescribed barbiturates; also reported as case No. 28 by Heubi et al[78] (1998) |
| Patel[84] (1992) | 13 y/female | 1000 mg per dose, unknown frequency, then 2500 mg once | "Some weeks," then acute overdose | Chronic headaches | Undetectable, 60 h | No | Death | 4 | Possible supratherapeutic dosing, followed by acute minor overdose |

**TABLE 3** Continued

| Report | Age/Gender | Acetaminophen Dose | Duration | Condition Being Treated | Acetaminophen Level; Time After Last Dose | Antidote Administered | Final Outcome | Naranjo Causality Score | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Entacher et al[85] (1993) (case 1) | 4 y/male | 3 episodes in 6 wk: 33, 28, and 31 mg/kg per d | 3, 4, and 3 d | Recurrent unexplained fevers | NR | No | Recovered | 4 | Diagnosis of hepatotoxicity doubtful (highest AST: 43 IU/L; highest ALT: 44 IU/L); palmar and plantar rash and electrocardiogram abnormalities in an immunocompromised child suggest an alternate process |
| Entacher et al[85] (1993) (case 2) | 4 wk/male | 55 mg/kg per d | 3.5 d | Fever | 9.9 μg/mL, 6 h; 0.22 μg/mL, 22 h | No | Recovered | 4 | Palmar and plantar rash and electrocardiogram abnormalities suggest an alternate process |
| Zweiner et al[86] (1994) | 9 y/female | 48 mg/kg per d | 1 day | Mercury poisoning | NR | No | Recovered | 3 | Authors attributed hepatotoxicity to synergistic toxicity between mercury and acetaminophen |
| Hartleb[87] (1994) | 17 y/NR | 1.5–2 g/d | ≥10d | Pain, headache | NR | No | Recovered | 6 | |
| Alonso et al[4] (1995) (patient 3) | 4.5 y/NR | 36 mg/kg per d | 4 d | 1-wk fever, URI | 35 μg/mL, time NR | NR | Recovered | 6 | |
| Alonso et al[4] (1995) (patient 4) | 5 m/NR | 42 mg/kg per d | 2 d | 3-wk fever | 6 μg/mL, time NR | NR | Recovered | 5 | |
| Alonso et al[4] (1995) (patient 5) | 3 m/NR | 23 mg/kg per d | 2 d | Diarrhea | Not measured | NR | Recovered | 5 | |
| Alonso et al[4] (1995) (patient 6) | 2 y/NR | "Therapeutic dose," exact quantity not documented | 3 d | Diarrhea, fever | 2 μg/mL, time NR | NR | Recovered | 5 | |
| Alonso et al[4] (1995) (patient 7) | 5 y/NR | "Therapeutic dose," exact quantity not documented | 1 wk | Fever | Not measured | NR | Recovered | 5 | |
| Hausmann et al[88] (1996) | 12 y/NR | 60 mg/kg per d | 4 d | Pain, tonsillectomy | NR | No | Death | 2 | |
| Miles et al[5] (1999) (case 5) | 2 y/NR | 71 mg/kg per d | 4 d | Unspecified prodromal illness | 24 μg/mL, time NR | NR | Recovered, severe brain damage | 6 | |
| Miles et al[5] (1999) (case 6) | 12 y/NR | 20 mg/kg per d | 7 d | Unspecified prodromal illness | 27 μg/mL, time NR | NR | Death | 5 | |
| Shinzawa et al[89] (2001) | 14 y/female | 450 mg daily | 4 d | Fever | NR | No | Recovered | 6 | Acute cholestatic hepatitis with eosinophilia; probable allergic mechanism |

Does not include ~7 patients reported in aggregate by James et al.[41] NR indicates not reported.

ham (United Kingdom) Children's Hospital between 1992 and 2002 became ill from correct therapeutic dosing, nor did any of the ~100 patients younger than 21 years admitted to the liver-transplant unit of Kings College Hospital (London, United Kingdom) from 1987 to 1993.[91,92] None of the 73 children treated for acetaminophen-induced hepatotoxicity in 5 pediatric-care centers in California (1985–1995) became ill from ingesting ≤75 mg/kg per day, nor did any of the 2157 children treated for poisoning in 17 Spanish tertiary care hospitals (2001–2002).[93,94] Investigators who reviewed the adverse-drug-reaction database of the Royal Children's Hospital (Melbourne, Australia) for 1999–2003 found 6 cases of acetaminophen-induced rash but no cases of hepatotoxicity.[95]

Although they cannot be used to determine incidence rates, case reports may provide important information about uncommon drug-related AEs that cannot be obtained from clinical trials. A 1998 review reported 47 cases of acetaminophen-induced hepatotoxicity occurring in children as a result of "therapeutic misadventures" during a period of at least 18 years (1978–1996).[78] These cases were compiled through a combination of a literature review (28 cases), review of records at a large pediatric referral center (3 cases), and reports made to the FDA (16 cases). Only 3 cases, all previously published, reported an acetaminophen dose of ≤75 mg/kg, and in 1 of these cases, the serum acetaminophen level (250 μg/mL) was incompatible with the reported dose.[81] In a 1991 literature review of pediatric acetaminophen poisoning, none of the 7 fatalities involved dosing of ≤75 mg/kg per day.[79] One of 11 cases of nonfatal hepatitis was attributed to therapeutic dosing; this case had been published separately.[77]

In our review of the literature, we discovered 11 additional published reports that described 18 additional patients reported to have developed hepatic injury after receiving therapeutic doses of acetaminophen. The quality of these reports, including the history of ingested dose and rigor of workup performed to exclude alternate causes of hepatic injury, varied greatly. On the basis of the Naranjo scoring system, most cases were associated with a possible causal relationship between acetaminophen exposure and liver inflammation. Taken together, these results make it clear that most of the cases of acetaminophen hepatotoxicity attributed to "therapeutic misadventures" are, in fact, chronic overdoses. Hepatotoxicity caused by ingestion of 75 mg/kg acetaminophen or less per day, if it occurs at all, is an exceedingly rare event.

## LIMITATIONS

The indexing strategies of medical databases is imperfect, and the process by which we manually searched more than 34 000 article titles and abstracts and key-worded more than 6500 articles may have introduced errors. Although we addressed this concern by using a redundant search strategy, it is possible that articles were missed.

Liver inflammation may have remained undetected in some children. Most studies did not conduct routine blood testing on children without signs or symptoms of liver injury; of the studies that performed routine testing, few described this surveillance in more than general terms. This is a major limitation of our approach. Incomplete safety reporting is common in published clinical trials.[96] This study should not be used to estimate the proportion of children taking acetaminophen who develop asymptomatic transaminase elevations. Had routine screening been performed in all studies, additional cases of hepatic enzyme elevation would likely have been revealed. The medical importance of transient transaminase elevations that do not produce signs or symptoms of illness is unclear.

The threshold criteria used to define severe liver injury are arbitrary. Most studies of acetaminophen overdosage used the criteria of an AST or ALT level of ≥1000 IU/L.[97] We chose not to adopt this standard because we believed that more modest transaminase elevations are important to clinicians. Although we adapted our major and minor hepatic AE definitions from criteria used by the Drug-Induced Liver Injury Network and the FDA, these criteria also are somewhat arbitrary.

Few children in these studies received exactly 75 mg/kg per day of acetaminophen, and many did not receive treatment for longer than 3 to 5 days. Therefore, the power of this study to detect infrequent hepatic AEs associated with prolonged therapy and/or maximal therapeutic dosing is weak. This study cannot be used to evaluate the safety of doses of acetaminophen (eg, 90 mg/kg per day) that often are recommended but exceed the recommendations of the FDA and American Academy of Pediatrics.[98,99]

Clinical trial subjects may vary from the general population of children who take acetaminophen. Enrollment-screening criteria may be more effective than routine clinical practice at excluding patients at high risk for hepatotoxicity. Also, the dosing instructions given by study investigators may be more explicit than those given in routine clinical practice. However, 8% of parents who participated in a recent clinical trial exceeded the maximum number of acetaminophen doses in a 24-hour period despite detailed instructions.[100]

Measurement of protein adducts of the toxic acetaminophen metabolite,

*N*-acetyl-*p*-benzo-quinoneimine, might improve the specificity with which hepatic AEs could be attributed to acetaminophen.[101] We identified only 1 study that used this technique.[41] None of the 7 patients with hepatic AEs in that study had detectable serum acetaminophen-protein adducts.

We only studied hepatic AEs and did not study other rare AEs, such as rash, allergy, or thrombocytopenia, that occur with acetaminophen use.[102,103] We did not compare the rate of hepatic AEs after acetaminophen use to other treatment options, such as nonsteroidal anti-inflammatory drugs, opioids, complimentary and alternative medicine, and no therapy.

Evaluation of case reports is always complicated by publication bias. Case reports are selected for publication on the basis of their novelty and positive results.[104] Assessment of causality in suspected drug-related AEs always involves some subjectivity and is influenced by strength of previous beliefs. Even when provided with access to all clinical data, experienced clinicians frequently disagree on the etiology of liver failure, particularly in cases of fulminate hepatic failure.[105,106] Attempting to assess causality from the limited data included in a case report is even more problematic. Although we chose a validated and widely accepted tool for causality assessment, we cannot provide a definitive answer about whether acetaminophen caused or contributed to liver toxicity in a given case. Although case reports provide exploratory data about vulnerable patients and high-risk situations, they cannot be used to estimate the risk to an individual patient or in a patient population.

No study can prove that a given AE never occurs. Although we can assert with confidence that less than 0.01% of children who receive acetaminophen in a dose, duration, and setting similar to those used in the clinical trials will develop symptomatic hepatotoxicity, translating even that low-risk estimate to the ~8.1 million US children who receive acetaminophen in an average week may not reassure everyone. Given that acetaminophen therapy provides symptomatic relief during a period of self-limited illness, one could argue that even a single drug-related AE is too many.

## CONCLUSIONS

Hepatoxicity after therapeutic dosing of acetaminophen (≤75 mg/kg per day) in children is rarely observed in defined-population studies, which suggests that the risk that a child will develop symptomatic hepatotoxicity from acetaminophen in the dose, duration, and other settings of these trials is less than 0.01%. The majority of published case reports that have described this association are associated with a possible causal relationship between acetaminophen use and liver injury.

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**APPENDIX 1** Search Strategies and Results

| Database | Search Terms | Date of Final Search | Citations Retrieved | Articles Included[a] |
|---|---|---|---|---|
| Medline (1966–2006) and Embase (1980–2006) | Acetaminophen (MeSH key word) or [acetaminophen or apap or paracetamol or 103-90-2].mp Limit: humans | Mar 2007 | ~34 265 | 43 |
| Old Medline (1950–1965) | Acetaminophen (MeSH key word) or [acetaminophen or apap or paracetamol or 103-90-2].mp | Mar 13, 2009 | 35 | 8 |
| Cochrane Central Register of Controlled Trials (1968–2006) | Acetaminophen [search all text] and children [search all text] | Aug 25, 2008 | 309 | 11 |
| Bibliographies of included articles[b] | NA | NA | 5 | 0 |
| Total | NA | NA | NA | 62 |

Medical Subject Headings (MeSH): Acetaminophen/ad [Administration & Dosage], Acetaminophen/ae [Adverse Effects], Acetaminophen/po [Poisoning], Acetaminophen/tu [Therapeutic Use], Adolescent, Alanine Transaminase/an [Analysis], Analgesics, Non-narcotic/ad [Administration & Dosage], Analgesics, Non-narcotic/ae [Adverse Effects], Analgesics, Non-narcotic/po [Poisoning], Analgesics, Non-narcotic/tu [Therapeutic Use], Child, Child, Preschool, Drug Administration Schedule, Humans, Infant, Liver failure, Acute/ci [Chemically induced], Liver failure, Acute/di [Diagnosis], Prospective Studies, Retrospective Studies, Systematic reviews, Transaminases/bl [Blood] NA indicates not applicable.

[a] Articles published in English, French, German, Italian, Japanese, Norwegian, and Spanish languages were eligible for inclusion.

[b] Includes only unique citations not found on other searches.

# Therapeutic Acetaminophen Is Not Associated With Liver Injury in Children: A Systematic Review

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